CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 200744

Name: Tacrolimus Ointment 0.03%, 0.1%

Sponsor: Fougera Pharmaceuticals Inc

Approval Date: September 9, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA200744Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200744Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200744

ANDA APPROVAL

Fougera Pharmaceuticals Inc.
Attention: Amy M. Byrom
Director, Regulatory Affairs
60 Baylis Road, P.O. Box 2006
Melville, NY 11747

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated April 8, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tacrolimus Ointment 0.03% and 0.1%.

We acknowledge receipt of your amendments dated September 9, October 15, and December 15, 2010; February 17, March 4, August 9, September 16, and December 23, 2011; February 24, February 29, March 15, May 4, June 11, July 24, July 25, and December 12, 2012; and August 23, November 20, December 6, December 12, and April 24, 2014.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Tacrolimus Ointment 0.03% and 0.1%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Protopic Ointment, 0.03% and 0.1%, respectively, of Astellas Pharma US, Inc.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory

requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

CAPT Jason J.Y. Woo, M.D., M.P.H.
Acting Director, Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

09/09/2014

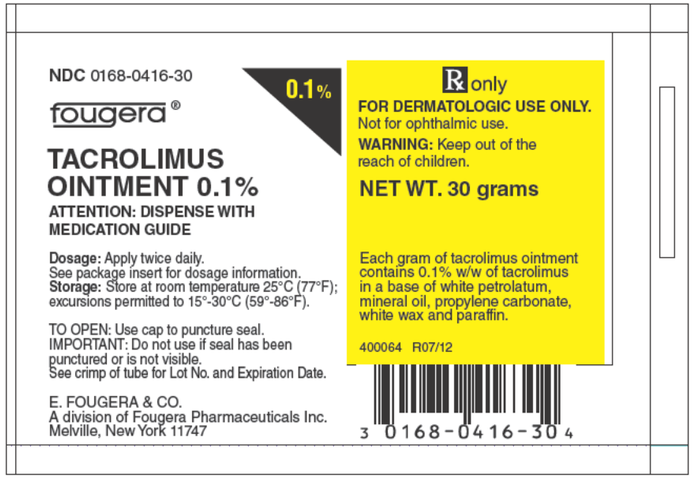
Associate Director for Review Quality, for
Jason Woo, M.D., M.P.H.

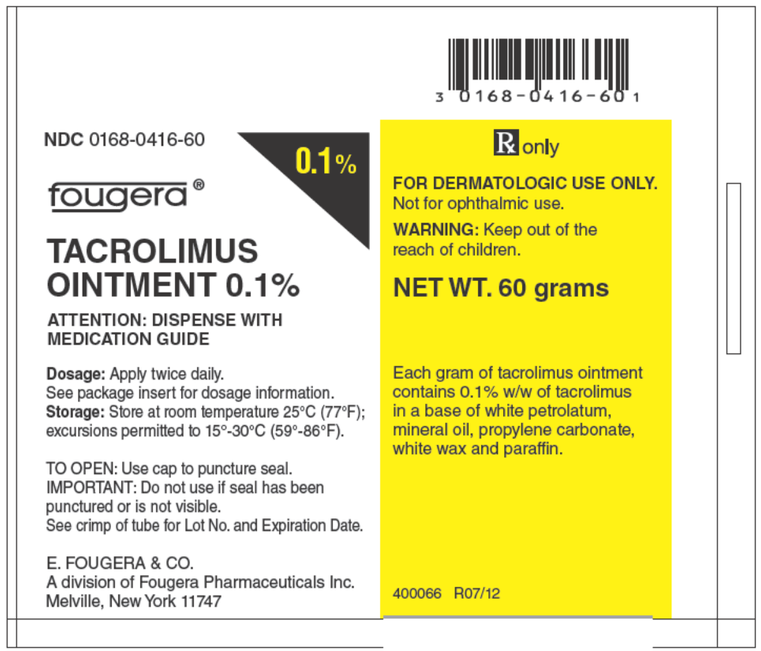
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200744Orig1s000

LABELING


NDC 0168-0416-30
0.1%
fougera®
TACROLIMUS
OINTMENT 0.1%
ATTENTION: DISPENSE WITH
MEDICATION GUIDE
Dosage: Apply twice daily.
See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F);
excursions permitted to 15°-30°C (59°-86°F).
TO OPEN: Use cap to puncture seal.
IMPORTANT: Do not use if seal has been
punctured or is not visible.
See crimp of tube for Lot No. and Expiration Date.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc.
Melville, New York 11747
℞ only
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the
reach of children.
NET WT. 30 grams
Each gram of tacrolimus ointment
contains 0.1% w/w of tacrolimus
in a base of white petrolatum,
mineral oil, propylene carbonate,
white wax and paraffin.
400064 R07/12
3 0168-0416-30 4


3 0168-0416-60 1
NDC 0168-0416-60
0.1%
fougera®
TACROLIMUS OINTMENT 0.1%
ATTENTION: DISPENSE WITH MEDICATION GUIDE
Dosage: Apply twice daily.
See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
TO OPEN: Use cap to puncture seal.
IMPORTANT: Do not use if seal has been punctured or is not visible.
See crimp of tube for Lot No. and Expiration Date.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc.
Melville, New York 11747
℞ only
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
NET WT. 60 grams
Each gram of tacrolimus ointment contains 0.1% w/w of tacrolimus in a base of white petrolatum, mineral oil, propylene carbonate, white wax and paraffin.
400066 R07/12

NDC 0168-0416-99

fougera®

0.1%

TACROLIMUS OINTMENT 0.1%

ATTENTION: DISPENSE WITH MEDICATION GUIDE

Dosage: Apply twice daily.
See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

TO OPEN: Use cap to puncture seal.
IMPORTANT: Do not use if seal has been punctured or is not visible.
See crimp of tube for Lot No. and Expiration Date.

E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc.
Melville, New York 11747

℞ only

FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.

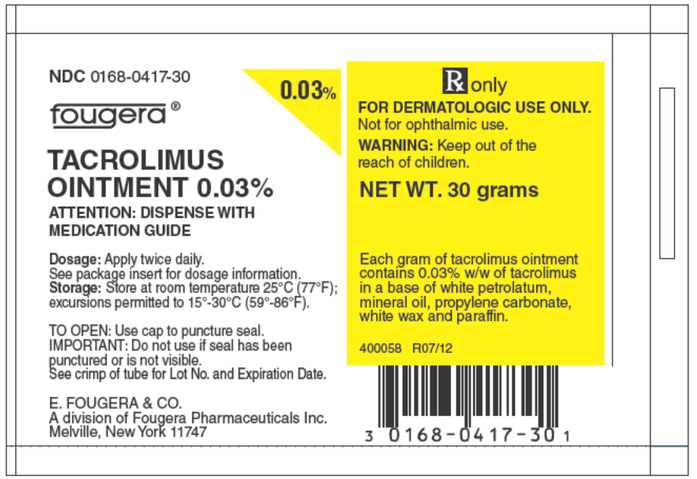
WARNING: Keep out of the reach of children.

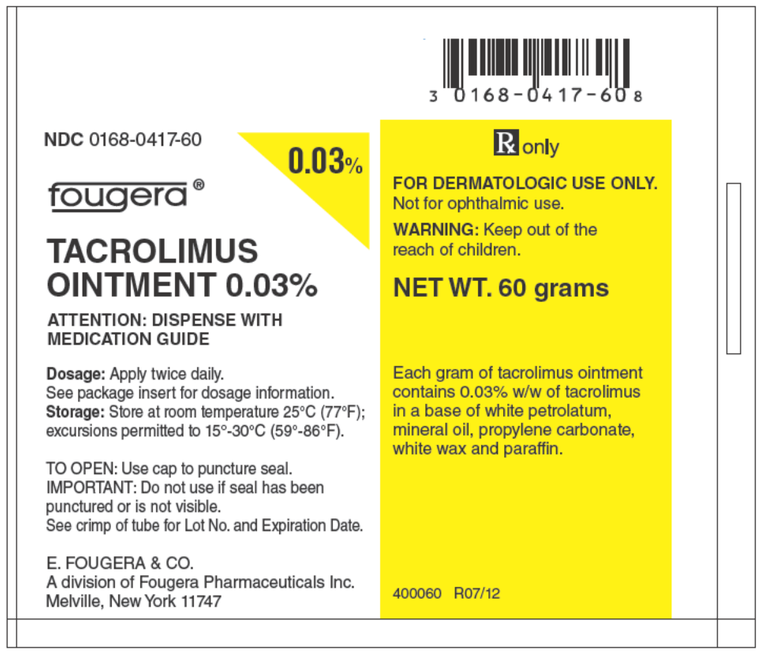
NET WT. 100 grams

Each gram of tacrolimus ointment contains 0.1% w/w of tacrolimus in a base of white petrolatum, mineral oil, propylene carbonate, white wax and paraffin.

400068A R09/13

3 0168-0416-99 1


NDC 0168-0417-30
0.03%
fougera®
TACROLIMUS
OINTMENT 0.03%
ATTENTION: DISPENSE WITH
MEDICATION GUIDE
Dosage: Apply twice daily.
See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F);
excursions permitted to 15°-30°C (59°-86°F).
TO OPEN: Use cap to puncture seal.
IMPORTANT: Do not use if seal has been
punctured or is not visible.
See crimp of tube for Lot No. and Expiration Date.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc.
Melville, New York 11747
℞ only
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the
reach of children.
NET WT. 30 grams
Each gram of tacrolimus ointment
contains 0.03% w/w of tacrolimus
in a base of white petrolatum,
mineral oil, propylene carbonate,
white wax and paraffin.
400058 R07/12
3 0168-0417-30 1


3 0168-0417-60 8
NDC 0168-0417-60
0.03%
fougera®
TACROLIMUS OINTMENT 0.03%
ATTENTION: DISPENSE WITH MEDICATION GUIDE
Dosage: Apply twice daily.
See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
TO OPEN: Use cap to puncture seal.
IMPORTANT: Do not use if seal has been punctured or is not visible.
See crimp of tube for Lot No. and Expiration Date.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc.
Melville, New York 11747
℞ only
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
NET WT. 60 grams
Each gram of tacrolimus ointment contains 0.03% w/w of tacrolimus in a base of white petrolatum, mineral oil, propylene carbonate, white wax and paraffin.
400060 R07/12

NDC 0168-0417-99

fougera®

0.03%

TACROLIMUS OINTMENT 0.03%

ATTENTION: DISPENSE WITH MEDICATION GUIDE

Dosage: Apply twice daily.
See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

TO OPEN: Use cap to puncture seal.
IMPORTANT: Do not use if seal has been punctured or is not visible.
See crimp of tube for Lot No. and Expiration Date.

E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc.
Melville, New York 11747

℞ only

FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.

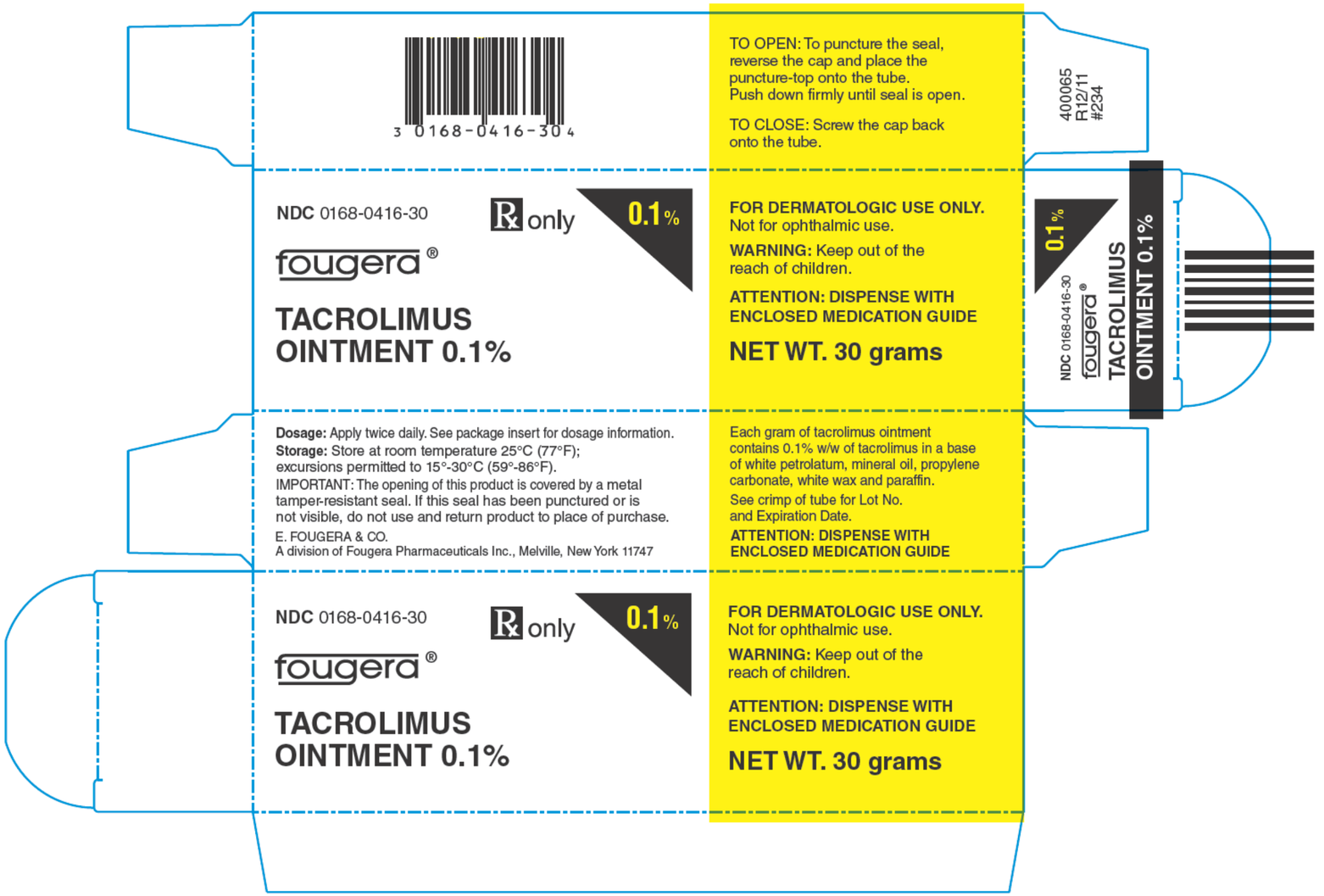
WARNING: Keep out of the reach of children.

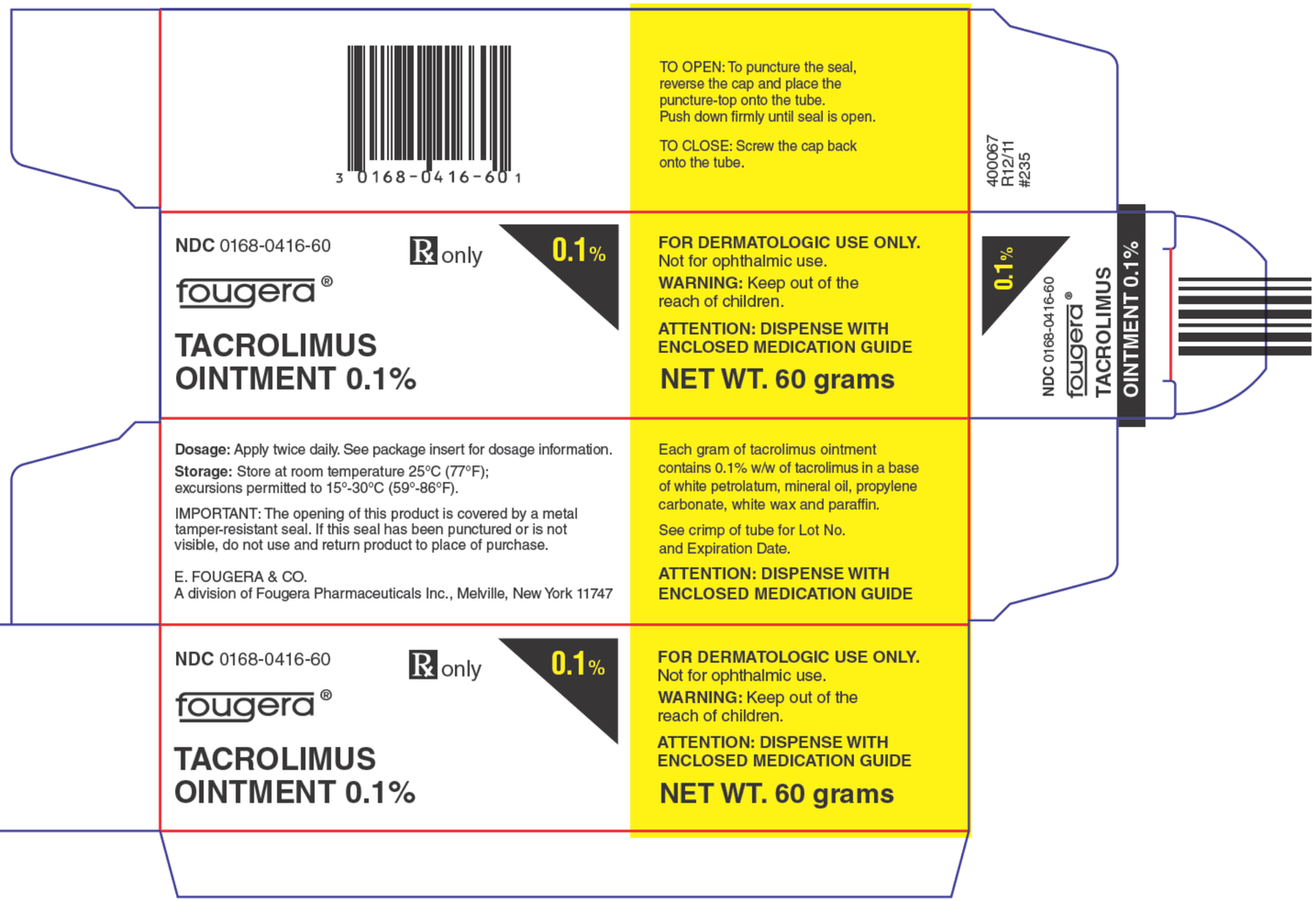
NET WT. 100 grams

Each gram of tacrolimus ointment contains 0.03% w/w of tacrolimus in a base of white petrolatum, mineral oil, propylene carbonate, white wax and paraffin.

400062A R09/13

3 0168-0417-99 8


3 0168-0416-30 4
TO OPEN: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open.
TO CLOSE: Screw the cap back onto the tube.
400065
R12/11
#234
NDC 0168-0416-30
Rx only
0.1%
fougera®
TACROLIMUS
OINTMENT 0.1%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 30 grams
Dosage: Apply twice daily. See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
IMPORTANT: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc., Melville, New York 11747
Each gram of tacrolimus ointment contains 0.1% w/w of tacrolimus in a base of white petrolatum, mineral oil, propylene carbonate, white wax and paraffin.
See crimp of tube for Lot No. and Expiration Date.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NDC 0168-0416-30
Rx only
0.1%
fougera®
TACROLIMUS
OINTMENT 0.1%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 30 grams


3 0168-0416-60 1
TO OPEN: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open.
TO CLOSE: Screw the cap back onto the tube.
400067
R12/11
#235
NDC 0168-0416-60
Rx only
0.1%
fougera®
TACROLIMUS
OINTMENT 0.1%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 60 grams
Dosage: Apply twice daily. See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
IMPORTANT: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc., Melville, New York 11747
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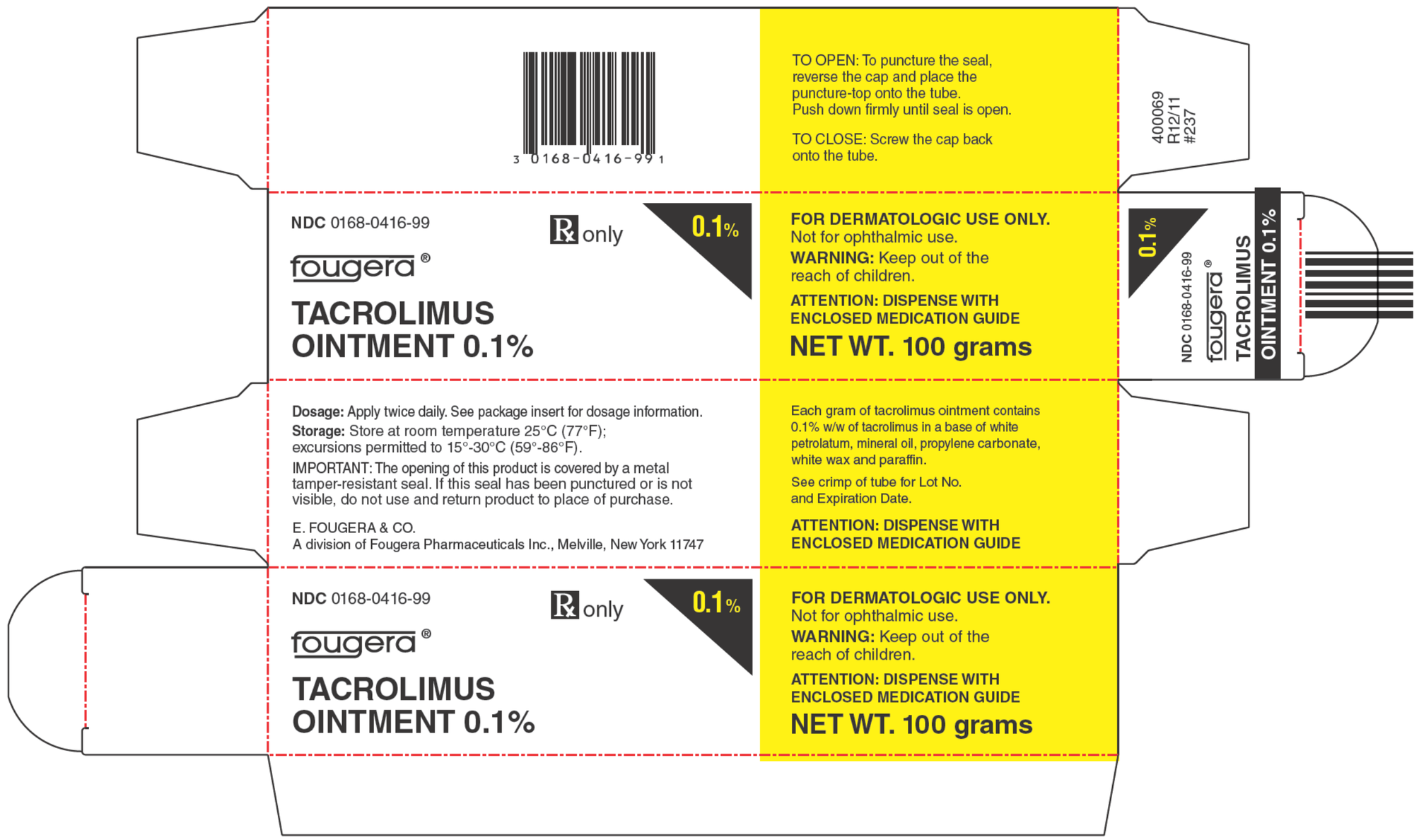
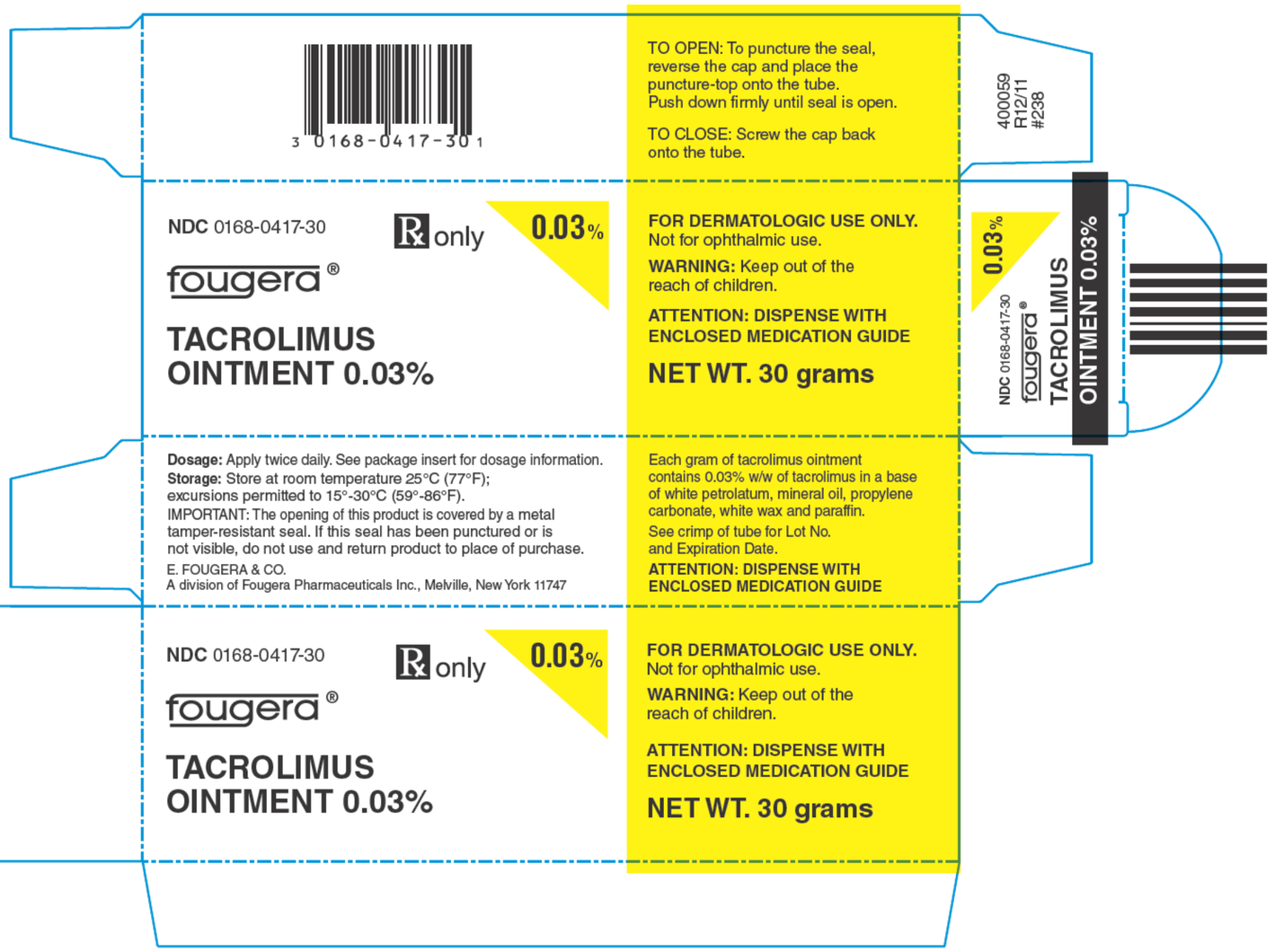
See crimp of tube for Lot No. and Expiration Date.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NDC 0168-0416-60
Rx only
0.1%
fougera®
TACROLIMUS
OINTMENT 0.1%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 60 grams


3 0168-0416-99 1
TO OPEN: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open.
TO CLOSE: Screw the cap back onto the tube.
400069
R12/11
#237
NDC 0168-0416-99
Rx only
0.1%
fougera®
TACROLIMUS
OINTMENT 0.1%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 100 grams
Dosage: Apply twice daily. See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
IMPORTANT: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc., Melville, New York 11747
Each gram of tacrolimus ointment contains 0.1% w/w of tacrolimus in a base of white petrolatum, mineral oil, propylene carbonate, white wax and paraffin.
See crimp of tube for Lot No. and Expiration Date.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NDC 0168-0416-99
Rx only
0.1%
fougera®
TACROLIMUS
OINTMENT 0.1%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 100 grams


3 0168-0417-30 1
NDC 0168-0417-30
Rx only
0.03%
fougera®
TACROLIMUS
OINTMENT 0.03%
Dosage: Apply twice daily. See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F);
excursions permitted to 15°-30°C (59°-86°F).
IMPORTANT: The opening of this product is covered by a metal
tamper-resistant seal. If this seal has been punctured or is
not visible, do not use and return product to place of purchase.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc., Melville, New York 11747
TO OPEN: To puncture the seal,
reverse the cap and place the
puncture-top onto the tube.
Push down firmly until seal is open.
TO CLOSE: Screw the cap back
onto the tube.
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the
reach of children.
ATTENTION: DISPENSE WITH
ENCLOSED MEDICATION GUIDE
NET WT. 30 grams
Each gram of tacrolimus ointment
contains 0.03% w/w of tacrolimus in a base
of white petrolatum, mineral oil, propylene
carbonate, white wax and paraffin.
See crimp of tube for Lot No.
and Expiration Date.
ATTENTION: DISPENSE WITH
ENCLOSED MEDICATION GUIDE
400059
R12/11
#238
0.03%
NDC 0168-0417-30
fougera®
TACROLIMUS
OINTMENT 0.03%
NDC 0168-0417-30
Rx only
0.03%
fougera®
TACROLIMUS
OINTMENT 0.03%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the
reach of children.
ATTENTION: DISPENSE WITH
ENCLOSED MEDICATION GUIDE
NET WT. 30 grams


3 0168-0417-60 8
TO OPEN: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open.
TO CLOSE: Screw the cap back onto the tube.
400061
R08/12
#242
NDC 0168-0417-60
Rx only
0.03%
fougera®
TACROLIMUS
OINTMENT 0.03%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 60 grams
Dosage: Apply twice daily. See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
IMPORTANT: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc., Melville, New York 11747
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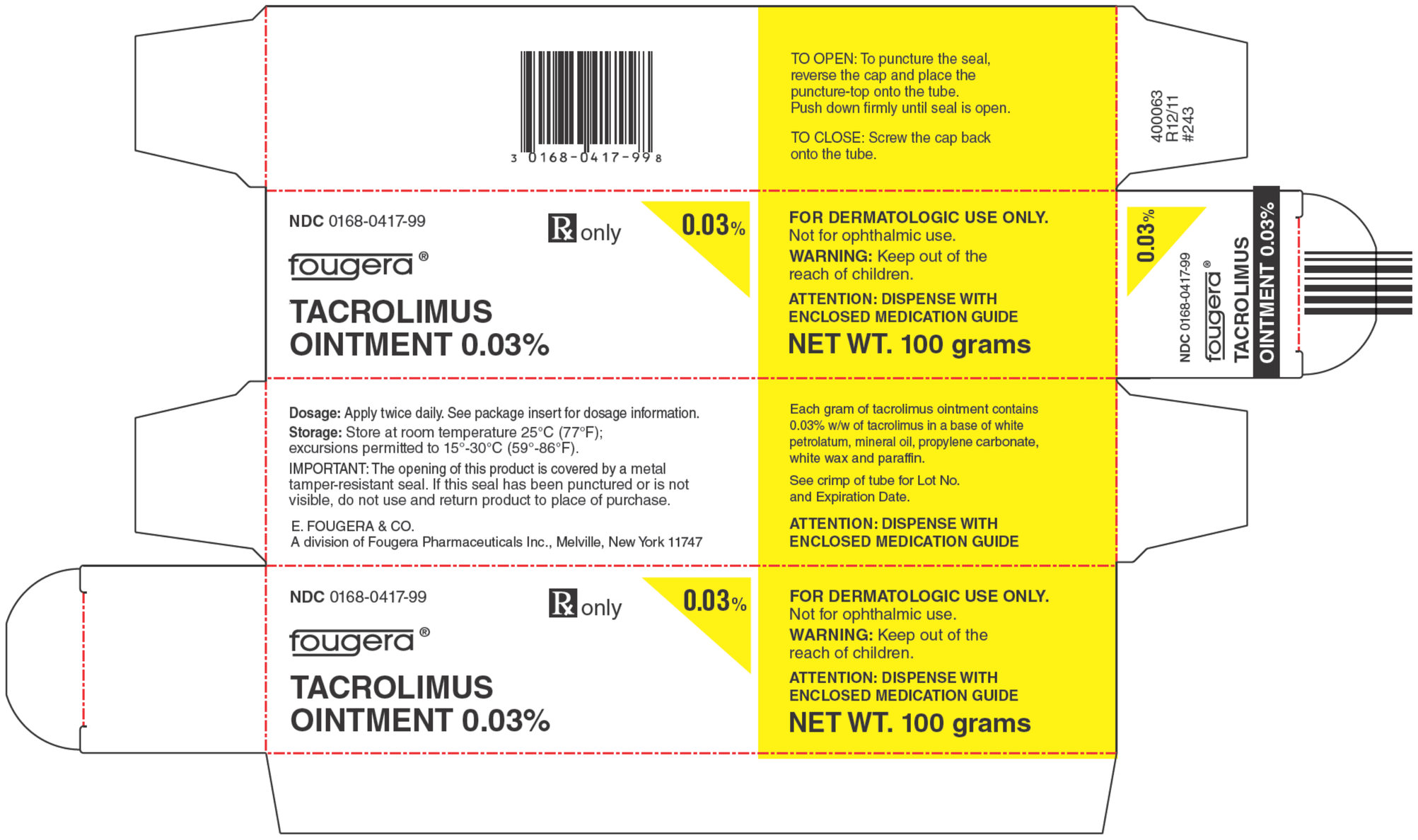
See crimp of tube for Lot No. and Expiration Date.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NDC 0168-0417-60
Rx only
0.03%
fougera®
TACROLIMUS
OINTMENT 0.03%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 60 grams


3 0168-0417-99 8
TO OPEN: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open.
TO CLOSE: Screw the cap back onto the tube.
400063
R12/11
#243
NDC 0168-0417-99
Rx only
0.03%
fougera®
TACROLIMUS
OINTMENT 0.03%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 100 grams
Dosage: Apply twice daily. See package insert for dosage information.
Storage: Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
IMPORTANT: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc., Melville, New York 11747
Each gram of tacrolimus ointment contains 0.03% w/w of tacrolimus in a base of white petrolatum, mineral oil, propylene carbonate, white wax and paraffin.
See crimp of tube for Lot No. and Expiration Date.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NDC 0168-0417-99
Rx only
0.03%
fougera®
TACROLIMUS
OINTMENT 0.03%
FOR DERMATOLOGIC USE ONLY.
Not for ophthalmic use.
WARNING: Keep out of the reach of children.
ATTENTION: DISPENSE WITH ENCLOSED MEDICATION GUIDE
NET WT. 100 grams

fougera®

℞ only

TACROLIMUS OINTMENT 0.03%
TACROLIMUS OINTMENT 0.1%

fougera®

℞ only

TACROLIMUS OINTMENT 0.03%
TACROLIMUS OINTMENT 0.1%

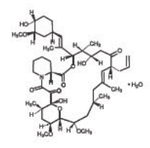
TACROLIMUS OINTMENT 0.03%
TACROLIMUS OINTMENT 0.1%

FOR DERMATOLOGIC USE ONLY NOT FOR OPHTHALMIC USE

Prescribing Information
See boxed WARNINGS concerning long-term safety of topical calcineurin inhibitors

DESCRIPTION

Tacrolimus ointment contains tacrolimus, a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. It is for topical dermatologic use only. Chemically, tacrolimus is designated as [3*S*[3*R**[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone, monohydrate.
It has the following structural formula:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}\cdot H_2O$ and a formula weight of 822.03.
Each gram of tacrolimus ointment contains (w/w) either 0.03% or 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white petrolatum and white wax.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of tacrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that tacrolimus inhibits T-lymphocyte activation by first binding to an intracellular protein, FKBP-12.
A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect has been shown to prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). Tacrolimus also inhibits the transcription for genes which encode IL-3, IL-4, IL-5, GM-CSF, and TNF-α, all of which are involved in the early stages of T-cell activation. Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and basophils, and to down regulate the expression of FcεRI on Langerhans cells.

PHARMACOKINETICS

Absorption

The pooled results from three pharmacokinetic studies in 88 adult atopic dermatitis patients indicate that tacrolimus is minimally absorbed after the topical application of tacrolimus ointment. Peak tacrolimus blood concentrations ranged from undetectable to 20 ng/mL after single or multiple doses of 0.03% and 0.1% tacrolimus ointment, with 85% (75/88) of the patients having peak blood concentrations less than 2 ng/mL. In general as treatment continued, systemic exposure declined as the skin returned to normal. In clinical studies with periodic blood sampling, a similar distribution of tacrolimus blood levels was also observed in adult patients, with 90% (1253/1391) of patients having a blood concentration less than 2 ng/mL.
The absolute bioavailability of tacrolimus from tacrolimus ointment in atopic dermatitis patients is approximately 0.5%. In adults with an average of 53% BSA treated, exposure (AUC) of tacrolimus from tacrolimus ointment is approximately 30-fold less than that seen with oral immunosuppressive doses in kidney and liver transplant patients. Mean peak tacrolimus blood concentrations following oral administration (0.3 mg/kg/day) in adult kidney transplant (n=26) and liver transplant (n=17) patients are 24.2±15.8 ng/mL and 68.5±30.0 ng/mL, respectively. The lowest tacrolimus blood level at which systemic effects (e.g., immunosuppression) can be observed is not known. Systemic levels of tacrolimus have also been measured in pediatric patients (see ***Special Populations: Pediatrics***).

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a US study, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67). There was no evidence based on blood concentrations that tacrolimus accumulates systemically upon intermittent topical application for periods of up to 1 year. As with other topical calcineurin inhibitors, it is not known whether tacrolimus is distributed into the lymphatic system.

Metabolism

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation *in vitro*. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In *in vitro* studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

The mean clearance following IV administration of tacrolimus is 0.040, 0.083 and 0.053 L/hr/kg in healthy volunteers, adult kidney transplant patients and adult liver transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine. In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy volunteers, the mean recovery of radiolabel was 77.8 ± 12.7%. Fecal elimination accounted for 92.4 ± 1.0% and the elimination half-life based on radioactivity was 48.1 ± 15.9 hours whereas it was 43.5 ± 11.6 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.029 ± 0.015 L/hr/kg and clearance of tacrolimus was 0.029 ± 0.009 L/hr/kg. When administered PO, the mean recovery of the radiolabel was 94.9 ± 30.7%. Fecal elimination accounted for 92.6 ± 30.7%, urinary elimination accounted for 2.3 ± 1.1% and the elimination half-life based on radioactivity was 31.9 ± 10.5 hours whereas it was 48.4 ± 12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226 ± 0.116 L/hr/kg and clearance of tacrolimus 0.172 ± 0.088 L/hr/kg.

Special Populations

Pediatrics

In a pharmacokinetic study of 14 pediatric atopic dermatitis patients, between the ages of 2-5 years, peak blood concentrations of tacrolimus ranged from undetectable to 14.8 ng/mL after single or multiple doses of 0.03% tacrolimus ointment, with 86% (12/14) of patients having peak blood concentrations below 2 ng/mL throughout the study. The highest peak concentration was observed in one patient with 82% BSA involvement on day 1 following application of 0.03% tacrolimus ointment. The peak concentrations for this subject were 14.8 ng/mL on day 1 and 4.1 ng/mL on day 14. Mean peak tacrolimus blood concentrations following oral administration in pediatric liver transplant patients (n = 9) were 48.4± 27.9 ng/mL. In a similar pharmacokinetic study with 61 enrolled pediatric patients (ages 6 -12 years) with atopic dermatitis, peak tacrolimus blood concentrations ranged from undetectable to 5.3 ng/mL after single or multiple doses of 0.1% tacrolimus ointment, with 91% (52/57) of evaluable patients having peak blood concentrations below 2 ng/mL throughout the study period. When detected, systemic exposure generally declined as treatment continued. In clinical studies with periodic blood sampling, a similar distribution of tacrolimus blood levels was also observed, with 98% (509/522) of pediatric patients having a blood concentration below 2 ng/mL.

Renal Insufficiency

The effect of renal insufficiency on the pharmacokinetics of topically administered tacrolimus has not been evaluated. The mean clearance of IV administered tacrolimus in patients with renal dysfunction was similar to that of normal volunteers. On the basis of this information dose-adjustment is not expected to be needed.

Hepatic Insufficiency

The effect of hepatic insufficiency on the pharmacokinetics of topically administered tacrolimus has not been evaluated but dose-adjustment is not expected to be needed.

CLINICAL STUDIES

Three randomized, double-blind, vehicle-controlled, multi-center, phase 3 studies were conducted to evaluate tacrolimus ointment for the treatment of patients with moderate to severe atopic dermatitis. One (Pediatric) study included 351 patients 2-15 years of age, and the other two (Adult) studies included a total of 632 patients 15-79 years of age. Fifty-five percent (55%) of the patients were women and 27% were black. At baseline, 58% of the patients had severe disease and the mean body surface area (BSA) affected was 46%. Over 80% of patients had atopic dermatitis affecting the face and/or neck region. In these studies, patients applied either tacrolimus ointment 0.03%, tacrolimus ointment 0.1%, or vehicle ointment twice daily to 10% - 100% of their BSA for up to 12 weeks.
In the pediatric study, a significantly greater ($p < 0.001$) percentage of patients achieved at least 90% improvement based on the physician's global evaluation of clinical response (the pre-defined primary efficacy endpoint) in the tacrolimus ointment 0.03% treatment group compared to the vehicle treatment group, but there was insufficient evidence that tacrolimus ointment 0.1% provided more efficacy than tacrolimus ointment 0.03%.
In both adult studies, a significantly greater ($p < 0.001$) percentage of patients achieved at least 90% improvement based on the physician's global evaluation of clinical response in the tacrolimus ointment 0.03% and tacrolimus ointment 0.1% treatment groups compared to the vehicle treatment group. There was evidence that tacrolimus ointment 0.1% may provide more efficacy than tacrolimus ointment 0.03%. The difference in efficacy between tacrolimus ointment 0.1% and 0.03% was particularly evident in adult patients with severe disease at baseline, adults with extensive BSA involvement, and black adults. Response rates for each treatment group are shown below by age groups. Because the two adult studies were identically designed, the results from these studies were pooled in this table.

Global Improvement over Baseline at the End-Of-Treatment in Three Phase 3 Studies

Physician's Global Evaluation of Clinical Response (% Improvement)	Pediatric Study (2-15 Years of Age)		Adult Studies		
	Vehicle Ointment N = 116	Tacrolimus Ointment 0.03% N = 117	Vehicle Ointment N = 212	Tacrolimus Ointment 0.03% N = 211	Tacrolimus Ointment 0.1% N = 209
100%	4 (3%)	14 (12%)	2 (1%)	21 (10%)	20 (10%)
≥ 90%	8 (7%)	42 (36%)	14 (7%)	58 (28%)	77 (37%)
≥ 75%	18 (16%)	65 (56%)	30 (14%)	97 (46%)	117 (56%)
≥ 50%	31 (27%)	85 (73%)	42 (20%)	130 (62%)	152 (73%)

A statistically significant difference in the percentage of adult patients with ≥ 90% improvement was achieved by week 1 for those treated with tacrolimus ointment 0.1%, and by week 3 for those treated with tacrolimus ointment 0.03%.
A statistically significant difference in the percentage of pediatric patients with ≥ 90% improvement was achieved by week 2 for those treated with tacrolimus ointment 0.03%.
In adult patients who had achieved ≥ 90% improvement at the end of treatment, 35% of those treated with tacrolimus ointment 0.03% and 41% of those treated with tacrolimus ointment 0.1%, regressed from this state of improvement at 2 weeks after end-of-treatment. In pediatric patients who had achieved ≥ 90% improvement, 54% of those treated with tacrolimus ointment 0.03% regressed from this state of improvement at 2 weeks after end-of-treatment. Because patients were not followed for longer than 2 weeks after end-of-treatment, it is not known how many additional patients regressed at periods longer than 2 weeks after cessation of therapy.
In both tacrolimus ointment treatment groups in adults and in the tacrolimus ointment 0.03% treatment group in pediatric patients, a significantly greater improvement compared to vehicle ($p < 0.001$) was observed in the secondary efficacy endpoints of percent body surface area involved, patient evaluation of pruritus, erythema, edema, excoriation, oozing, scaling, and lichenification.

The following two graphs depict the time course of improvement in the percent body surface area affected in adult and in pediatric patients as a result of treatment.

Figure 1 - Adult Patients Body Surface Area Over Time

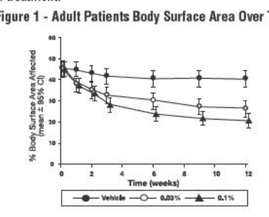
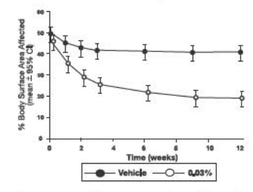


Figure 2 – Pediatric Patients Body Surface Area Over Time



The following two graphs depict the time course of improvement in erythema in adult and in pediatric patients as a result of treatment.

Figure 3 - Adult Patients Mean Erythema Over Time

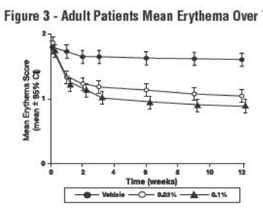
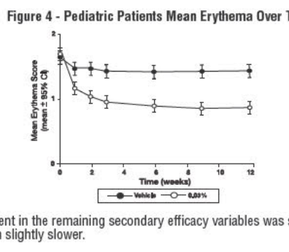


Figure 4 - Pediatric Patients Mean Erythema Over Time



The time course of improvement in the remaining secondary efficacy variables was similar to that of erythema, with improvement in lichenification slightly slower.

INDICATIONS AND USAGE

Tacrolimus ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.
Tacrolimus ointment is not indicated for children younger than 2 years of age (see boxed WARNING, WARNINGS and PRECAUTIONS: Pediatric Use).

CONTRAINDICATIONS

Tacrolimus ointment is contraindicated in patients with a history of hypersensitivity to tacrolimus or any other component of the ointment.

WARNINGS

WARNING
Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including tacrolimus ointment.
Therefore:
- Continuous long-term use of topical calcineurin inhibitors, including tacrolimus ointment, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- Tacrolimus ointment is not indicated for use in children less than 2 years of age. Only 0.03% tacrolimus ointment is indicated for use in children 2-15 years of age.

Prolonged systemic use of calcineurin inhibitors for sustained immunosuppression in animal studies and transplant patients following systemic administration has been associated with an increased risk of infections, lymphomas, and skin malignancies. These risks are associated with the intensity and duration of immunosuppression.
Based on the information above and the mechanism of action, there is a concern about potential risk with the use of topical calcineurin inhibitors, including tacrolimus ointment. While a causal relationship has not been established, rare cases of skin malignancy and lymphoma have been reported in patients treated with topical calcineurin inhibitors, including tacrolimus ointment. Therefore:
- Tacrolimus ointment should not be used in immunocompromised adults and children.
- If signs and symptoms of atopic dermatitis do not improve within 6 weeks, patients should be re-examined by their healthcare provider and their diagnosis be confirmed (see **PRECAUTIONS: General**).
- The safety of tacrolimus ointment has not been established beyond one year of non-continuous use. (See **CLINICAL PHARMACOLOGY**, boxed **WARNINGS**, **INDICATIONS AND USAGE**, and **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS

General

The use of tacrolimus ointment should be avoided on pre-malignant and malignant skin conditions. Some malignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), may mimic atopic dermatitis.
The use of tacrolimus ointment is not recommended in patients having skin conditions with a skin barrier defect where there is the potential for increased systemic absorption of tacrolimus, including but not limited to, Netherton's syndrome, lamellar ichthyosis, generalized erythroderma or cutaneous Graft Versus Host Disease. Oral application is also not recommended. Post-marketing cases of increased tacrolimus blood level have been reported in these conditions.
The use of tacrolimus ointment may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of tacrolimus ointment application and typically improve as the lesions of atopic dermatitis resolve. With tacrolimus ointment 0.1%, 90% of the skin burning events had a duration between 2 minutes and 3 hours (median 15 minutes). 90% of the pruritus events had a duration between 3 minutes and 10 hours (median 20 minutes). (see **ADVERSE REACTIONS**).

Bacterial and Viral Skin Infections

Before commencing treatment with tacrolimus ointment, cutaneous bacterial or viral infections at treatment sites should be resolved. Studies have not evaluated the safety and efficacy of tacrolimus ointment in the treatment of clinically infected atopic dermatitis. While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with tacrolimus ointment may be independently associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum.

Patients with Lymphadenopathy

In clinical studies, 112/13494 (0.8%) cases of lymphadenopathy were reported and were usually related to infections (particularly of the skin) and noted to resolve upon appropriate antibiotic therapy. Of these 112 cases, the majority had either a clear etiology or were known to resolve. Transplant patients receiving immunosuppressive regimens (e.g., systemic tacrolimus) are at increased risk for developing lymphoma; therefore, patients who receive tacrolimus ointment and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, tacrolimus ointment should be discontinued. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

Sun Exposure

During the course of treatment, patients should minimize or avoid natural or artificial sunlight exposure, even while tacrolimus is not on the skin. It is not known whether tacrolimus ointment interferes with skin response to ultraviolet damage.

Immunocompromised Patients

The safety and efficacy of tacrolimus ointment in immunocompromised patients have not been studied.

Renal Insufficiency

Rare post-marketing cases of acute renal failure have been reported in patients treated with tacrolimus ointment. Systemic absorption is more likely to occur in patients with epidermal barrier defects especially when tacrolimus is applied to large body surface areas. Caution should also be exercised in patients predisposed to renal impairment.

Information for Patients (continued on back page)
(See MEDICATION GUIDE)

Patients using tacrolimus ointment should receive and understand the information in the Medication Guide.
Please refer to the Medication Guide for providing instruction and information to the patient.

What is the most important information patients should know about tacrolimus ointment?

The safety of using tacrolimus ointment for a long period of time is not known. A very small number of people who have used tacrolimus ointment have had cancer (for example, skin or lymphoma). However, a link with tacrolimus ointment has not been shown.
Because of this concern, instruct patients:
- Do not use tacrolimus ointment continuously for a long time.
- Use tacrolimus ointment only on areas of skin that have eczema.
- Do not use tacrolimus ointment on a child under 2 years old.

Tacrolimus ointment comes in two strengths:
- Only tacrolimus ointment 0.03% is for use on children aged 2 to 15 years.
- Either tacrolimus ointment 0.03% or 0.1% can be used by adults and children 16 years and older.

Advise patients to talk to their prescriber for more information.

MEDICATION GUIDE

TACROLIMUS (ta-KROE-li-mus)
Ointment 0.03%
Ointment 0.1%

Read the Medication Guide every time you or a family member gets tacrolimus ointment. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment. If you have questions about tacrolimus ointment, ask your doctor or pharmacist.

What is the most important information I should know about tacrolimus ointment?

The safety of using tacrolimus ointment for a long period of time is not known. A very small number of people who have used tacrolimus ointment have had cancer (for example, skin or lymphoma). However, a link with tacrolimus ointment has not been shown.
Because of this concern:
- Do not use tacrolimus ointment continuously for a long time.
- Use tacrolimus ointment only on areas of your skin that have eczema.
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Tacrolimus ointment comes in two strengths:
- Only tacrolimus ointment 0.03% is for use on children aged 2 to 15 years.
- Either tacrolimus ointment 0.03% or 0.1% can be used by adults and children 16 years and older.

Talk to your doctor for more information.

What is tacrolimus ointment?

Tacrolimus ointment is a prescription medicine used on the skin (topical) to treat eczema (atopic dermatitis). Tacrolimus ointment is in a class of medicines called topical calcineurin inhibitors. It is for adults and children 2 years of age and older who do not have a weakened immune system. Tacrolimus ointment is used on the skin for short periods, and if needed, treatment may be repeated with breaks in between. Tacrolimus ointment is for use after other prescription medicines have not worked for you, or if your doctor recommends that other prescription medicines should not be used.

Who should not use tacrolimus ointment?
Tacrolimus ointment should not be used:
- on children younger than 2 years of age.
- if you are allergic to tacrolimus ointment or anything in it.
  See the end of this Medication Guide for a complete list of ingredients.

What should I tell my doctor before starting tacrolimus ointment?

Before you start using tacrolimus, you and your doctor should talk about all of your medical conditions, including if you:
- have a skin disease called Netherton's syndrome (a rare inherited condition).
- have any infection on your skin including chicken pox or herpes.
- have been told you have a weakened immune system.
- are pregnant, breastfeeding, or planning to become pregnant.

Tell your doctor about all the medicines you take and skin products you use including prescription and nonprescription medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

How should I use tacrolimus ointment?
- Use tacrolimus ointment exactly as prescribed.
- Use tacrolimus ointment only on areas of your skin that have eczema.
- Use tacrolimus ointment for short periods, and if needed, treatment may be repeated with breaks in between.
- Stop tacrolimus ointment when the signs and symptoms of eczema, such as itching, rash, and redness go away, or as directed by your doctor.
- Follow your doctor's advice if symptoms of eczema return after treatment with tacrolimus ointment.
- Call your doctor if:
  - your symptoms get worse with tacrolimus ointment.
  - you get an infection on your skin.
  - your symptoms do not improve after 6 weeks of treatment. Sometimes other skin diseases can look like eczema.

How should tacrolimus ointment be used?
Advise patients to:
- Use tacrolimus ointment exactly as prescribed.
- Use tacrolimus ointment only on areas of skin that have eczema.
- Use tacrolimus ointment for short periods, and if needed, treatment may be repeated with breaks in between.
- Stop tacrolimus ointment when the signs and symptoms of eczema, such as itching, rash, and redness go away, or as directed.
- Follow their doctor's advice if symptoms of eczema return after treatment with tacrolimus ointment.
- Call their doctor if:
  - Their symptoms get worse with tacrolimus ointment.
  - They get an infection on their skin.
  - Their symptoms do not improve after 6 weeks of treatment. Sometimes other skin diseases can look like eczema.

To apply tacrolimus ointment:
Advise patients:
- Wash their hands before applying tacrolimus.
- Apply a thin layer of tacrolimus ointment twice daily to the areas of skin affected by eczema.
- Use the smallest amount of tacrolimus ointment needed to control the signs and symptoms of eczema.
- If they are a caregiver applying tacrolimus ointment to a patient, or if they are a patient who is not treating their hands, wash their hands with soap and water after applying tacrolimus. This should remove any ointment left on the hands.
- Do not bathe, shower, or swim right after applying tacrolimus. This could wash off the ointment.
- Moisturizers can be used with tacrolimus ointment. Make sure they check with their doctor first about the products that are right for them. Because the skin of patients with eczema can be very dry, it is important to keep up good skin care practices. If they use moisturizers, apply them after tacrolimus ointment.

What should patients avoid while using tacrolimus ointment?
Advise patients:
- Do not use ultraviolet light therapy, sun lamps, or tanning beds during treatment with tacrolimus ointment.
- Limit sun exposure during treatment with tacrolimus ointment even when the medicine is not on their skin. If patients need to be outdoors after applying tacrolimus ointment, wear loose fitting clothing that protects the treated area from the sun. Doctors should advise what other types of protection from the sun patients should use.
- Do not cover the skin being treated with bandages, dressings or wraps. Patients can wear normal clothing.
- Avoid getting tacrolimus ointment in the eyes or mouth. Do not swallow tacrolimus ointment. Patients should call their doctor if they swallow tacrolimus ointment.

Drug Interactions
Formal topical drug interaction studies with tacrolimus ointment have not been conducted. Based on its extent of absorption, interactions of tacrolimus ointment with systemically administered drugs are unlikely to occur but cannot be ruled out (see **CLINICAL PHARMACOLOGY**). The concomitant administration of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.
Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes. Oral (feed) carcinogenicity studies have been carried out with systemically administered tacrolimus in male and female rats and mice. In the 80-week mouse study and in the 104-week rat study no relationship of tumor incidence to tacrolimus dosage was found at daily doses up to 3 mg/kg [9X the Maximum Recommended Human Dose (MRHD) based on AUC comparisons] and 5 mg/kg (3X the MRHD based on AUC comparisons), respectively.
A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03% - 3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m²/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment) (26X MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment) (10X MRHD based on AUC comparisons).
In a 52-week photocarcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with tacrolimus ointment at ≥0.1% tacrolimus.
Reproductive toxicology studies were not performed with topical tacrolimus. In studies of oral tacrolimus no impairment of fertility was seen in male and female rats. Tacrolimus, given orally at 1.0 mg/kg (0.12X MRHD based on body surface area [BSA]) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and with adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (0.43X MRHD based on BSA), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.
Pregnancy Teratogenic Effects: Pregnancy Category C
There are no adequate and well-controlled studies of topically administered tacrolimus in pregnant women. The experience with tacrolimus ointment when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy. Reproduction studies were carried out with systemically administered tacrolimus in rats and rabbits. Adverse effects on the fetus were observed mainly at oral dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0.04X-0.12X MRHD based on BSA) during organogenesis in rabbits was associated with maternal toxicity as well as an increase in incidence of abortions. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg (0.04X-0.12X MRHD based on BSA) to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights. No reduction in male or female fertility was evident. There are no adequate and well-controlled studies of systemically administered tacrolimus in pregnant women. Tacrolimus is transferred across the placenta. The use of systemically administered tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus ointment should be used during pregnancy only if the potential benefit to the mother justifies a potential risk to the fetus.
Nursing Mothers
Although systemic absorption of tacrolimus following topical applications of tacrolimus ointment is minimal relative to systemic administration, it is known that tacrolimus is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tacrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use
Tacrolimus ointment is not indicated for children less than 2 years of age.
Only the lower concentration, 0.03%, of tacrolimus ointment is recommended for use as a *second-line therapy* for short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised children 2 to 15 years of age who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable. The long-term safety and effects of tacrolimus ointment on the developing immune system are unknown (see boxed **WARNING**, **WARNINGS** and **INDICATIONS AND USAGE**). Four studies were conducted involving a total of about 4,400 patients 2-15 years of age: one 12-week randomized vehicle-controlled study and three open-label safety studies of one to three years duration. About 2,500 of these patients were 2 to 6 years of age.
The most common adverse events from these studies associated with tacrolimus ointment application in pediatric patients were skin burning and pruritus (see **ADVERSE REACTIONS**). In addition to skin burning and pruritus, the less common events (< 5%) of varicella zoster (mostly chicken pox), and vesiculobullous rash were more frequent in patients treated with tacrolimus ointment 0.03% compared to vehicle. In the open-label safety studies, the incidence of adverse events, including infections, did not increase with increased duration of study drug exposure or amount of ointment used. In about 4,400 pediatric patients treated with tacrolimus ointment, 24 (0.5%) were reported with eczema herpeticum. Since the safety and efficacy of tacrolimus ointment have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended. In an open-label study, immune response to a 23-valent pneumococcal polysaccharide vaccine was assessed in 23 children 2 to 12 years old with moderate to severe atopic dermatitis treated with tacrolimus ointment 0.03%. Protective antibody titers developed in all patients. Similarly, in a seven-month, double-blind trial, the vaccination response to meningococcal serogroup C was equivalent in children 2 to 11 years old with moderate to severe atopic dermatitis treated with tacrolimus ointment 0.03% (n=121), a hydrocortisone ointment regimen (n=111), or normal children (n=44).
Geriatric Use
Four hundred and four (404) patients ≥ 65 years old received tacrolimus ointment in phase 3 studies. The adverse event profile for these patients was consistent with that for other adult patients.
ADVERSE REACTIONS
No phototoxicity and no photoallergenicity were detected in clinical studies with 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study. In three 12 week randomized vehicle-controlled studies and four safety studies, 655 and 9,163 patients respectively, were treated with tacrolimus ointment.
The duration of follow-up for adult and pediatric patients in the safety studies is tabulated below.

Duration of Follow-up in Four Open-label Safety Studies

Time on Study	Adult	Pediatrics	Total
< 1 year	4682	4481	9163
≥ 1 year	1185	1349	2534
≥ 2 years	200	275	475
≥ 3 years	118	182	300

The following table depicts the adjusted incidence of adverse events pooled across the 3 identically designed 12-week controlled studies for patients in vehicle, and tacrolimus ointment 0.03%, and tacrolimus ointment 0.1% treatment groups. The table also depicts the unadjusted incidence of adverse events in four safety studies, regardless of relationship to study drug.

Incidence of Treatment Emergent Adverse Events

	12-Week, Randomized, Double-Blind, Phase 3 Studies 12-Week Adjusted Incidence Rate (%)					Open-Label Studies (up to 3 years) 0.1% and 0.03% Tacrolimus Ointment Incidence Rate (%)		
	Adult			Pediatric		Adult	Pediatric	Total
	Vehicle (n=212) %	0.03% Tacrolimus Ointment (n=210) %	0.1% Tacrolimus Ointment (n=209) %	Vehicle (n=116) %	0.03% Tacrolimus Ointment (n=118) %	(n=4682) %	(n=4481) %	(n=9163) %
Skin Burning*	26	46	58	29	43	28	20	24
Pruritus*	37	46	46	27	41	25	19	22
Flu-like symptoms*	19	23	31	25	28	22	34	28
Allergic Reaction	8	12	6	8	4	9	13	11
Skin Erythema	20	25	28	13	12	12	7	9
Headache*	11	20	19	8	5	13	9	11
Skin Infection	11	12	5	14	10	9	16	12
Fever	4	4	1	13	21	2	14	8
Infection	1	1	2	9	7	6	10	8
Cough Increased	2	1	1	14	18	3	10	6
Asthma	4	6	4	6	6	4	13	8
Herpes Simplex	4	4	4	2	0	4	3	3
Eczema Herpeticum	0	1	1	0	2	0	0	0
Pharyngitis	3	3	4	11	6	4	12	8
Accidental Injury	4	3	6	3	6	6	8	7
Pustular Rash	2	3	4	3	2	2	7	5
Folliculitis*	1	6	4	0	2	4	2	3
Rhinitis	4	3	2	2	6	2	4	3
Otitis Media	4	0	1	6	12	2	11	6
Sinusitis*	1	4	2	8	3	6	7	6
Diarrhea	3	3	4	2	5	2	4	3
Urticaria	3	3	6	1	1	3	4	4
Lack of Drug Effect	1	1	0	1	1	6	6	6
Bronchitis	0	2	2	3	3	4	4	4
Vomiting	0	1	1	7	6	1	4	3
Maculopapular Rash	2	2	2	3	0	2	1	1
Rash*	1	5	2	4	2	2	3	3
Abdominal Pain	3	1	1	2	3	1	3	2
Fungal Dermatitis	0	2	1	3	0	2	4	3
Gastroenteritis	1	2	2	3	0	2	4	3
Alcohol Intolerance*	0	3	7	0	0	4	0	2
Acne*	2	4	7	1	0	3	2	3
Sunburn	1	2	1	0	0	2	1	1
Skin Disorder	2	2	1	1	4	2	2	2
Conjunctivitis	0	2	2	2	1	3	3	3
Pain	1	2	1	0	1	2	1	2
Vesiculobullous Rash*	3	3	2	0	4	2	1	1
Lymphadenopathy	2	2	1	0	3	1	2	1
Nausea	4	3	2	0	1	2	1	2
Skin Tingling*	2	3	8	1	2	2	1	1
Face Edema	2	2	1	2	1	1	1	1
Dyspepsia*	1	1	4	0	0	2	2	2
Dry Skin	7	3	3	0	1	1	1	1
Hyperesthesia*	1	3	7	0	0	2	0	1
Skin Neoplasm Benign†	1	1	1	0	0	1	2	2
Back Pain*	0	2	2	1	1	3	0	2
Peripheral Edema	2	4	3	0	0	2	0	1
Varicella Zoster/ Herpes Zoster*‡	0	1	0	0	5	1	2	2
Contact Dermatitis	1	3	3	3	4	2	2	2
Asthenia	1	2	3	0	0	1	0	1
Pneumonia	0	1	1	2	0	1	3	2
Eczema	2	2	2	0	0	1	0	1
Insomnia	3	4	3	1	1	2	0	1
Exfoliative Dermatitis	3	3	1	0	0	0	1	0
Dysmenorrhea	2	4	4	0	0	2	1	1
Periodontal Abscess	1	0	1	0	0	1	1	1
Myalgia*	0	3	2	0	0	2	1	1
Cyst*	0	1	3	0	0	1	0	1
Cellulitis	1	1	1	0	0	1	1	1
Exacerbation of Untreated Area	1	0	1	1	0	1	1	1
Procedural Complication	1	0	0	1	0	1	1	1
Hypertension	0	0	1	0	0	2	0	1
Tooth Disorder	0	1	1	1	0	2	1	1
Arthralgia	1	1	3	2	0	2	1	2
Depression	1	2	1	0	0	1	0	1
Paresthesia	1	3	3	0	0	2	1	2
Alopecia	0	1	1	0	0	1	1	1
Urinary Tract Infection	0	0	1	0	0	2	1	2
Ear Pain	1	0	1	0	1	0	1	1

* May be reasonably associated with the use of this drug product
† Generally "warts".
‡ All the herpes zoster cases in the pediatric 12-week study and the majority of cases in the open-label pediatric studies were reported as chicken pox.

Other adverse events which occurred at an incidence between 0.2% and less than 1% in clinical studies in the above table include: abnormal vision, abscess, anaphylactoid reaction, anemia, anorexia, anxiety, arthritis, arthrosis, bilirubinemia, blepharitis, bone disorder, breast neoplasm benign, bursitis, cataract NOS, chest pain, chills, colitis, conjunctival edema, constipation, cramps, cutaneous moniliasis, cystitis, dehydration, dizziness, dry eyes, dry mouth/nose, dyspnea, ear disorder, ecchymosis, edema, epistaxis, eye pain, furunculosis, gastritis, gastrointestinal disorder, hernia, hypercholesterolemia, hypertonia, hypothyroidism, joint disorder, laryngitis, leukoderma, lung disorder, malaise, migraine, moniliasis, mouth ulceration, nail disorder, neck pain, neoplasm benign, oral moniliasis, otitis externa, photosensitivity reaction, rectal disorder, seborrhea, skin carcinoma, skin discoloration, skin hypertrophy, skin ulcer, stomatitis, tendon disorder, thinking abnormal, tooth caries, sweating, syncope, tachycardia, taste perversion, unintended pregnancy, vaginal moniliasis, vaginitis, valvular heart disease, vasodilatation, and vertigo.
Post-Marketing Events
The following adverse reactions have been identified during postapproval use of tacrolimus ointment. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
CNS
Seizures
Infections
Bullous impetigo, osteomyelitis, septicemia
Neoplasms
Lymphomas, basal cell carcinoma, squamous cell carcinoma, malignant melanoma
Renal
Acute renal failure in patients with or without Netherton's syndrome, renal impairment
Skin
Rosacea, application site edema
OVERDOSAGE
Tacrolimus ointment is not for oral use. Oral ingestion of tacrolimus ointment may lead to adverse effects associated with systemic administration of tacrolimus. If oral ingestion occurs, medical advice should be sought.
DOSAGE AND ADMINISTRATION
Adult Tacrolimus ointment 0.03% and 0.1%
- Apply a thin layer of tacrolimus ointment to the affected skin twice daily. The minimum amount should be rubbed in gently and completely to control signs and symptoms of atopic dermatitis. Stop using when signs and symptoms of atopic dermatitis resolve.
- If signs and symptoms (e.g. itch, rash, and redness) do not improve within 6 weeks, patients should be re-examined by their healthcare provider to confirm the diagnosis of atopic dermatitis.
- Continuous long-term use of topical calcineurin inhibitors, including tacrolimus ointment should be avoided, and application should be limited to areas of involvement with atopic dermatitis.

The safety of tacrolimus ointment under occlusion, which may promote systemic exposure, has not been evaluated. Tacrolimus ointment should not be used with occlusive dressings.
PEDIATRIC – FOR CHILDREN 2-15 YEARS
Tacrolimus ointment 0.03%
- Apply a thin layer of tacrolimus ointment, 0.03% to the affected skin twice daily. The minimum amount should be rubbed in gently and completely to control signs and symptoms of atopic dermatitis. Stop using when signs and symptoms of atopic dermatitis resolve.
- If signs and symptoms (e.g. itch, rash, and redness) do not improve within 6 weeks, patients should be re-examined by their healthcare provider to confirm the diagnosis of atopic dermatitis.
- Continuous long-term use of topical calcineurin inhibitors, including tacrolimus ointment should be avoided, and application should be limited to areas of involvement with atopic dermatitis.

The safety of tacrolimus ointment under occlusion, which may promote systemic exposure, has not been evaluated.
Tacrolimus ointment should not be used with occlusive dressings.
HOW SUPPLIED
Tacrolimus ointment 0.03%
NDC 0168-0417-30 30 gram laminate tube
NDC 0168-0417-60 60 gram laminate tube
NDC 0168-0417-99 100 gram laminate tube
Tacrolimus ointment 0.1%
NDC 0168-0416-30 30 gram laminate tube
NDC 0168-0416-60 60 gram laminate tube
NDC 0168-0416-99 100 gram laminate tube
Store at room temperature 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
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Other side effects include acne, swollen or infected hair follicles, headache, increased sensitivity of the skin to hot or cold temperatures, or flu-like symptoms such as the common cold and stuffy nose, skin tingling, upset stomach, muscle pain, swollen glands (enlarged lymph nodes), or skin infections including cold sores, chicken pox or shingles. Talk to your doctor if you have a skin infection or if side effects (for example, swollen glands) continue or bother you. While you are using tacrolimus, drinking alcohol may cause the skin or face to become flushed or red and feel hot. These are not all the side effects with tacrolimus ointment. Ask your doctor or pharmacist for more information. Call your doctor for medical side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store tacrolimus ointment?
- Store tacrolimus ointment at room temperature (59° to 86°F). Do not leave tacrolimus ointment in your car in cold or hot weather. Make sure the cap on the tube is tightly closed.
- **Keep tacrolimus ointment and all medicines out of the reach of children.**

General advice about tacrolimus ointment
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use tacrolimus ointment for a condition for which it was not prescribed. Do not give tacrolimus ointment to other people, even if they have the same symptoms you have. It may not be right for them.

This Medication Guide summarizes the most important information about tacrolimus ointment. If you would like more information, talk with your doctor.

Your doctor or pharmacist can give you information about tacrolimus ointment that is written for health care professionals. To download the professional package insert you can also visit the tacrolimus ointment website at www.fougera.com or call 1-800-645-9833.

What are the ingredients in tacrolimus ointment?
Active Ingredient: tacrolimus, either 0.03% or 0.1%
Inactive Ingredients: mineral oil, paraffin, propylene carbonate, white petrolatum and white wax.

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PHARMACEUTICALS INC.
Melville, New York 11747

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R10/13

To apply tacrolimus ointment:
- Wash your hands before applying tacrolimus.
- Apply a thin layer of tacrolimus ointment twice daily to the areas of skin affected by eczema.
- Use the smallest amount of tacrolimus ointment needed to control the signs and symptoms of eczema.
- If you are a caregiver applying tacrolimus ointment to a patient, or if you are a patient who is not treating your hands, wash your hands with soap and water after applying tacrolimus. This should remove any ointment left on the hands.
- Do not bathe, shower, or swim right after applying tacrolimus. This could wash off the ointment.
- You can use moisturizers with tacrolimus ointment. Make sure you check with your doctor first about the products that are right for you. Because the skin of patients with eczema can be very dry, it is important to keep up good skin care practices. If you use moisturizers, apply them after tacrolimus ointment.

What should I avoid while using tacrolimus ointment?
- Do not use ultraviolet light therapy, sun lamps, or tanning beds during treatment with tacrolimus ointment.
- Limit sun exposure during treatment with tacrolimus ointment even when the medicine is not on your skin. If you need to be outdoors after applying tacrolimus ointment, wear loose fitting clothing that protects the treated area from the sun. Ask your doctor what other types of protection from the sun you should use.
- Do not cover the skin being treated with bandages, dressings or wraps. You can wear normal clothing.
- Avoid getting tacrolimus ointment in the eyes or mouth. Do not swallow tacrolimus ointment. If you do, call your doctor.

What are the possible side effects of tacrolimus ointment?
Please read the first section of this Medication Guide.
The most common side effects of tacrolimus ointment at the skin application site are stinging, burning, or itching of the skin treated with tacrolimus. These side effects are usually mild to moderate, are most common during the first few days of treatment, and usually go away as your skin heals.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200744Orig1s000

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200744

Date of Submission: December 12, 2013

Applicant's Name: Fougera Pharmaceuticasl Inc.

Established Name: Tacrolimus Ointment 0.1% and 0.03%

Labeling Comments below are considered:

☐ Minor Deficiency*
*Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable

☒ No Comments **(**Labeling Approval Summary #2)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions at this time based on your labeling Submission dated December 12, 2013.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address http://service.govdelivery.com/service/subscribe.html?code=USFD20A_17

Note RPM - Labeling comments end here

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☐ No
Communication plan (505-1(e))	☐ Yes	☐ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☐ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☐ No
Timetable for assessment (505-1(d))	☐ Yes	☐ No

ANDA REMS acceptable?

☐ Yes ☐ No ☒ N/A

APPROVAL SUMMARY
(List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? YES

Container
0.1%
30 g - Satisfactory in FPL as of December 12, 2013 electronic submission.
60 g – Satisfactory in FPL as of December 12, 2013 electronic submission.
100 g – Satisfactory in FPL as of December 12, 2013 electronic submission.
0.03%
30 g - Satisfactory in FPL as of December 12, 2013 electronic submission.
60 g – Satisfactory in FPL as of December 12, 2013 electronic submission.
100 g – Satisfactory in FPL as of December 12, 2013 electronic submission.
Carton
0.1%
30 g - Satisfactory in FPL as of December 12, 2013 electronic submission.
60 g – Satisfactory in FPL as of December 12, 2013 electronic submission.
100 g – Satisfactory in FPL as of December 12, 2013 electronic submission.
0.03%
30 g - Satisfactory in FPL as of December 12, 2013 electronic submission.
60 g – Satisfactory in FPL as of December 12, 2013 electronic submission.
100 g – Satisfactory in FPL as of December 12, 2013 electronic submission.
Package Insert: Satisfactory in FPL as of December 12, 2013 electronic submission.
Medication Guide: Satisfactory in FPL as of December 12, 2013 electronic submission.
SPL Data Elements: Satisfactory as of December 12, 2013 electronic submission.

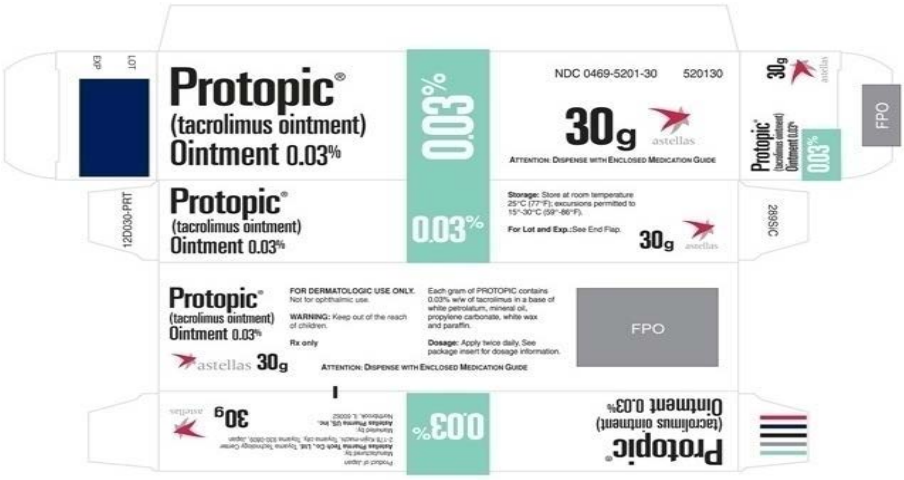
BASIS OF APPROVAL:

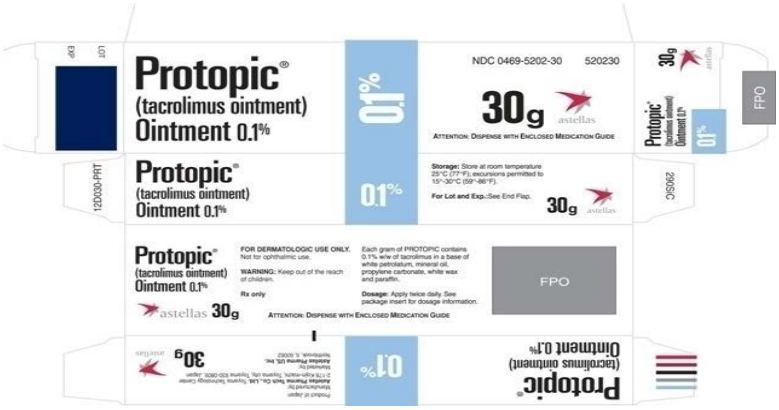
- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Tacrolimus Ointment, 0.1% and 0.03%
- NDA Number: 050777
- NDA Drug Name: Protopic Ointment 0.1% and 0.03%
- NDA Firm: Astellas Pharma U.S., Inc.
- Date of Approval of NDA Insert and supplement: 050777/S-018: Approved: November 04, 2011
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Revisions needed post-approval: NO
- Patents/Exclusivities: None

FOR THE RECORD:

1. **MODEL LABELING:** Review based on the labeling for the reference listed drug, Protopic Ointment (NDA 050777/S-018: Approved: November 04, 2011). This supplemental new drug application provides for changes to the Precautions and Adverse Reactions/Postmarketing Events sections of the label. The proposed changes include skin conditions with a skin barrier defect in which there is the potential for increased systemic tacrolimus absorption and to add the event of "application site edema."

2. **RLD Labels:**





3. **USP:** This drug product is not the subject of a USP monograph. However, the drug substance is compendial.

4. **PATIENTS/EXCLUSIVTIES:**

Patent Data – NDA 050777

No	Expiration	Use Code	Use	File
5385907 5665727	Jan 31, 2012 Sep 9, 2014	U-919	FOR THE TREATMENT OF DERMATITIS	IV IV

Exclusivity Data - NDA 050777

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		NONE

5. **INACTIVE INGREDIENTS**

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Ingredient	Grade	Nycomed's Proposed formulation w/w%		RLD Protopic® w/w%[1]		Function[2]
Tacrolimus	N/A	0.1%	0.03%	0.1%	0.03%	Active
Paraffin						
(b) (4)						
(White Wax)*						
Mineral Oil						
White Petrolatum						
Propylene Carbonate						

(b) (4)

(b) (4)

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: None
- RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].
- ANDA: Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F)

8. PACKAGE CONFIGURATION

- RLD: 30 g, 60 g and 100 g (b) (4) tubes
- ANDA: 30 g, 60 g and 100 g laminated (b) (4) tubes with white polypropylene caps.

9. CONTAINER/CLOSURE

(b) (4)

Please note as of December 12, 2013 submission, Fougera (b) (4) (b) (4) The 100 g laminate tube

(b) (4) Also, ANDA firm submitted amendment dated December 12, 2013 to chemistry for review.

10. **FNISHED DOSAGE FORM**
    - RLD: Ointment
    - ANDA: Ointment

11. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
    Fougera Pharmaceuticals Inc.
    60 Baylis Road
    Melville, NY 11747

12. **CONTACT INFORMATION:**
    Amy Byrom
    Phone (631) 719-2098
    Fax: (631) 756-5114
    Email Address**:** **amy.byrom@fougera.com**

Date of Submission: December 12, 2013

Primary Reviewer: Beverly Weitzman

Team Leader: John Grace

1.14.2.2 Final Package Insert

The following revisions were made to the Tacrolimus Ointment Package Insert since the last submission:

- Extended the length of insert by 2.0625 inches to allow for manual insertion of the insert into the carton.
- Changed “in vitro” to italics in 2 places in Metabolism section.
- Corrected spelling from “erthroderma” to “erythroderma” in PRECAUTIONS General section.
- Added phonetic spelling of “Tacrolimus” to the Medication Guide as required.
- Resize and reflow to fit.
- Revised item number to SHAPE format.
- Updated revision date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEVERLY WEITZMAN
12/18/2013

JOHN F GRACE
12/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200744Orig1s000

CHEMISTRY REVIEWS

ANDA 200744

Tacrolimus Ointment, 0.1% and 0.03%

Fougera Pharmaceuticals Inc.

Gil-Jong Kang
OGD/DCI

Chemistry Review #5

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 200744

2. REVIEW #: 5

3. REVIEW DATE: 29-AUG-2014

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original Submission	**04/08/2010**
Acceptable for filing	09/09/2010
Amendment (Response to Regulatory Support)	09/09/2010
Amendment (Patent)	09/23/2010
Amendment (Clinical)	10/15/2010
Amendment (Patent)	11/02/2010
Amendment (New Strength, 0.03%)	**11/19/2010**
Amendment (Patent)	12/01/2010
Amendment (Response to Regulatory Support)	12/15/2010
Amendment (Patent)	12/17/2010
Amendment (Response for information)	02/17/2011
Amendment (Response for information)	03/04/2011
Minor Amendment (Bioequivalence)	08/9/2011
Minor Amendment (Chemistry)	09/15/2011
Minor Amendment (Chemistry)	02/24/2012
Amendment (Bioequivalence)	02/29/2012
Reclassification from Minor to Major Amendment (Chemistry)	03/15/2012
Minor Amendment (Chemistry)	06/11/2012
Telephone Amendment	07/24/2012
Telephone Amendment	07/25/2012
Review #4	08/31/2012

Gratuitous amendment (Withdrawal of outside testing Laboratory)	12/12/2012
Response to ECD	11/20/2013
Response to ECD	12/06/2013
Addendum to review #4	02/28/2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (Major)	12/12/2013
Amendment (DS process change)*	04/24/2014

(b) (4)

[redacted]

7. NAME & ADDRESS OF APPLICANT:

Name: Fougera Pharmaceuticals Inc.

Address: P.O. Box 2006
60 Baylis Road
Melville, NY 11747

Representative: Amy Byrom

Telephone: 631-454-7677 X 2098

Fax: 631-756-5114

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A

Non-Proprietary Name (USAN): Tacrolimus Ointment, 0.1% and 0.03%

Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

The applicant, Nycomed US Inc., hereby states that, to the best of the applicant's knowledge, the following United States Patents are listed in the United States Food and Drug Administration's Electronic *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.1% (NDA 50777), manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc. The expiration dates indicated below are those stated in the Orange Book.

U.S. Patent No. 5,385,907 – Expires January 31, 2012
U.S. Patent No. 5,665,727– Expires September 9, 2014

Paragraph IV Certification – United States Patent Nos. 5,385,907 and 5,665,727 Nycomed US Inc. certifies that United States Patent Nos. 5,385,907 and 5,665,727 are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Tacrolimus Ointment 0.03% for which this application amendment is submitted.

In addition, Nycomed US Inc. further certifies that it will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

Exclusivity Statement
Under the provisions set forth in Section 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act, there is no unexpired exclusivity for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.03%, manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc.

Indication
Indicated as *second-line therapy* for the short-term and non-continuous treatment of moderate to severe atopic dermatitis in non-immunocompromised adults who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

10. PHARMACOLOGY CATEGORY:

Tacrolimus Ointment is a *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

11. DOSAGE FORM:

Ointment

12. STRENGTH/POTENCY:

0.03% and 0.1%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

____x__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature:

[3S, 4R, 5S, 8R, 9E, 12S, 14S, 15R, 16S, 18R, 19R, 26aS)-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-Hexadecahydro-5,19-Dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4-oxaazacyclotricosine-1,7,-20,21(4H,23H) tetrone monohydrate.

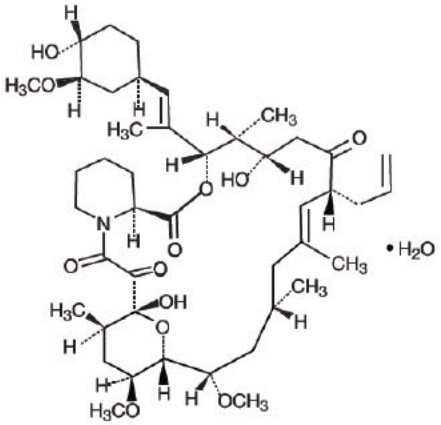
Or

17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone monohydrate.

Or

3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5, 19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate

Molecular Structure:



Molecular Formula: $C_{44}H_{69}NO_{12}.H_2O$
Molecular Weight: 804.0 g/mol; 822.0 as monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	19-DEC-2013	Reviewed by G. Kang.
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
							(b) (4)

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Chemistry Review Data Sheet

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	21-NOV-2013	
Methods Validation			
Labeling	Acceptable	18-DEC-2013	B. Weitzman
Bioequivalence	Acceptable	18-OCT-2013	S. H. Seung
EA	Categorical exclusion requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below

Chemistry Review for ANDA 200744

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC becomes acceptable.
Bio, labeling sections are acceptable. EES is acceptable.

(b) (4)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance-
Tacrolimus is a white to off-white crystalline powder. It is an (b) (4) (b) (4) (b) (4), but insoluble in water. (b) (4) (b) (4)

Drug Product-
Tacrolimus ointment is a non-steroidal topical ointment for the treatment of the signs and symptoms of atopic dermatitis, more commonly known as eczema. The drug product is 0.03% and 0.1% ointment containing Tacrolimus and the inactive ingredients white petrolatum, mineral oil, propylene carbonate, (b) (4) (b) (4) (white wax) and paraffin. *The proposed expiration dating for the drug product is 18 months.*

Tacrolimus Ointment, 0.1%, a white to off white, (b) (4) ointment will be marketed in the following containers:

=

- 30, 60 and 100 g laminated [redacted] (b) (4) tubes with white polypropylene caps.

Tacrolimus Ointment, 0.03%, a white to off white, [redacted] (b) (4) ointment will be marketed in the following containers:

- 30, 60 and 100 g laminated [redacted] (b) (4) tubes with white polypropylene caps.

B. Description of How the Drug Product is Intended to be Used

Strength(s): 0.03% and 0.1%
Route of Administration: Topical
Proposed Indication(s):
Tacrolimus Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

Dosage and Administration

[redacted] (b) (4)

[redacted] (b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[1]
- [redacted] (b) (4)
- Coverage of 100% of the body would require 20.1g of an ointment[2]

[redacted] (b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of $\leq$ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)
[redacted] (b) (4)

[1] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert
[2] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

Executive Summary Section

=

Therefore, based on Tacrolimus Ointment 0.1%, IT for drug substance Tacrolimus is 0.10%

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, QT for drug substance Tacrolimus is 0.15%

(b) (4)

(b) (4)

(b) (4)

IT = 0.10% QT = 0.15%

NOTE: As per instructions in ICH Q3A and Q3B, ICH guidelines do not apply to fermentation products.

C. Basis for Approvability or Not-Approval Recommendation

CMC becomes acceptable.

64 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

A APPENDICES

A.1 Facilities and Equipment (biotech only)

A.2 Adventitious Agents Safety Evaluation

A.3 Novel Excipients

R REGIONAL INFORMATION

R.1 Executed Batch Records

Executed batch records were provided in Section 3.2.R.1 for batches: Z432, 709C, Z035 and Z431.

R.2 Comparability Protocols

The firm did not include this section in their submission.

R.3 Methods Validation Package

(b) (4)

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert: provided.

B. Environmental Assessment Or Claim Of Categorical Exclusion: provided.

cc: ANDA 200744
ANDA DUP
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
Chemist/Gil Kang/
Team Leader/James Fan/
Project Manager/Hany S. Edward /9/4/14

\\fdswv04385\documents\54806-200744.doc

TYPE OF LETTER: ANDA is Approvable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GIL JONG KANG
09/08/2014

HANY S EDWARD
09/08/2014

RICHARD R CHANG on behalf of JAMES M FAN
09/08/2014

BING CAI
09/08/2014

Addendum to review #4 dated 31-AUG-2012 in DARRTS (Easily Correctable Deficiencies).

ANDA 200744

Tacrolimus Ointment, 0.1% and 0.03%

Fougera Pharmaceuticals Inc.

Anurag Sharadendu, Ph.D./ Gil-Jong Kang
OGD/DCI

Chemistry Review #4_Addendum

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 200744

2. REVIEW #: 4_Addendum

3. REVIEW DATE: 18-FEB-2014

4. REVIEWER: Anurag Sharadendu, Ph.D./ Gil Kang

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original Submission	04/08/2010
Acceptable for filing	09/09/2010
Amendment (Response to Regulatory Support)	09/09/2010
Amendment (Patent)	09/23/2010
Amendment (Clinical)	10/15/2010
Amendment (Patent)	11/02/2010
Amendment (New Strength, 0.03%)	11/19/2010
Amendment (Patent)	12/01/2010
Amendment (Response to Regulatory Support)	12/15/2010
Amendment (Patent)	12/17/2010
Amendment (Response for information)	02/17/2011
Amendment (Response for information)	03/04/2011
Minor Amendment (Bioequivalence)	08/9/2011
Minor Amendment (Chemistry)	09/15/2011
Minor Amendment (Chemistry)	02/24/2012
Amendment (Bioequivalence)	02/29/2012
Reclassification from Minor to Major Amendment (Chemistry)	03/15/2012
Minor Amendment (Chemistry)	06/11/2012
Telephone Amendment	07/24/2012
Telephone Amendment	07/25/2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Gratuitous amendment (Withdrawal of outside testing Laboratoy)	12/12/2012
Response to ECD	11/20/2013
Response to ECD	12/06/2013

7. NAME & ADDRESS OF APPLICANT:

Name: Fougera Pharmaceuticals Inc.

Address: P.O. Box 2006
60 Baylis Road
Melville, NY 11747

Representative: Amy Byrom

Telephone: 631-454-7677 X 2098

Fax: 631-756-5114

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Tacrolimus Ointment, 0.1% and 0.03%

Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

The applicant, Nycomed US Inc., hereby states that, to the best of the applicant's knowledge, the following United States Patents are listed in the United States Food and Drug Administration's Electronic *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.1% (NDA 50777), manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc. The expiration dates indicated below are those stated in the Orange Book.

U.S. Patent No. 5,385,907 – Expires January 31, 2012
U.S. Patent No. 5,665,727– Expires September 9, 2014

Paragraph IV Certification – United States Patent Nos. 5,385,907 and 5,665,727 Nycomed US Inc. certifies that United States Patent Nos. 5,385,907 and 5,665,727 are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Tacrolimus Ointment 0.03% for which this application amendment is submitted.

In addition, Nycomed US Inc. further certifies that it will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

Exclusivity Statement

Under the provisions set forth in Section 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act, there is no unexpired exclusivity for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.03%, manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc.

Indication

Indicated as *second-line therapy* for the short-term and non-continuous treatment of moderate to severe atopic dermatitis in non-immunocompromised adults who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

10. PHARMACOLOGY CATEGORY:

Tacrolimus Ointment is a *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

11. DOSAGE FORM:

Ointment

12. STRENGTH/POTENCY:

0.03% and 0.1%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

____x__Not a NANO product

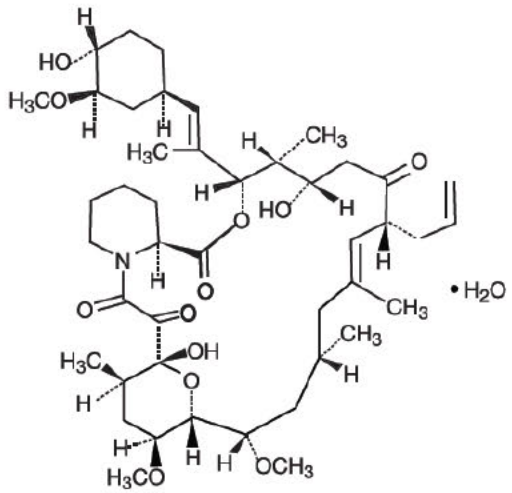
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature:
[3S, 4R, 5S, 8R, 9E, 12S, 14S, 15R, 16S, 18R, 19R, 26aS)-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-Hexadecahydro-5,19-Dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4-oxaazacyclotricosine-1,7,-20,21(4H,23H) tetrone monohydrate.

Or
17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone monohydrate.

Or
3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5, 19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate

Molecular Structure:



Molecular Formula: $C_{44}H_{69}NO_{12}.H_2O$
Molecular Weight: 804.0 g/mol; 822.0 as monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	19-DEC-2013	Reviewed by G. Kang.
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	21-NOV-2013	
Methods Validation			
Labeling	Acceptable	18-DEC-2013	B. Weitzman
Bioequivalence	Acceptable	18-OCT-2013	S.H. Seung
EA	Categorical exclusion requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

ECD

Chemistry Review for ANDA 200744

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA is approvable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance-

Tacrolimus is a white to off-white crystalline powder. It is an (b) (4) (b) (4) (b) (4) but insoluble in water. (b) (4)

1. (b) (4)
2.

Drug Product-

Tacrolimus ointment is a non-steroidal topical ointment for the treatment of the signs and symptoms of atopic dermatitis, more commonly known as eczema. The drug product is 0.03% and 0.1% ointment containing Tacrolimus and the inactive ingredients white petrolatum, mineral oil, propylene carbonate, (b) (4) (b) (4) (white wax) and paraffin. (b) (4) (b) (4)

Tacrolimus Ointment, 0.1%, a white to off white, (b) (4) ointment will be marketed in the following containers:

- 30, 60 and 100 g laminated (b) (4) tubes with white polypropylene caps

Tacrolimus Ointment, 0.03%, a white to off white, (b) (4) ointment will be marketed in the following containers:

- 30, 60 and 100 g laminated (b) (4) tubes with white polypropylene caps

B. Description of How the Drug Product is Intended to be Used

Strength(s): 0.03% and 0.1%
Route of Administration: Topical
Proposed Indication(s):
Tacrolimus Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

Dosage And Administration

(b) (4)

(b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[1]
- (b) (4)
- Coverage of 100% of the body would require 20.1g of an ointment[2]

(b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of $\leq$ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)

(b) (4)

[1] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert
[2] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

Executive Summary Section

=

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, QT for drug substance Tacrolimus is 0.15%

(b) (4)

(b) (4)

(b) (4)

IT = 0.10% QT = 0.15%

NOTE: As per instructions in ICH Q3A and Q3B, ICH guidelines do not apply to fermentation products.

C. Basis for Approvability or Not-Approval Recommendation

The CMC issues were classified as ECD and they were satisfactorily resolved through ECD amendments. CMC section becomes acceptable.

A APPENDICES

A.1 Facilities and Equipment (biotech only)

A.2 Adventitious Agents Safety Evaluation

A.3 Novel Excipients

R REGIONAL INFORMATION

R.1 Executed Batch Records

Executed batch records were provided in Section 3.2.R.1 for batches: Z432, 709C, Z035 and Z431.

R.2 Comparability Protocols

The firm did not include this section in their submission.

R.3 Methods Validation Package

(b) (4)

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert: provided.

B. Environmental Assessment Or Claim Of Categorical Exclusion: provided.

cc: ANDA 200744
ANDA DUP 200744
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
Chemist/G. Kang/
Team Leader/James Fan/
Project Manager/Hany S. Edward / 2/21/14

\\fdswv04385\documents\48820-200744.doc

TYPE OF LETTER: ANDA is Approvable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GIL JONG KANG
02/25/2014

HANY S EDWARD
02/25/2014

RICHARD R CHANG on behalf of JAMES M FAN
02/27/2014

ANDRE S RAW
02/28/2014

ANDA 200744

Tacrolimus Ointment, 0.1% and 0.03%

Fougera Pharmaceuticals Inc.

Anurag Sharadendu, Ph.D.
OGD/DCI

Chemistry Review #4

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 200744

2. REVIEW #: 4

3. REVIEW DATE: 29-JUN-2012

4. REVIEWER: Anurag Sharadendu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original Submission	04/08/2010
Acceptable for filing	09/09/2010
Amendment (Response to Regulatory Support)	09/09/2010
Amendment (Patent)	09/23/2010
Amendment (Clinical)	10/15/2010
Amendment (Patent)	11/02/2010
Amendment (New Strength, 0.03%)	11/19/2010
Amendment (Patent)	12/01/2010
Amendment (Response to Regulatory Support)	12/15/2010
Amendment (Patent)	12/17/2010
Amendment (Response for information)	02/17/2011
Amendment (Response for information)	03/04/2011
Minor Amendment (Bioequivalence)	08/9/2011
Minor Amendment (Chemistry)	09/15/2011
Minor Amendment (Chemistry)	02/24/2012
Amendment (Bioequivalence)	02/29/2012
Reclassification from Minor to Major Amendment (Chemistry)	03/15/2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (Chemistry)	06/11/2012
Telephone Amendment	07/24/2012

Telephone Amendment 07/25/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Fougera Pharmaceuticals Inc.

Address: P.O. Box 2006
60 Baylis Road
Melville, NY 11747

Representative: Amy Byrom

Telephone: 631-454-7677 X 2098

Fax: 631-756-5114

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Tacrolimus Ointment, 0.1% and 0.03%

Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

The applicant, Nycomed US Inc., hereby states that, to the best of the applicant's knowledge, the following United States Patents are listed in the United States Food and Drug Administration's Electronic *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.1% (NDA 50777), manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc. The expiration dates indicated below are those stated in the Orange Book.

U.S. Patent No. 5,385,907 – Expires January 31, 2012
U.S. Patent No. 5,665,727– Expires September 9, 2014

Paragraph IV Certification – United States Patent Nos. 5,385,907 and 5,665,727 Nycomed US Inc. certifies that United States Patent Nos. 5,385,907 and 5,665,727 are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Tacrolimus Ointment 0.03% for which this application amendment is submitted.

In addition, Nycomed US Inc. further certifies that it will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives

and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

Exclusivity Statement
Under the provisions set forth in Section 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act, there is no unexpired exclusivity for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.03%, manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc.

Indication
Indicated as *second-line therapy* for the short-term and non-continuous treatment of moderate to severe atopic dermatitis in non-immunocompromised adults who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

10. PHARMACOLOGY CATEGORY:

Tacrolimus Ointment is a *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

11. DOSAGE FORM:

Ointment

12. STRENGTH/POTENCY:

0.03% and 0.1%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

___x__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature:

[3S, 4R, 5S, 8R, 9E, 12S, 14S, 15R, 16S, 18R, 19R, 26aS)-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-Hexadecahydro-5,19-Dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4-oxaazacyclotricosine-1,7,-20,21(4H,23H) tetrone monohydrate.

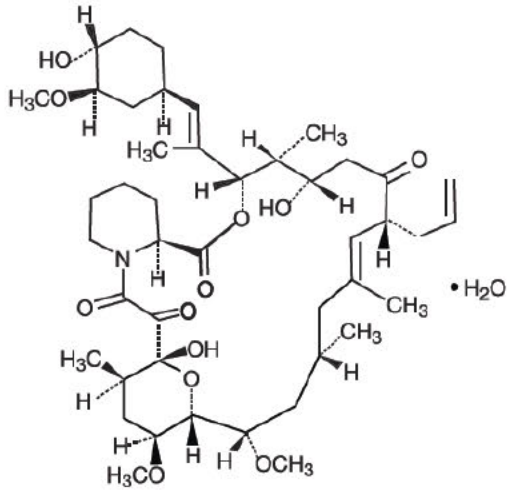
Or

17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone monohydrate.

Or

3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5, 19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate

Molecular Structure:



Molecular Formula: $C_{44}H_{69}NO_{12}.H_2O$
Molecular Weight: 804.0 g/mol; 822.0 as monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	08/19/2012	Reviewed by A. Sharadendu
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Withhold	8/23/12	
Methods Validation			
Labeling	Acceptable	1/4/12	B. Weitzman
Bioequivalence	Pending		
EA	Categorical exclusion requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 200744

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is approvable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance-
Tacrolimus is a white to off-white crystalline powder. It is an [redacted] but insoluble in water.

1. [redacted]

2. [redacted]

Drug Product-
Tacrolimus ointment is a non-steroidal topical ointment for the treatment of the signs and symptoms of atopic dermatitis, more commonly known as eczema. The drug product is 0.03% and 0.1% ointment containing Tacrolimus and the inactive ingredients white petrolatum, mineral oil, propylene carbonate, [redacted] (white wax) and paraffin. [redacted]

Tacrolimus Ointment, 0.1%, a white to off white, [redacted] ointment will be marketed in the following containers:

- 30, 60 and 100 g laminated [redacted] tubes with white polypropylene caps

Tacrolimus Ointment, 0.03%, a white to off white, [redacted] ointment will be marketed in the following containers:

=

- 30, 60 and 100 g laminated (b) (4) tubes with white polypropylene caps

B. Description of How the Drug Product is Intended to be Used

Strength(s): 0.03% and 0.1%
Route of Administration: Topical
Proposed Indication(s):
Tacrolimus Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

Dosage And Administration

(b) (4)

(b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[1]
- (b) (4)
- Coverage of 100% of the body would require 20.1g of an ointment[2]

(b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of $\leq$ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)

[1] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert
[2] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

Executive Summary Section

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(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, IT for drug substance Tacrolimus is 0.10%

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, QT for drug substance Tacrolimus is 0.15%

(b) (4)

(b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[3]
- (b) (4)
- Coverage of 100% of the body would require 20.1g of an ointment[4]

(b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of $\leq$ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)

(b) (4)

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

[3] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert

[4] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

=

Therefore, based on Tacrolimus Ointment 0.03%, QT for drug substance Tacrolimus is 0.15%

NOTE: As per instructions in ICH Q3A and Q3B, ICH guidelines do not apply to fermentation products.

C. Basis for Approvability or Not-Approval Recommendation

The CMC is approvable.

cc: ANDA 200744
ANDA DUP 200744
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
Chemist/A. Sharadendu, Ph.D./ 6/27/12; 7/26/12
Team Leader/J. Fan/7/26/12
Project Manager/T. Tran/7/26/12

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TYPE OF LETTER: CMC is Approvable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANURAG SHARADENDU
08/30/2012

SIMON S ENG on behalf of TRANG Q TRAN
08/31/2012

JAMES M FAN
08/31/2012

ANDA 200744

Tacrolimus Ointment, 0.1% and 0.03%

Fougera Pharmaceuticals Inc.

Anurag Sharadendu, Ph.D.
OGD/DCI

Chemistry Review #3

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 200744

2. REVIEW #: 3

3. REVIEW DATE: **20**-MAR-2012

4. REVIEWER: Anurag Sharadendu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original Submission	04/08/2010
Acceptable for filing	09/09/2010
Amendment (Response to Regulatory Support)	09/09/2010
Amendment (Patent)	09/23/2010
Amendment (Clinical)	10/15/2010
Amendment (Patent)	11/02/2010
Amendment (New Strength, 0.03%)	11/19/2010
Amendment (Patent)	12/01/2010
Amendment (Response to Regulatory Support)	12/15/2010
Amendment (Patent)	12/17/2010
Amendment (Response for information)	02/17/2011
Amendment (Response for information)	03/04/2011
Minor Amendment (Bioequivalence)	08/9/2011
Minor Amendment (Chemistry)	09/15/2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (Chemistry)	02/24/2012
Amendment (Bioequivalence)	02/29/2012
Reclassification from Minor to Major Amendment (Chemistry)	03/15/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Fougera Pharmaceuticals Inc.

Address: P.O. Box 2006
60 Baylis Road
Melville, NY 11747

Representative: Amy Byrom

Telephone: 631-454-7677 X 2098

Fax: 631-756-5114

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Tacrolimus Ointment, 0.1% and 0.03%

Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

The applicant, Nycomed US Inc., hereby states that, to the best of the applicant's knowledge, the following United States Patents are listed in the United States Food and Drug Administration's Electronic *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.1% (NDA 50777), manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc. The expiration dates indicated below are those stated in the Orange Book.

U.S. Patent No. 5,385,907 – Expires January 31, 2012
U.S. Patent No. 5,665,727– Expires September 9, 2014

Paragraph IV Certification – United States Patent Nos. 5,385,907 and 5,665,727 Nycomed US Inc. certifies that United States Patent Nos. 5,385,907 and 5,665,727 are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Tacrolimus Ointment 0.03% for which this application amendment is submitted.

In addition, Nycomed US Inc. further certifies that it will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

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Under the provisions set forth in Section 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act, there is no unexpired exclusivity for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.03%, manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc.

Indication

Indicated as *second-line therapy* for the short-term and non-continuous treatment of moderate to severe atopic dermatitis in non-immunocompromised adults who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

10. PHARMACOLOGY CATEGORY:

Tacrolimus Ointment is a *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

11. DOSAGE FORM:

Ointment

12. STRENGTH/POTENCY:

0.03% and 0.1%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

___x__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature:

[3S, 4R, 5S, 8R, 9E, 12S, 14S, 15R, 16S, 18R, 19R, 26aS)-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-Hexadecahydro-5,19-Dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4-oxaazacyclotricosine-1,7,-20,21(4H,23H) tetrone monohydrate.

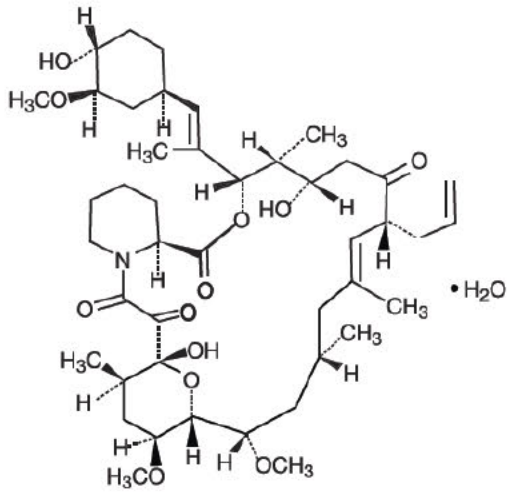
Or

17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone monohydrate.

Or

3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5, 19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate

Molecular Structure:



Molecular Formula: $C_{44}H_{69}NO_{12}.H_2O$
Molecular Weight: 804.0 g/mol; 822.0 as monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate with IR	03/5/2012 by S. Han	
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation			
Labeling	Acceptable	1/4/12	B. Weitzman
Bioequivalence	Pending		
EA	Categorical exclusion requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 200744

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA is not approvable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance-
Tacrolimus is a white to off-white crystalline powder. (b) (4) (b) (4) (b) (4) but insoluble in water. (b) (4)

(b) (4)

Drug Product-
Tacrolimus ointment is a non-steroidal topical ointment for the treatment of the signs and symptoms of atopic dermatitis, more commonly known as eczema. The drug product is 0.03% and 0.1% ointment containing Tacrolimus and the inactive ingredients white petrolatum, mineral oil, propylene carbonate, (b) (4) (b) (4) (white wax) and paraffin. (b) (4) (b) (4)

Tacrolimus Ointment, 0.1%, a white to off white, (b) (4) ointment will be marketed in the following containers:

- 30, 60 and 100 g laminated (b) (4) tubes with white polypropylene caps

Tacrolimus Ointment, 0.03%, a white to off white, (b) (4) ointment will be marketed in the following containers:

=

- 30, 60 and 100 g laminated [redacted] (b) (4) tubes with white polypropylene caps

B. Description of How the Drug Product is Intended to be Used

Strength(s): 0.03% and 0.1%
Route of Administration: Topical
Proposed Indication(s):
Tacrolimus Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

Dosage And Administration

[redacted] (b) (4)

[redacted] (b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[1]
- [redacted] (b) (4)
- Coverage of 100% of the body would require 20.1g of an ointment[2]

[redacted] (b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of $\leq$ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)

[1] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert
[2] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

Executive Summary Section

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(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, IT for drug substance Tacrolimus is 0.10%

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, QT for drug substance Tacrolimus is 0.15%

Maximum Daily Dose (MDD) of Tacrolimus Ointment 0.03%

(b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[3]
- (b) (4).
- Coverage of 100% of the body would require 20.1g of an ointment[4]

(b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of $\leq$ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)

(b) (4)

Therefore, based on Tacrolimus Ointment 0.03%, IT for drug substance Tacrolimus is 0.10%

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

[3] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert

[4] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

=

Therefore, based on Tacrolimus Ointment 0.03%, QT for drug substance Tacrolimus is 0.15%

NOTE: As per instructions in ICH Q3A and Q3B, ICH guidelines do not apply to fermentation products.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is non-approvable for minor deficiencies.

139 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

CHEMISTRY COMMENTS TO BE PROVIDED TO APPLICANT.

ANDA: 200744 APPLICANT: Fougera Pharmaceuticals Inc.

DRUG PRODUCT: Tacrolimus Ointment, 0.03% and 0.1%

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term drug product stability data.

2. We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions. A risk-based, scientifically sound submission would be expected to include the following:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs) of the drug product
- Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
- Process design and understanding including identification of critical process parameters and in-process material attributes

- Control strategy and justification

An example illustrating QbD concepts can be found online at FDA's Generic Drugs: Information for Industry webpage:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200744
ANDA DUP 200744
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
Chemist/A. Sharadendu, Ph.D./ 4/13/12
Team Leader/J. Fan/4/16/12
Project Manager/T. Tran/4/20/12

M:\2011\1011\200744.R03.doc

TYPE OF LETTER: Not Approvable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANURAG SHARADENDU
04/20/2012

TRANG Q TRAN
04/20/2012

JAMES M FAN
04/20/2012

ANDA 200744

Tacrolimus Ointment, 0.1% and 0.03%

Nycomed US Inc.

Anurag Sharadendu, Ph.D.
OGD/DCI

Chemistry Review #2

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 200744

2. REVIEW #: 2

3. REVIEW DATE: 14-OCT-2011

4. REVIEWER: Anurag Sharadendu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original Submission	04/08/2010
Acceptable for filing	09/09/2010
Amendment (Response to Regulatory Support)	09/09/2010
Amendment (Patent)	09/23/2010
Amendment (Clinical)	10/15/2010
Amendment (Patent)	11/02/2010
Amendment (New Strength, 0.03%)	11/19/2010
Amendment (Patent)	12/01/2010
Amendment (Response to Regulatory Support)	12/15/2010
Amendment (Patent)	12/17/2010
Amendment (Response for information)	02/17/2011
Amendment (Response for information)	03/04/2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (Bioequivalence)	08/9/2011
Minor Amendment (Chemistry)	09/15/2011

7. NAME & ADDRESS OF APPLICANT:

Name: Nycomed US Inc.

P.O. Box 2006
Address: 60 Baylis Road
Melville, NY 11747

Representative: Amy Byrom

Telephone: 631-454-7677 X 2098

Fax: 631-756-5114

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Tacrolimus Ointment, 0.1% and 0.03%

Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

The applicant, Nycomed US Inc., hereby states that, to the best of the applicant's knowledge, the following United States Patents are listed in the United States Food and Drug Administration's Electronic *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.1% (NDA 50777), manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc. The expiration dates indicated below are those stated in the Orange Book.

U.S. Patent No. 5,385,907 – Expires January 31, 2012
U.S. Patent No. 5,665,727– Expires September 9, 2014

Paragraph IV Certification – United States Patent Nos. 5,385,907 and 5,665,727 Nycomed US Inc. certifies that United States Patent Nos. 5,385,907 and 5,665,727 are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Tacrolimus Ointment 0.03% for which this application amendment is submitted.

In addition, Nycomed US Inc. further certifies that it will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

Exclusivity Statement
Under the provisions set forth in Section 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act, there is no unexpired exclusivity for the Reference Listed Drug, Protopic® (tacrolimus)

Ointment 0.03%, manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc.

Indication

Indicated as *second-line therapy* for the short-term and non-continuous treatment of moderate to severe atopic dermatitis in non-immunocompromised adults who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

10. PHARMACOL. CATEGORY:

Tacrolimus Ointment is a *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

11. DOSAGE FORM:

Ointment

12. STRENGTH/POTENCY:

0.03% and 0.1%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

____x__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature:

[3S, 4R, 5S, 8R, 9E, 12S, 14S, 15R, 16S, 18R, 19R, 26aS)-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-Hexadecahydro-5,19-Dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4-oxaazacyclotricosine-1,7,-20,21(4H,23H) tetrone monohydrate.

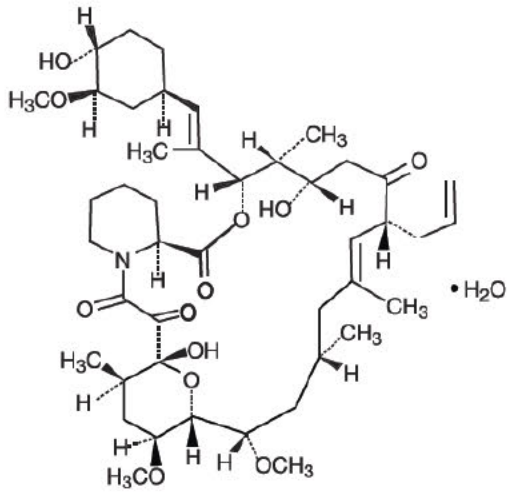
Or

17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone monohydrate.

Or

3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5, 19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate

Molecular Structure:



Molecular Formula: $C_{44}H_{69}NO_{12}.H_2O$
Molecular Weight: 804.0 g/mol; 822.0 as monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	01/22/2010 by Joseph P Wong	
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation			
Labeling	Pending		
Bioequivalence	Pending		
EA	Categorical exclusion requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 200744

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA is not approvable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance-
Tacrolimus is a white to off-white crystalline powder. It is an [redacted] but insoluble in water. [redacted]

1. [redacted]
2. [redacted]

Drug Product-
Tacrolimus ointment is a non-steroidal topical ointment for the treatment of the signs and symptoms of atopic dermatitis, more commonly known as eczema. The drug product is 0.03% and 0.1% ointment containing Tacrolimus and the inactive ingredients white petrolatum, mineral oil, propylene carbonate, [redacted] (white wax) and paraffin. [redacted]

Tacrolimus Ointment, 0.1%, a white to off white, [redacted] ointment will be marketed in the following containers:

- 30, 60 and 100 g laminated [redacted] tubes with white polypropylene caps

Tacrolimus Ointment, 0.03%, a white to off white, [redacted] ointment will be marketed in the following containers:

=

- 30, 60 and 100 g laminated (b) (4) tubes with white polypropylene caps

B. Description of How the Drug Product is Intended to be Used

Strength(s): 0.03% and 0.1%
Route of Administration: Topical
Proposed Indication(s):
Tacrolimus Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

Dosage And Administration

(b) (4)

(b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[1]
- (b) (4)
- Coverage of 100% of the body would require 20.1g of an ointment[2]

(b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of $\leq$ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)

[1] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert
[2] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

Executive Summary Section

=

(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, IT for drug substance Tacrolimus is 0.10%

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, QT for drug substance Tacrolimus is 0.15%

(b) (4)

(b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[3]
- (b) (4)
- Coverage of 100% of the body would require 20.1g of an ointment[4]

(b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of ≤ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)

(b) (4)

Therefore, based on Tacrolimus Ointment 0.03%, IT for drug substance Tacrolimus is 0.10%

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

[3] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert

[4] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

=

Therefore, based on Tacrolimus Ointment 0.03%, QT for drug substance Tacrolimus is 0.15%

NOTE: As per instructions in ICH Q3A and Q3B, ICH guidelines do not apply to fermentation products.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is non-approvable for minor deficiencies.

7. (b) (4)

8.

9.

10.

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200744
ANDA DUP 200744
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
Chemist/A. Sharadendu, Ph.D./ 10/21/11
Team Leader/J. Fan/10/21/11
Project Manager/T. Tran/10/24/11; 11/8/11

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TYPE OF LETTER: Not Approvable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANURAG SHARADENDU
11/09/2011

TRANG Q TRAN
11/09/2011

JAMES M FAN
11/09/2011

ANDA 200744

Tacrolimus Ointment, 0.1% and 0.03%

Nycomed US Inc.

Deborah F Johnson
OGD/DCI

Chemistry Review #1

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 200744

2. REVIEW #: 1

3. REVIEW DATE: 15 Mar 2011

4. REVIEWER: Deborah F. Johnson

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	04/08/2010
Acceptable for filing	09/09/2010
Amendment (Response to Regulatory Support)	09/09/2010
Amendment (Patent)	09/23/2010
Amendment (Clinical)	10/15/2010
Amendment (Patent)	11/02/2010
Amendment (New Strength, 0.03%)	11/19/2010
Amendment (Patent)	12/01/2010
Amendment (Response to Regulatory Support)	12/15/2010
Amendment (Patent)	12/17/2010
Amendment (Response for information)	02/17/2011
Amendment (Response for information)	03/04/2011

7. NAME & ADDRESS OF APPLICANT:

Name: Nycomed US Inc.

Chemistry Review Data Sheet

P.O. Box 2006
Address: 60 Baylis Road
Melville, NY 11747

Representative: Amy Byrom

Telephone: 631-454-7677 X 2098

Fax: 631-756-5114

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Tacrolimus Ointment, 0.1% and 0.03%

Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

The applicant, Nycomed US Inc., hereby states that, to the best of the applicant's knowledge, the following United States Patents are listed in the United States Food and Drug Administration's Electronic *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.1% (NDA 50777), manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc. The expiration dates indicated below are those stated in the Orange Book.
U.S. Patent No. 5,385,907 – Expires January 31, 2012
U.S. Patent No. 5,665,727– Expires September 9, 2014

Paragraph IV Certification – United States Patent Nos. 5,385,907 and 5,665,727
Nycomed US Inc. certifies that United States Patent Nos. 5,385,907 and 5,665,727 are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Tacrolimus Ointment 0.03% for which this application amendment is submitted.

In addition, Nycomed US Inc. further certifies that it will comply with the requirements under § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

Exclusivity Statement
Under the provisions set forth in Section 505(j)(4)(D) of the Federal Food, Drug and

Cosmetic Act, there is no unexpired exclusivity for the Reference Listed Drug, Protopic® (tacrolimus) Ointment 0.03%, manufactured by Astellas Toyama Co., Ltd. and marketed by Astellas Pharma US, Inc.

Indication
Indicated as *second-line therapy* for the short-term and non-continuous treatment of moderate to severe atopic dermatitis in non-immunocompromised adults who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

10. PHARMACOL. CATEGORY:

Tacrolimus Ointment is a *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

11. DOSAGE FORM:

Ointment

12. STRENGTH/POTENCY:

0.03% and 0.1%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

____x__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature:

[3S, 4R, 5S, 8R, 9E, 12S, 14S, 15R, 16S, 18R, 19R, 26aS)-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-Hexadecahydro-5,19-Dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4-oxaazacyclotricosine-1,7,-20,21(4H,23H) tetrone monohydrate.

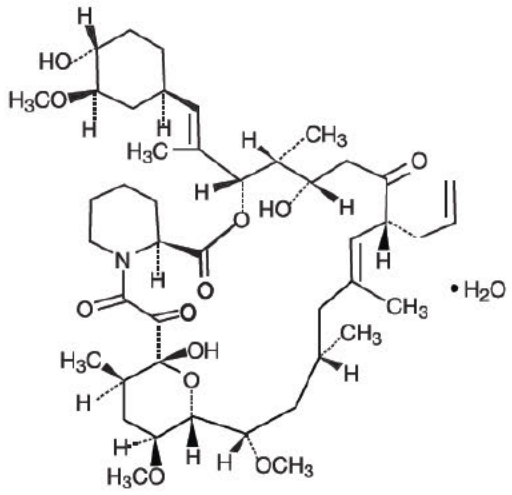
Or

17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone monohydrate.

Or

3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5, 19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate

Molecular Structure:



Molecular Formula: $C_{44}H_{69}NO_{12}.H_2O$
Molecular Weight: 804.0 g/mol; 822.0 as monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	01/22/2010 by Joseph P Wong	
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation			
Labeling	Pending		
Bioequivalence	Pending		
EA	Categorical exclusion requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 200744

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA is not approvable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance-
Tacrolimus is a white to off-white crystalline powder. It is an (b) (4) (b) (4) (b) (4) but insoluble in water. (b) (4)

1. (b) (4)
2.

Drug Product-
Tacrolimus ointment is a non-steroidal topical ointment for the treatment of the signs and symptoms of atopic dermatitis, more commonly known as eczema. The drug product is 0.03% and 0.1% ointment containing Tacrolimus and the inactive ingredients white petrolatum, mineral oil, propylene carbonate, (b) (4) (b) (4) (white wax) and paraffin. (b) (4) (b) (4)

Tacrolimus Ointment, 0.1%, a white to off white, (b) (4) ointment will be marketed in the following containers:

- 30, 60 and 100 g laminated (b) (4) tubes with white polypropylene caps

Tacrolimus Ointment, 0.03%, a white to off white, (b) (4) ointment will be marketed in the following containers:

=

- 30, 60 and 100 g laminated (b) (4) tubes with white polypropylene caps

B. Description of How the Drug Product is Intended to be Used

Strength(s): 0.03% and 0.1%
Route of Administration: Topical
Proposed Indication(s):
Tacrolimus Ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2 to 15 years, is indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

Dosage And Administration

(b) (4)

(b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[1]
- (b) (4)
- Coverage of 100% of the body would require 20.1g of an ointment[2]

(b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of $\leq$ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)

[1] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert
[2] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, IT for drug substance Tacrolimus is 0.10%

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

Therefore, based on Tacrolimus Ointment 0.1%, QT for drug substance Tacrolimus is 0.15%

(b) (4)

(b) (4)

IT = 0.10% QT = 0.15%

Assumptions:

- Tacrolimus Ointment is indicated for the topical treatment of atopic dermatitis and is to be applied twice daily.
- "The absolute bioavailability of tacrolimus from PROTOPIC in atopic dermatitis patients is approximately 0.5%"[3]
- (b) (4)
- Coverage of 100% of the body would require 20.1g of an ointment[4]

(b) (4)

Based on ICH Q3A, the identification and qualification thresholds for a drug substance with a maximum daily dose of ≤ 2 g drug substance/day are:

Identification Threshold: 0.10% or 1.0 mg TDI (whichever is lower)

(b) (4)

Therefore, based on Tacrolimus Ointment 0.03%, IT for drug substance Tacrolimus is 0.10%

Qualification Threshold: 0.15% or 1.0 mg TDI (whichever is lower)

(b) (4)

[3] *Pharmacokinetics* section of current Protopic Ointment 0.1% package insert
[4] C.C. Long, and A.Y. Finlay, The Finger-tip unit – a new practical measure, Clinical and Experimental Dermatology, 1991; 16:444-447

=

Therefore, based on Tacrolimus Ointment 0.03%, QT for drug substance Tacrolimus is 0.15%

NOTE: As per instructions in ICH Q3A and Q3B, ICH guidelines do not apply to fermentation products.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is non-approvable for minor deficiencies.

2. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

3. Please provide all available long-term drug product stability data.

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph.D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200744
ANDA DUP 200744
DIV FILE
Field Copy

Endorsement (Draft and Final with Dates):
Chemist/D. Johnson/ 3/16/2011; 4/25/11; 4/28/11; 5/4/11;5/24/11
Team Leader/J. Fan/ 5/9/11
Project Manager/T. Tran/5/11/11

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TYPE OF LETTER: Not Approvable

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DEBORAH F JOHNSON
05/25/2011

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05/25/2011

JAMES M FAN
05/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200744Orig1s000

STATISTICAL REVIEW

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number:	200744
Drug Name:	Tacrolimus Ointment, 0.1% and 0.03%
Indication(s):	Treatment of Atopic Dermatitis
Reference Listed Drug:	Protopic ® Ointment 0.1% and 0.03%, Astellas
Applicant:	Fougera Pharmaceuticals Inc.
Date(s):	Submitted April 8, 2010 September 8, 2010 November 18, 2010 February 29, 2012
Biometrics Division:	DB6
Statistical Reviewer:	Fairouz Makhlouf, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D.
Medical Division:	Division of Clinical Review (DCR) in OGD
Clinical Team:	Sarah H. Seung, Pharm.D.
Keywords:	Bioequivalence, treatment success, difference, proportion

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1 Executive Summary

1.1 Conclusions and Recommendations

Study ALT 0416-01-01: Bioequivalence Study for Tacrolimus Ointment 0.1% Strength

The equivalence test did pass for the FDA per-protocol population (FPP) for the proportion of subjects with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the Investigator's Global Assessment of Disease Severity at the end of the treatment (Visit 3 Day 14 (-1/+3 Days)). Also, the two active treatments are statistically significantly better than the placebo for the FDA modified intent-to-treat population (FMITT).

Study ALT 0417-01-01: Bioequivalence Study for Tacrolimus Ointment 0.03% Strength

The equivalence test did pass for the FDA per-protocol population (FPP) for the proportion of subjects with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the Investigator's Global Assessment of Disease Severity at the end of the treatment (Visit 4 Day 28 (± 3 Days)). Also, the two active treatments are statistically significantly better than the placebo for the FDA modified intent-to-treat population (FMITT).

1.2 Brief Overview of the Clinical Studies

There were two clinical end point bioequivalence studies for this application. Both were randomized, multiple-center, double blind, parallel design, placebo controlled studies for the treatment of atopic dermatitis. The first study ALT 0416-01-01 was conducted between 1/28/2008 and 8/12/2009. The second study ALT 0417-01-01 was conducted between 1/10/2008 and 9/11/2009. More description for each study is given below:

Study ALT 0416-01-01: Bioequivalence Study for Tacrolimus Ointment 0.1% Strength

Study ALT 0416-01-01 was a multi-center, randomized, double blind, parallel design, comparative study of Nycomed US Inc. Ointment, 0.1%, versus the reference listed drug, PROTOPIC® (Tacrolimus) Ointment, 0.1%, in the treatment of atopic dermatitis (AD). Seven hundred ninety three (793) subjects at least 18 years old were randomized in a 1:1:1 ratio to receive the test, reference or vehicle ointments twice daily for two weeks.

The sponsor defined the primary endpoint for this study as the proportion of subjects in each treatment group who had an IGE rating of "Clear" or "Almost Clear" for atopic dermatitis (success) at the end of treatment (Visit 3 Day 14 (-1/+3 Days)). Also, the sponsor's secondary endpoints included

1. the mean change from baseline in the total individual clinical signs and symptoms (ie, erythema, induration/papulation, lichenification, scaling, oozing/crusting, and excoriation) per body region (ie, head and neck, trunk, upper extremities, and lower extremities),
2. the mean change from baseline in pruritus, and
3. the mean change from baseline in the % of body surface area (BSA).affected

Study ALT 0417-01-01: Bioequivalence Study for Tacrolimus Ointment 0.03% Strength

Study ALT 0417-01-01 was a multi-center, randomized, double blind, parallel design, comparative study of Nycomed US Inc. Ointment, 0.03%, versus the reference listed drug, PROTOPIC® (Tacrolimus) Ointment, 0.03%, in the treatment of atopic dermatitis (AD). Nine hundred (900) subjects at least 8 years old were randomized in a 1:1:1 ratio to receive the test, reference or vehicle ointments twice daily for 28 days.

The sponsor defined the primary endpoint for this study as the proportion of subjects in each treatment group who had an IGE rating of "Clear" or "Almost Clear" for atopic dermatitis (success) at the end of treatment (Visit 4 Day 28 (±3 Days)). Also, the sponsor's secondary endpoints included

1. the mean change from baseline in the total individual clinical signs and symptoms (ie, erythema, induration/papulation, lichenification, scaling, oozing/crusting, and excoriation) per body region (ie, head and neck, trunk, upper extremities, and lower extremities),
2. the mean change from baseline in pruritus, and
3. the mean change from baseline in the % BSA affected.

1.3 Statistical Issues/Results

Study ALT 0416-01-01: Bioequivalence Study for Tacrolimus Ointment 0.1% Strength

The primary efficacy endpoint was the proportion of subjects in each treatment group who had an IGE rating of "Clear" or "Almost Clear" (hereafter referred to as "success") for atopic dermatitis at Visit 3 (End of Study Day 14 (-1/+3 Days)). No secondary endpoints were requested for this analysis based on the FDA medical reviewer. This was a change from the sponsor who considered secondary endpoints (see section 1.2 of this review).

The sponsor's per-protocol population (SPP) and the sponsor's modified intent-to-treat population (FMITT) had to be changed to exclude or include some subjects based on the FDA

medical reviewer recommendations for various reasons. These exclusions and inclusions resulted in creating the FDA per protocol population (FPP) and the FDA modified intent-to-treat population (FMITT). Table 30, Table 31 and Table 32 in Appendix 1 provide listings for these subjects with their corresponding exclusion/inclusion reasons.

Using the FPP population, the 90% confidence interval for the difference in proportion of the treatment success rates of the test product and the reference product at Visit 3/Day 14 is -15.023% to 3.048%. The 90% confidence interval is included in the interval -20% and 20% which implies that the equivalence test passed for the FDA per-protocol population. Also, using the FMITT, we conclude that the two active treatments are statistically significantly better than Placebo (p-value < 0.001 using Fisher's exact test).

A last-observation-carried-forward (LOCF) approach was used for missing efficacy results in the FMITT population and for the FPP subjects who discontinued due to lack of treatment effect.

Study ALT 0417-01-01: Bioequivalence Study for Tacrolimus Ointment 0.03% Strength

The primary efficacy endpoint was the proportion of subjects in each treatment group who had an IGE rating of "Clear" or "Almost Clear" (hereafter referred to as "success") for atopic dermatitis at Visit 4 (End of Study Day 28 (± 3Days)). No secondary endpoints were requested for this analysis based on the FDA medical reviewer. This was a change from the sponsor who considered secondary endpoints (see section 1.2 of this review).

The sponsor's per-protocol population and the sponsor's modified intent-to-treat population had to be changed to exclude some subjects based on the FDA medical reviewer recommendations for various reasons. These exclusions resulted in creating the FDA per protocol population (FPP) and the FDA modified intent-to-treat population (FMITT). Table 36 and Table 37 in Appendix 2 provide listings for these subjects with their corresponding exclusion reasons.

Using the FPP population, the 90% confidence interval for the difference in proportion of the treatment success rates of the test product and the reference product at Visit 4/Day 28 is -7.584% to 10.314%. The 90% confidence interval is included in the interval -20% and 20% which implies that the equivalence test passed for the FDA per-protocol population. Also, using the FMITT, we conclude that the two active treatments are statistically significantly better than Placebo (p-value < 0.001 using Fisher's exact test).

A last-observation-carried-forward (LOCF) approach was used for missing efficacy results in the FMITT population and for the FPP subjects who discontinued due to lack of treatment effect.

2 Introduction

2.1 Overview

Atopic dermatitis (AD) is a chronic, pruritic eczematous disease that nearly always begins in childhood and follows a remitting/flaring course that could continue throughout life. The disease often moderates with age, but subjects carry a life-long skin sensitivity to irritants. AD is divided into three phases: infant, childhood and adult, and the disease characteristics vary with age. Infants have facial and patchy or generalized body eczema while adolescents and adults have eczema in flexural areas and on the hands. AD starts with itching and it is the scratching that creates most of the characteristic patterns of the disease. Several patterns and types of lesions may be produced by exposure to external stimuli or may be precipitated by scratching. Acute inflammation begins with erythematous papules and erythema. Subacute dermatitis is associated with erythematous, excoriated, scaling papules. Chronic dermatitis is the result of scratching over an extended period causing thickened skin, accentuated skin markings (lichenification) and fibrotic papules. Inflammation resolves slowly, leaving the skin in a dry, scaly, compromised condition called xerosis. All types of reactions can coexist in the same individual.

Treatment goals consist of attempting to eliminate inflammation and infection, preserving and restoring the stratum corneum barrier by using emollients, using antipruritic agents to reduce the self-inflicted damage to the involved skin, and controlling exacerbating factors. Inflammation is treated with topical steroids and the nonsteroidal anti-inflammatory agents pimecrolimus (Elidel) and tacrolimus (Protopic). They are immunosuppressant topical medications that are thought to block the early phase of T-cell activation, degranulation of mast cells and multiple cytokines required to activate cellular immunity. They potentially block Langerhans' cells' function and do not cause dermal atrophy.

2.1.1 INDs, Protocols, and/or Control Documents submitted by other sponsors

This is the first generic application for this drug product. Several other protocols and controls have been submitted by other sponsors for this drug product.

2.1.2 Other ANDA submissions for same or related product

(b) (4)

2.2 Data Sources

Study ALT 0416-01-01: Bioequivalence Study for Tacrolimus Ointment 0.1% Strength

The data were submitted electronically. The data files for Study ALT 0416-01-01 (Bioequivalence Study for Tacrolimus Ointment 0.1% Strength) are located under module 0001 (Application date 09/09/2010) of this electronic ANDA.

Study ALT 0417-01-01: Bioequivalence Study for Tacrolimus Ointment 0.03% Strength

The data were submitted electronically. The data files for Study ALT 0417-01-01 (Bioequivalence Study for Tacrolimus Ointment 0.03% Strength) are located under module 0005 (Application date 11/22/2010) of this electronic ANDA.

3 Statistical Evaluation

3.1 Evaluation of Study ALT 0416-01-01 (Tacrolimus Ointment 0.1%)

3.1.1 Study Design and Endpoints Objectives (Tacrolimus Ointment 0.1%)

Objectives

The objectives of this study were to compare the safety and efficacy profiles of Nycomed US Inc.'s tacrolimus ointment, 0.1% to those of Astellas Pharma US, Inc.'s PROTOPIC® (tacrolimus) Ointment 0.1% and to demonstrate the superior efficacy of the two active ointments over that of the Nycomed US Inc. Vehicle (placebo) in the treatment of atopic dermatitis in subjects at least 18 years old.

Study Design

This was a multi-center, randomized, double-blind, vehicle-controlled, parallel-group study conducted in subjects at least 18 years of age with moderate to severe atopic dermatitis with ≥ 10% body surface area (BSA) affected. Seven hundred ninety three (793) subjects were enrolled and randomized in 1:1:1 ratio to one of the three treatment groups. The three ointments were the test product Nycomed US Inc.'s generic tacrolimus ointment 0.1%, the reference product Astellas Pharma US, Inc.'s PROTOPIC® (tacrolimus) Ointment 0.1% and the placebo Nycomed US Inc.'s Vehicle. Subjects applied the study medication topically twice-daily (morning and evening, after washing with non-medicated, non-irritating soap) approximately 12 hours apart for two weeks (14 days). Subjects returned to the office for follow up evaluations at Day 4 (-0, +2 days/Visit 2) and Day 14 (-1, +3 days/Visit 3). A blood sample was drawn for the assay of

tacrolimus concentration at Visit 2. The signs and symptoms at the target sites were assessed and the investigator's evaluations were recorded at Visit 2 and Visit 3. The subjects' concomitant medications were assessed and recorded, along with any adverse events (AEs). Subjects returned at each visit with the study medication and subject diaries. Compliance with study medication applications were assessed via the subject diary, and at Visit 3, all study medication was collected.

Treatments

A total of 793 subjects were enrolled in the study. They were randomized to receive the test product Nycomed US Inc.'s generic Tacrolimus Ointment 0.1%, the reference product Astellas Pharma US, Inc.'s PROTOPIC® (tacrolimus) Ointment 0.1% and the placebo Nycomed US Inc.'s Vehicle in a 1:1:1 ratio respectively.

Article	Description
Test	Tacrolimus Ointment, 0.1% Manufacturer: Nycomed US Inc. Lot # Z432
Reference	Protopic® (tacrolimus) Ointment 0.1% Manufactured: Astellas Pharma US, Inc Lot # 26181
Placebo	Vehicle of Test product Manufacturer: Nycomed US Inc. Lot # Z033

Outcome variables

Investigator's Global Evaluation (IGE): The investigator made an independent global evaluation for overall assessment of the subject's atopic dermatitis. The same investigator, to the greatest extent possible, was to perform the Investigator's Global Evaluation at each visit. This assessment incorporated evaluations for erythema, induration/papulation, amount of involvement, and a general clinical assessment.

The IGE was evaluated using the following scale:

Score	Grade	Definition
0	Clear	Minor, residual discoloration, no erythema or induration/papulation, no oozing/crusting
1	Almost Clear	Trace, faint pink erythema with almost no induration/population and no oozing/crusting
2	Mild	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation, possibly with some oozing/crusting
4	Severe	Deep/bright red erythema with severe induration/papulation with oozing/crusting

In addition to the IGE the following signs and symptoms were to be evaluated: Erythema, Induration/Papulation, Lichenification, Scaling, Oozing/Crusting, and Excoriation.

The signs and symptoms were each graded by the sponsor on a scale of 0 to 3 as follows:

Erythema defined by the sponsor as redness; residual hyperpigmentation, hypopigmentation, pigmented macules, or diffuse slight pink coloration were not included as erythema

Score	Grade	Definition
0	None	No erythema present
1	Mild	Slight erythema, very light-pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red

Induration/papulation (defined as inflammation; swelling)

Score	Grade	Definition
0	None	No elevation
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation

Lichenification (defined as thickening upper layers of skin)

Score	Grade	Definition
0	None	No lichenification
1	Mild	Slight thickening of the skin discernable only by touch and with skin markings minimally exaggerated
2	Moderate	Definite thickening of the skin with skin marking exaggerated so that they form a visible criss-cross pattern
3	Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern

Scaling (defined as flakes or shedding of the stratum corneum)

Score	Grade	Definition
0	None	No evidence of scaling
1	Mild	Occasional fine, flaky scale predominates
2	Moderate	Coarse scale predominates
3	Severe	Thick, coarse, crusted scale predominates

Oozing/crusting (defined as seeping of tissue fluid; dried blood or tissue fluids)

Score	Grade	Definition
0	None	No evidence of oozing/crusting
1	Mild	Evidence of exudation
2	Moderate	Serous brown, yellow, or green exudations and/or drying of the discharge
3	Severe	Many dry scabs and/or exudations

Excoriation (defined as the loss of the top layer of the skin caused by scratching)

Score	Grade	Definition
0	None	No evidence of excoriation
1	Mild	Scant evidence of excoriation with no signs of deeper skin damage (erosion, crust)
2	Moderate	Several linear marks on the skin with some showing evidence of deeper skin injury (erosion, crust)
3	Severe	Many erosive or crusty lesions

Pruritus Assessment: Subjects evaluated their overall itching/scratching/discomfort in the preceding 24 hours based on the following scale:

Score	Grade	Definition
0	None	None
1	Mild	Occasional, slight itching/scatching
2	Moderate	Constant or intermittent itching/scratching/discomfort that does not disturb sleep
3	Severe	Bothersome itching/scratching/discomfort that disturbs sleep

Clinical response was evaluated at Visit 3/Day14 (-1, +3 Days) by the IGE scores.

Clinical Response

Clinical success is defined by the FDA medical reviewer according to the Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012) as a grade of "Clear" or "Almost Clear"; a score of 0 or 1 within all treatment areas based on the Investigator's Global Assessment of disease Severity which is the same as the sponsor's IGE at the end of treatment (week 2 visit; study day 15) for atopic dermatitis. The sponsor's definition of clinical response is accepted by the medical reviewer in accordance with the Draft Guidance. The only discrepancy is that the end of treatment assessment was done on Day 14 by the sponsor instead of Day 15 based on the draft guidance. This was accepted by the medical reviewer.

Endpoints

The primary endpoint of this study is the proportion of subjects in the per-protocol population with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the Investigator's Global Assessment of Disease Severity (which is the same as the sponsor's IGE) at the end of treatment (Week 2 visit; study day 14). Note that the sponsor's primary endpoint is in accordance with the Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012) and is acceptable.

The secondary endpoints are the change in severity from baseline to Visit 3 Day 14 (-1/+3 Days) of four individual signs and symptoms of atopic dermatitis (i.e., erythema, induration/papulation, lichenification and pruritus) and are considered supportive information. The secondary endpoints are considered supportive information and the medical reviewer did not request analysis of them.

3.1.2 Subject Disposition (Tacrolimus Ointment 0.1%)

Seven hundred ninety three (793) subjects were enrolled and randomized in 1:1:1 ratio to one of the three treatment groups. The sponsor's intention-to-treat (SITT), modified intention-to-treat

(SMITT) and per-protocol (SPP) populations had 793, 758 and 616 subjects respectively. The FDA's modified intention-to-treat (FMITT) and per-protocol (FPP) populations have 671 and 528 respectively. The differences between the Sponsor's populations and the FDA's populations are due to excluding/including subjects as follows:

FMITT:

In addition to the thirty five (35) subjects excluded from the enrolled and randomized population to form the SMITT, a total of eighty seven (87) subjects from the SMITT population were excluded to form the FMITT population: Twenty nine (29) subjects in the test treatment group, twenty (20) subjects in the reference treatment group and thirty eight (38) subjects from the Placebo group. These subjects were excluded because of one or more of the following reasons:

- Subjects had inappropriate washout period for an exclusionary medication prior to study entry.
- Subjects had inappropriate washout period for an exclusionary medication prior to study entry and continued to use the prohibited concomitant medication during the study.
- Subjects had an exclusionary medical condition.
- The medical monitor disagreed with the investigator's assessment of inclusion/exclusion criteria.

Table 30 in Appendix 1 provides a listing of the subjects excluded from the SMITT to form the FMITT population.

FPP:

In addition to the one hundred and seventy seven (177) subjects excluded from the enrolled and randomized population to form the SPP, a total of eighty nine (89) subjects from the SPP population were excluded to form the FPP: Twenty nine (29) subjects in the test treatment group, twenty two (22) subjects in the reference treatment group and thirty eight (38) subjects from the Placebo group. These subjects were excluded because of one or more of the following reasons:

- Subjects had inappropriate washout period for an exclusionary medication prior to study entry.
- Subjects had inappropriate washout period for an exclusionary medication prior to study entry and continued to use the prohibited concomitant medication during the study.
- Subjects had an exclusionary medical condition.
- Subjects had inappropriate washout period for an exclusionary medication.

One subject (Subject (b) (6) in the reference treatment group was excluded from the SPP population for not having Visit 2 data. This subject has Visit 3 data and has no other reason to be

excluded from the FPP population. Visit 2 is not the test-of-cure visit and therefore, Subject (b) (6) should be included in the FPP population.

A listing of the subjects excluded from the SPP and another listing of the subjects included back to form the FPP population are given in Table 31 and Table 32 respectively, both tables are found Appendix 1.

The subject dispositions for the sponsor's and the FDA's populations are given in Table 1 and Table 2 Number of Subjects in the FDA's MITT and PP Populations: ALT 0416-01-01 (Tacrolimus 0.1%)
respectively.

Table 1 Number of Subjects in the Sponsor's ITT, MITT and PP Populations: ALT 0416-01-01 (Tacrolimus 0.1%)

	Total	Tacrolimus 0.1%	Protopic® 0.1%	Placebo
Enrolled and Randomized	**793**	**269**	**260**	**264**
Total sponsor ITT population	793	269	260	264
Total exclusion from the sponsor's ITT population	0	0	0	0
Total sponsor MITT population	**758**	**257**	**252**	**249**
Total exclusion from the sponsor's MITT population	35	12	8	15
Reason for exclusion from sponsor's MITT				
Did Not Have Any Post baseline IGE	26	10	7	9
Did Not Meet Inclusion/Exclusion Criteria	9	2	1	6
Total sponsor PP population	**616**	**210**	**211**	**195**
Total Exclusion from the sponsor's PP population	177	59	49	69
Reason for exclusion from sponsor's PP				
Excluded from MITT	35	12	8	15
Diary Not Returned	3	1	1	1
Inappropriate Washout Period	3	0	3	0
Lost To Follow-Up	1	1	0	0
Medical Monitor disagrees with Inclusion/Exclusion Criteria	1	1	0	0
Misdosed	1	1	0	0
Potentially Misdosed	4	4	0	0
Prohibited Medication	13	4	4	5
Study Diary Not Returned	1	1	0	0
Study Medication and Diary Not Returned	1	0	0	1
Unblinded Study Medication	14	4	1	9
Visit 2 Not Done	1	0	1	0
Diary and Study Medication Not ReturnedPotentially Misdosed	1	1	0	0
Did Not Have 85%-120% Compliance Rate;	16	6	6	4
Did Not Have At Least 7 Days Of Treatment	33	9	11	13
Out Of Window For Visit 3	45	13	13	19
Protocol Violation	4	1	1	2

Table 2 Number of Subjects in the FDA's MITT and PP Populations: ALT 0416-01-01 (Tacrolimus 0.1%)

	Total	Tacrolimus 0.1%	Protopic® 0.1%	Placebo
Enrolled and Randomized	**793**	**269**	**260**	**264**
Total FDA MITT population	**671**	**228**	**232**	**211**
Total exclusion from the FDA's MITT population	122	41	28	53
Reason for exclusion from FDA's MITT				
Did Not Have Any Post baseline IGE	26	10	7	9
Did Not Meet Inclusion/Exclusion Criteria	12	3	1	8
The use of exclusionary Medication with no or inappropriate washout period prior to the study entry.	81	27	19	35
Has exclusionary medical condition.	3	1	1	1
Total FDA PP population	**528**	**181**	**190**	**157**
Total Exclusion from the FDA PP population	265	88	70	107
Reason for exclusion from FDA's PP				
Excluded from FDA MITT	122	41	28	53
Diary Not Returned	3	1	1	1
Inappropriate Washout Period	3	0	3	0
Lost To Follow-Up	1	1	0	0
Misdosed	1	1	0	0
Potentially Misdosed	4	4	0	0
Prohibited Medication	13	4	4	5
Study Diary Not Returned	1	1	0	0
Study Medication and Diary Not Returned	1	0	0	1
Unblinded Study Medication	14	4	1	9
Diary and Study Medication Not ReturnedPotentially Misdosed	1	1	0	0
Did Not Have 85%-120% Compliance Rate;	16	6	6	4
Did Not Have At Least 7 Days Of Treatment	33	9	11	13
Out Of Window For Visit 3	44	13	13	18
Protocol Violation	3	1	1	1
Concomitant Med during the Study	5	1	2	2

3.1.3 Demographics and Baseline ALT 0416-01-01 (Tacrolimus 0.1%)

The demographic characteristics for the FMITT population at baseline are presented in Table 3. Table 4 presents the total individual clinical signs and symptoms scores at baseline per body region for the FMITT population. Table 5 presents the frequency and percentage for the IGE scores at baseline for the FMITT population. Tables 6 and 7 present the summary and the frequency and percentage of the overall pruritus scores at baseline for the FMITT population. In addition, Table 8 presents the summary of the % total surface area affected at baseline for the FMITT population.

From these tables we conclude that gender, race, age, IGE scores, pruritus, and body surface area affected were comparable at baseline among all of the treatment groups for the FMITT population. Age, pruritus, and body surface area affected were analyzed using a general linear model with treatment and site as factors. Gender, Race and IGE scores were analyzed using a Chi-square test.

Table 3 Demographic Characteristics for the FMITT Population: ALT 0416-01-01 (Tacrolimus 0.1%)

	Total N=671	Tacrolimus 0.1% N=228	Protopic® 0.1% N=232	Placebo N=211	p-value
Gender					
Female	386	128	135	123	0.8729
Male	285	100	97	88	
Race					
Black	234	86	76	72	0.7725
White	379	124	133	122	
Other [a]	58	18	23	17	
Age (years)					
Mean (STD)	43.04 (16.83)	42.45 (16.34)	43.30 (17.04)	43.39 (17.20)	0.7598
Median	43	42	43	44	
Range	18-90	18-90	18-86	18-88	

[a] The "other" races were “Asian”, “American Indian or Alaska Native”, “Native Hawaiian or other Pacific Islander” or “Other”.

Table 4 Summary of the Total Individual Clinical Signs and Symptoms Scores at Baseline per Body Region for the FMITT Population: ALT 0416-01-01 (Tacrolimus 0.1%)

	Total N=671	Tacrolimus 0.1% N=228	Protopic® 0.1% N=232	Placebo N=211	p-value[a]
Head and Neck					
Mean (Std)	4.17 (4.86)	4.26 (4.80)	4.17 (4.89)	4.08 (4.90)	0.7257
Median	1.0	2.5	1.0	0.0	
Range	0-18	0-16	0-16	0-18	
Upper Extremities					
Mean (Std)	8.73 (4.62)	8.59 (4.55)	8.83 (4.81)	8.76 (4.51)	0.8229
Median	9.0	9.0	9.0	9.0	
Range	0-18	0-18	0-18	0-18	
Trunk					
Mean (Std)	6.17 (5.16)	6.11 (5.28)	6.30 (5.15)	6.11 (5.06)	0.8911
Median	7.0	7.0	7.0	7.0	
Range	0-18	0-17	0-18	0-18	
Lower Extremities					
Mean (Std)	8.06 (5.20)	7.78 (5.15)	8.18 (5.34)	8.24 (5.11)	0.6841
Median	9.0	8.0	9.0	9.0	
Range	0-18	0-18	0-18	0-18	

[a] p-values were obtained from using a general linear model with treatment and site as factors.

Table 5 Frequency and Percentage of the Investigator's Global Evaluation (IGE) at Baseline for the FMITT Population: ALT 0416-01-01 (Tacrolimus 0.1%)

IGE Score[a]	Grade	Total N=671	Tacrolimus 0.1% N=228	Protopic® 0.1% N=232	Placebo N=211	p-value[b]
3	Moderate	598 (89.12%)	205 (89.91%)	201 (86.64%)	192 (91.00%)	0.3032
4	Severe	73 (10.88%)	23 (10.09%)	31 (13.36%)	19 (9.00%)	

[a] no subject had IGE score of 0,1 or 2 (Grade Clear, Almost Clear and Mild respectively)
[b] p-values were obtained using a Chi-square test

The percentage of the IGE scores at baseline for the FMITT population is illustrated in Figure 1. The figure shows that the IGE scores at baseline are comparable among all of the treatment groups in the FMITT population.

Figure 1 Percent of the IGE Scores at Baseline for the FMITT Population: ALT 0416-01-01 (Tacrolimus 0.1%)

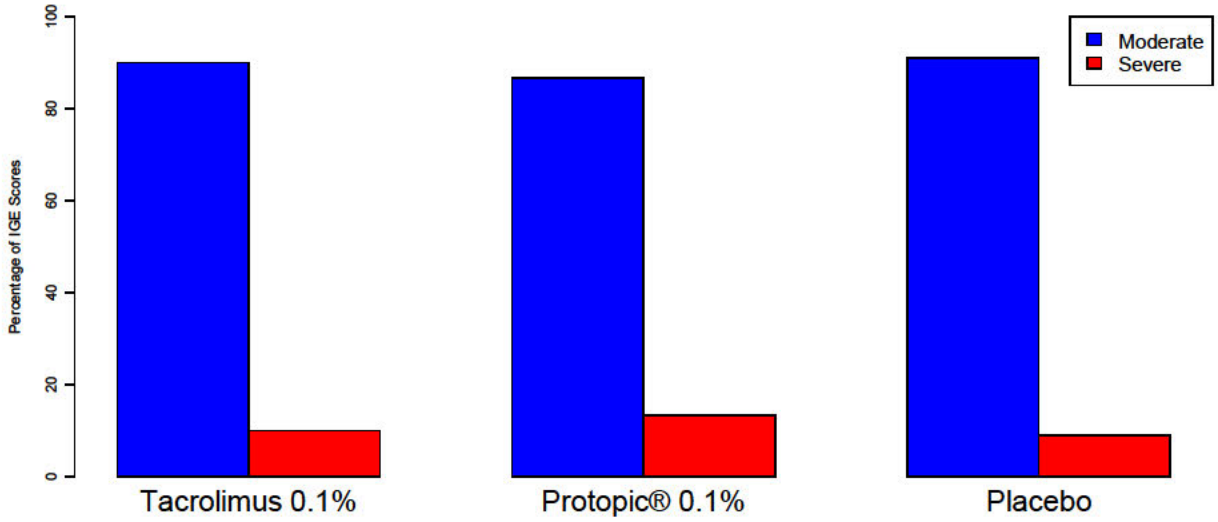


Table 6 Summary of the Pruritus Scores at Baseline for the FMITT: ALT 0416-01-01 (Tacrolimus 0.1%)

	Total N=671	Tacrolimus 0.1% N=228	Protopic® 0.1% N=232	Placebo N=211	p-value[a]
Pruritus (Itching)					
Mean (STD)	2.41 (0.67)	2.40 (0.67)	2.42 (0.69)	2.40 (0.64)	0.9766
Median	2.0	2.0	3.0	2.0	
Range	0-3	0-3	0-3	1-3	

[a] p-values were obtained from using a general linear model with treatment and site as factors.

Table 7 Frequency and Percentage of the Overall Pruritus Scores at Baseline for the FMITT Population: ALT 0416-01-01 (Tacrolimus 0.1%)

Pruritus Score	Grade	Total N=671	Tacrolimus 0.1% N=228	Protopic® 0.1% N=232	Placebo N=211
0	None	7 (1.04%)	3 (1.32%)	4 (1.72%)	0 (0.00%)
1	Mild	47 (7.00%)	15 (6.58%)	15 (6.47%)	17 (8.06%)
2	Moderate	283 (42.18%)	97 (42.54%)	93 (40.09%)	93 (44.08%)
3	Severe	334 (49.78%)	113 (49.56%)	120 (51.72%)	101 (47.87%)

Table 8 Summary of % Total Body Surface Area Affected at Baseline for the FMITT Population: ALT 0416-01-01 (Tacrolimus 0.1%)

% Body Surface Area	Total N=671	Tacrolimus 0.1% N=228	Protopic®0.1% N=232	Placebo N=211	p-value[a]
Mean (STD)	22.34 (17.65)	22.38 (17.69)	22.56 (18.28)	22.05 (16.97)	0.6687
Median	15	15	16	15	
Range	10-99	10-99	10-97	10-99	

[a] p-values were obtained from using a general linear model with treatment and site as factors

Demographic and baseline characteristics for the FPP populations were similar to those of the FMITT population.

3.1.4 Statistical methodologies (Tacrolimus Ointment 0.1%)

Statistical analysis methods

Efficacy Analysis

All treatment arms should be similar for signs/symptoms scores at the enrollment visit. The active treatments should be more distinguishable from placebo as the study progresses. The efficacy analyses for the proportion of subjects with treatment success were carried out by using Fisher's exact test (two-sided) for each active treatment versus placebo with two-sided significance level of $\alpha = 0.05$.

Equivalence Analysis

Based on the usual method used in the Office of Generic Drugs (OGD) for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within -0.20 to 0.20 in order to establish equivalence. The overall success rates at Visit 3 in the FPP populations were used as the primary outcomes for the clinical equivalence analysis.

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -0.20$
or $p_T - p_R > 0.20$

versus

H_A : $-0.20 \leq p_T - p_R \leq 0.20$

where

p_T = success rate of test treatment and p_R = success rate of reference treatment.

Let

n_T = sample size of test treatment, n_R = sample size of reference treatment,

and

$$se = (\hat{p}_T(1-\hat{p}_T)/n_T + \hat{p}_R(1-\hat{p}_R)/n_R)^{1/2}$$

where

$\hat{p}_T$ = observed success rates for the test treatment and

$\hat{p}_R$ = observed success rates for reference treatment.

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using the Wald test with Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\, se - (1/n_T + 1/n_R)/2$$
$$U = (\hat{p}_T - \hat{p}_R) + 1.645\, se + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

3.1.5 Results and conclusions (Tacrolimus Ointment 0.1%)

3.1.5.1 Sponsor's analysis results (Tacrolimus Ointment 0.1%)

Table 9 below summarizes the results of the sponsor's analyses. Based on these results, the sponsor concluded that the equivalence test passed for the SPP for the proportion of subjects with treatment success at Visit 3 (Day 14 (-1/+3 Days)). Also, that the two active treatments are statistically significantly better than the Placebo in the SMITT population. It is important to note that the definition of clinical success, defined by the sponsor as the proportion of subjects in each treatment group who had an IGE rating of "Clear" or "Almost Clear" for atopic dermatitis.

Table 9 Efficacy and Equivalence Analyses for the Proportion of Subjects with Treatment success at Visit 3 (Day 14 (-1/+3 Days)) per Sponsor: ALT 0417-01-01 (Tacrolimus 0.1%)

Sponsor's Population	Test[a] % successes (No. of successes /total)	Reference[a] % successes (No. of successes /total)	Placebo[a] % successes (No. of successes /total)	p-value[b] for Test vs. Placebo	p-value[b] for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)
SPP	49.52 (104/210)	57.35 (121/211)	34.36 (67/195)			-16.271%, 0.627%
SMITT	48.25 (124/257)	54.76 (138/252)	33.33 (83/249)	<0.001	<0.001	

[a] The rate of success equals the number of successes divided by the total number, then multiplied by 100.
[b] The p-values are from Fisher's exact test (two-sided).

A last-observation-carried-forward (LOCF) approach was used for missing efficacy data in the SMITT population and for SPP subjects who discontinued due to lack of treatment effect.

3.1.5.2 Reviewer's results (Tacrolimus Ointment 0.1%)

Efficacy and equivalence analysis results

Table 10 summarizes the results of the efficacy and equivalence analysis for the proportion of subjects with treatment success at the end of treatment Visit 3 (Day 14 (-1/+3 Days)) for the FMITT and FPP populations respectively. Based on these results, we conclude that the equivalence test passed for the FPP population for the proportion of subjects with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the Investigator's Global Assessment of Disease Severity) at the end of treatment Visit 3 (Day 14 (-1/+3 Days)). Also, using Fisher's exact test (two-sided) we conclude that the two active treatments are statistically significantly better than the Placebo in the FMITT population.

Table 10 Efficacy and Equivalence Analyses for the Proportion of Subjects with Treatment success1 at Visit 3 (Day 14 (-1/+3 Days)) for the FDA Populations: ALT 0416-01-01 (Tacrolimus 0.1%)

Population	Test[a] % successes (No. of successes /total)	Reference[a] % successes (No. of successes /total)	Placebo[a] % successes (No. of successes /total)	p-value[b] for Test vs. Placebo	p-value[b] for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
FPP	51.38 (93/181)	57.37 (109/190)	33.76 (53/157)			-15.023%, 3.048%	Yes
FMITT	49.56 (113/228)	53.88 (125/232)	33.18 (70/211)	< 0.001	< 0.001		

[a]The rate of success equals the number of successes divided by the total number, then multiplied by 100.
[b]The p-values are from Fisher's exact test (two-sided).

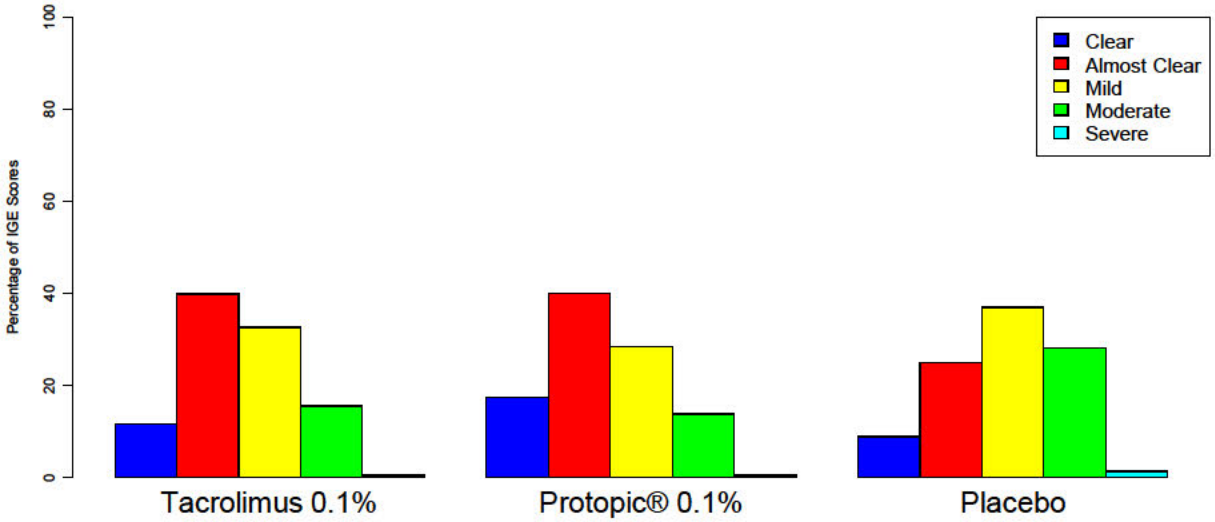
The frequency and percentage of the IGE scores at Visit 3 (Day 14 (-1/+3 Days)) for the FPP population is summarized in Table 11. A similar table for the FMITT population is found in Appendix 1, Table 27.

Table 11 Frequency and Percentage of the IGE Scores at Visit 3 (Day 14 (-1/+3 Days)) for the FPP Population: ALT 0416-01-01 (Tacrolimus 0.1%)

IGE Score	Grade	Total N=528	Tacrolimus 0.1% N=181	Protopic® 0.1% N=190	Placebo N=157
0	Clear	68 (12.88%)	21 (11.60%)	33 (17.37%)	14 (8.92%)
1	Almost Clear	187 (35.42%)	72 (39.78%)	76 (40.00%)	39 (24.84%)
2	Mild	171 (32.39%)	59 (32.60%)	54 (28.42%)	58 (36.94%)
3	Moderate	98 (18.56%)	28 (15.47%)	26 (13.68%)	44 (28.03%)
4	Severe	4 (0.76%)	1 (0.55%)	1 (0.53%)	2 (1.27%)

The percentage of the IGE scores at Visit 3 (Day 14 (-1/+3 Days)) for the FPP population is illustrated in the Figure 2). The figure shows that the IGE scores at Visit 3 (Day 14 (-1/+3 Days)) are comparable for the Test versus the Reference drug and that both are better than placebo in the FPP population.

Figure 2 **Percent of the IGE Scores at Visit 3 (Day 14 (-1/+3 Days)) for the FPP Population: ALT 0416-01-01 (Tacrolimus 0.1%)**



The frequency and percentage of the overall pruritus scores at Visit 3 (Day 14 (-1/+3 Days)) for the FPP population is summarized in Table 12. A similar table for the FMITT population is found in Appendix 1, Table 28.

Table 12 **Frequency and Percentage of the Overall Pruritus Scores at Visit 3 (Day 14 (-1/+3 Days)) for the FPP Population: ALT 0416-01-01 (Tacrolimus 0.1%)**

Pruritus Score	Grade	Total N=528	Tacrolimus 0.1% N=181	Protopic® 0.1% N=190	Placebo N=157
0	None	165 (31.25%)	56 (30.94%)	65 (34.21%)	44 (28.03%)
1	Mild	222 (42.05%)	81 (44.75%)	82 (43.16%)	59 (37.58%)
2	Moderate	99 (18.75%)	36 (19.89%)	31 (16.32%)	32 (20.38%)
3	Severe	42 (7.96%)	8 (4.42%)	12 (6.32%)	22 (14.01%)

The summary of the % total body surface area affected at Visit 3 (Day 14 (-1/+3 Days)) for the FPP population is summarized in Table 13. A similar table for the FMITT population is found in Appendix 1, Table 29.

Table 13 Summary of % Total Body Surface Area Affected at Visit 3 (Day 14 (-1/+3 Days)) for the FPP Population: ALT 0416-01-01 (Tacrolimus 0.1%)

% Body Surface Area	Total N=528	Tacrolimus 0.1% N=181	Protopic® 0.1% N=190	Placebo N=157	p-value[a]
Mean (STD)	13.16 (14.86)	13.50 (15.73)	12.55 (15.50)	13.52 (12.98)	0.7599
Median	10	10	10	10	
Range	0-90	0-90	0-90	0-80	

[a] p-values were obtained from using a general linear model with treatment and site as factors

3.2 Evaluation of Study ALT 0417-01-01 (Tacrolimus Ointment 0.03%)

3.2.1 Study Design and Endpoints Objectives (Tacrolimus Ointment 0.03%)

Objectives

The objectives of this study were to compare the safety and efficacy profiles of Nycomed US Inc.'s tacrolimus ointment, 0.03% to those of Astellas Pharma US, Inc.'s PROTOPIC® (tacrolimus) Ointment 0.03% and to demonstrate the superior efficacy of the two active ointments over that of the Nycomed US Inc. Vehicle (placebo) in the treatment of atopic dermatitis in subjects at least 8 years old.

Study Design

This was a multi-center, randomized, double-blind, vehicle-controlled, parallel-group study conducted in subjects at least 8 years of age with moderate to severe atopic dermatitis with ≥ 10% body surface area (BSA) affected. Nine hundred (900) subjects were enrolled and randomized in 1:1:1 ratio to one of the three treatment groups. The three ointments were the test product Nycomed US Inc.'s generic tacrolimus ointment 0.03%, the reference product Astellas Pharma US, Inc.'s PROTOPIC® (tacrolimus) Ointment 0.03% and the placebo Nycomed US Inc.'s Vehicle. Subjects applied the study medication topically twice-daily (morning and evening, after washing with non-medicated, non-irritating soap) approximately 12 hours apart for four weeks (28 days). Subjects returned to the office for follow up evaluations at Day 4 (-0, +2 days/Visit 2), Day 14 (± 3 days/Visit 3) and Day 28 (± 3 days/Visit 4). A blood sample was drawn for the assay of tacrolimus concentration at Visit 2. The signs and symptoms of the target sites were assessed and the investigator's evaluations were recorded at Visit 2, Visit 3 and Visit 4. The subjects's concomitant medications were assessed and recorded, along with any adverse events (AEs). Subjects returned at each visit with the study medication and subject diaries. Compliance with study medication applications were assessed via the subject diary, and at Visit 4, all study medication was collected.

Treatments

A total of 900 subjects were enrolled in the study. They were randomized to receive the test product Nycomed US Inc.'s generic tacrolimus ointment 0.03%, the reference product Astellas Pharma US, Inc.'s PROTOPIC® (tacrolimus) Ointment 0.03% and the placebo Nycomed US Inc.'s Vehicle in a 1:1:1 ratio respectively.

Article	Description
Test	Tacrolimus Ointment, 0.03% Manufacturer: Nycomed US Inc. Lot #s Z431 and 710C
Reference	Protopic® (tacrolimus) Ointment 0.03% Manufactured: Astellas Pharma US, Inc Lot #s 26471 and 30221
Placebo	Vehicle of Test product Manufacturer: Nycomed US Inc. Lot #s Z034 and 711C

Outcome variables

Investigator's Global Evaluation: The investigator made an independent global evaluation for overall assessment of the subject's atopic dermatitis. The same investigator, to the greatest extent possible, was to perform the Investigator's Global Evaluation (IGE) at each visit. This assessment incorporated evaluations for erythema, induration/papulation, amount of involvement, and a general clinical assessment.

The IGE was evaluated using the following scale:

Score	Grade	Definition
0	Clear	Minor, residual discoloration, no erythema or induration/papulation, no oozing/crusting
1	Almost Clear	Trace, faint pink erythema with almost no induration/population and no oozing/crusting
2	Mild	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation, possibly with some oozing/crusting
4	Severe	Deep/bright red erythema with severe induration/papulation with oozing/crusting

In addition to the IGE the following signs and symptoms were to be evaluated: Erythema, Induration/Papulation, Lichenification, Scaling, Oozing/Crusting, and Excoriation

The signs and symptoms were each graded by the sponsor on a scale of 0 to 3 as follows:

Erythema defined by the sponsor as redness; residual hyperpigmentation, hypopigmentation, pigmented macules, or diffuse slight pink coloration were not included as erythema

Score	**Grade**	**Definition**
0	None	No erythema present
1	Mild	Slight erythema, very light-pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red

Induration/papulation (defined as inflammation; swelling)

Score	**Grade**	**Definition**
0	None	No elevation
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation

Lichenification (defined as thickening upper layers of skin)

Score	**Grade**	**Definition**
0	None	No lichenification
1	Mild	Slight thickening of the skin discernable only by touch and with skin markings minimally exaggerated
2	Moderate	Definite thickening of the skin with skin marking exaggerated so that they form a visible criss-cross pattern
3	Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern

Scaling (defined as flakes or shedding of the stratum corneum)

Score	**Grade**	**Definition**
0	None	No evidence of scaling
1	Mild	Occasional fine, flaky scale predominates
2	Moderate	Coarse scale predominates
3	Severe	Thick, coarse, crusted scale predominates

Oozing/crusting (defined as seeping of tissue fluid; dried blood or tissue fluids)

Score	Grade	Definition
0	None	No evidence of oozing/crusting
1	Mild	Evidence of exudation
2	Moderate	Serous brown, yellow, or green exudations and/or drying of the discharge
3	Severe	Many dry scabs and/or exudations

Excoriation (defined as the loss of the top layer of the skin caused by scratching)

Score	Grade	Definition
0	None	No evidence of excoriation
1	Mild	Scant evidence of excoriation with no signs of deeper skin damage (erosion, crust)
2	Moderate	Several linear marks on the skin with some showing evidence of deeper skin injury (erosion, crust)
3	Severe	Many erosive or crusty lesions

Pruritus Assessment: Subjects evaluated their overall itching/scratching/discomfort in the preceding 24 hours based on the following scale:

Score	Grade	Definition
0	None	None
1	Mild	Occasional, slight itching/scatching
2	Moderate	Constant or intermittent itching/scratching/discomfort that does not disturb sleep
3	Severe	Bothersome itching/scratching/discomfort that disturbs sleep

Clinical response was evaluated at Visit 4/Day28 (±3 Days) by the IGE scores.

Clinical Response

Clinical success is defined by the FDA medical reviewer according to the Draft Guidance on Tacrolimus Ointment/Topical, 0.03% (March 2012) as a grade of "Clear" or "Almost Clear"; a score of 0 or 1 within all treatment areas based on the Investigator's Global Assessment of Disease Severity which is the same as the sponsor's IGE at the end of treatment (week 4 visit; study day 29) for atopic dermatitis. The sponsor's definition of clinical response is accepted by the medical reviewer in accordance with the Draft Guidance. The only discrepancy is that the

end of treatment assessment was done on Day 28 by the sponsor instead of Day 29 based on the draft guidance. This was accepted by the medical reviewer.

Endpoints

The primary endpoint of this study is the proportion of subjects in the per-protocol population with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the Investigator's Global Assessment of Disease Severity (which is the same as the sponsor's IGE) at the end of treatment (Week 4 visit; study day 28). Note that the sponsor's primary endpoint is in accordance with the Draft Guidance on Tacrolimus Ointment/Topical, 0.03% (March 2012) and is acceptable.

The secondary endpoints are the change in severity from baseline to Visit 4 Day 28 (±3 Days) of four individual signs and symptoms of atopic dermatitis (i.e., erythema, induration/papulation, lichenification and pruritus) and are considered supportive information. It is recommended that pruritus be assessed by questioning the subject or the subject's parent/legal guardian regarding the intensity of overall itching/scratching/discomfort in the 24 hours prior to the visit. The secondary endpoints are supportive information the medical reviewer did not request analysis.

3.2.2 Subject Disposition (Tacrolimus Ointment 0.03%)

Nine hundred (900) subjects were enrolled and randomized in 1:1:1 ratio to one of the three treatment groups. The sponsor's ITT (SITT), MITT (SMITT) and PP (SPP) populations had 899, 874 and 692 subjects respectively. The FDA's MITT (FMITT) and PP (FPP) populations have 716 and 556 respectively. The differences between the Sponsor's populations and the FDA's populations are due to excluding more subjects as follows:

FMITT:

In addition to the twenty six (26) subjects excluded from the enrolled and randomized population to form the SMITT population, a total of one hundred fifty eight (158) subjects in the SMITT population were excluded to form the FMITT population: Fifty four (54) subjects in the test treatment group, forty seven (47) subjects in the reference treatment group and fifty seven (57) subjects from the Placebo group. These subjects were excluded because of one or more of the following reasons:

- Subjects had inappropriate washout period for an exclusionary medication prior to study entry and continued to use the prohibited concomitant medication during the study.
- Subjects had an exclusionary medical condition.
- The medical monitor disagreed with the investigator's assessment of inclusion/exclusion criteria.

A listing of the subjects excluded from the SMITT to form the FMITT population is found in Appendix 2, Table 36.

FPP:

In addition to the two hundred and eight subjects (208) excluded from the enrolled and randomized population to form the SPP population, a total of one hundred and thirty six (136) subjects in the SPP population were excluded to form the FPP population: Forty four (44) subjects in the test treatment group, forty subjects (40) in the reference treatment group and fifty two (52) subjects from the Placebo group. These subjects were excluded because of one or more of the following reasons:

- Subjects had inappropriate washout period for an exclusionary medication prior to study entry and continued to use the prohibited concomitant medication during the study.
- Subjects used prohibited concomitant medication during the study.
- Subjects had an exclusionary medical condition.

A listing of the subjects excluded from the SMITT to form the FMITT population is found in Appendix 2, Table 37.

The subject dispositions for the sponsor's and the FDA's populations are given in Table 14 and Table 15 respectively.

Table 14 Number of Subjects in the Sponsor's ITT, MITT and PP Populations: ALT 0417-01-01 (Tacrolimus 0.03%)

	Total	Tacrolimus 0.03%	Protopic ®0.03%	Placebo
Enrolled and Randomized	**900**	**303**	**297**	**300**
Total sponsor ITT population	899	302	297	300
Total exclusion from the sponsor's ITT population	1	1	0	0
Total sponsor MITT population	**874**	**294**	**287**	**293**
Total exclusion from the sponsor's MITT population	26	9	10	7
Reason for exclusion from sponsor's MITT				
Did Not Have Any Post baseline IGE	21	7	7	7
Did Not Meet Inclusion/Exclusion Criteria	4	1	3	0
Not in ITT; Did Not Have Any Post baseline IGE	1	1	0	0
Total sponsor PP population	**692**	**226**	**238**	**228**
Total Exclusion from the sponsor's PP population	208	77	59	72
Reason for exclusion from sponsor's PP				
Excluded from MITT	26	9	10	7
Diary Not Returned	2	1	1	0
Infected AD	1	0	0	1
Sponsor and Medical Monitor disagrees with Inclusion/Exclusion Criteria	1	0	0	1
Misdosed	4	0	0	4
Unblinded Study Medication	9	7	1	1
Potentially Misdosed	6	0	0	6
Prohibited Medication	11	4	3	4
Did Not Have 85%-120% Compliance Rate;	15	7	7	1
Did Not Have At Least 14 Days Of Treatment;	56	16	13	27
Out Of Window For Visit 4	67	27	21	19
Protocol Violation	10	6	3	1

Table 15 Number of Subjects in the FDA's MITT and PP Populations: ALT 0417-01-01 (Tacrolimus 0.03%)

	Total	Tacrolimus 0.03%	Protopic ®0.03%	Placebo
Enrolled and Randomized	**900**	**303**	**297**	**300**
Total FDA MITT population	**716**	**240**	**240**	**236**
Total exclusion from the FDA's MITT population	184	63	57	64
Reason for exclusion from FDA's MITT				
Did Not Have Any Post baseline IGE	21	7	7	7
Did Not Meet Inclusion/Exclusion Criteria	4	1	3	0
Not in ITT; Did Not Have Any Post baseline IGE	1	1	0	0
Did Not Meet Inclusion/Exclusion Criteria	2	1	0	1
The use of exclusionary Medication with no or inappropriate washout period prior to the study entry.	12	4	3	5
The use of exclusionary Medication with no or inappropriate washout period and continued to use the prohibited concomitant medication during the study	128	43	37	48
Has exclusionary medical condition.	8	4	3	1
The use of exclusionary Medication with no or inappropriate washout period and continued to use the prohibited concomitant medication during the study with exclusionary medical condition	4	0	3	1
The use of prohibited concomitant medication during the study with exclusionary medical condition	3	2	1	0
The use of prohibited concomitant medication with no or inappropriate washout period prior to the study entry with exclusionary medical condition	1	0	0	1
Total FDA PP population	**556**	**182**	**198**	**176**
Total Exclusion from the FDA PP population	344	121	99	124
Reason for exclusion from FDA's PP				
Excluded from FDA MITT	184	63	57	64
Diary Not Returned	2	1	1	0
Infected AD	1	0	0	1
Misdosed	4	0	0	4
Unblinded Study Medication	7	5	1	1
Potentially Misdosed	5	0	0	5
Prohibited Medication	25	8	5	12
Did Not Have 85%-120% Compliance Rate;	12	6	5	1
Did Not Have At Least 14 Days Of Treatment;	42	13	10	19
Out Of Window For Visit 4	55	21	18	16
Protocol Violation	7	4	2	1

3.2.3 Demographics and Baseline ALT 0417-01-01 (Tacrolimus 0.03%)

The demographic characteristics for the FMITT population at baseline are presented in Table 16. Table 17 presents the total individual clinical signs and symptoms scores at baseline per body region for the FMITT population. Table 18 presents the frequency and percentage of the Investigator's Global Evaluation at baseline for the FMITT Population. Table 19 and 20 present the summary and the frequency and percentage of the overall pruritus scores at baseline for the FMITT population respectively. In addition, Table 21 presents the summary of the % total surface area affected at baseline for the FMITT population.

From these tables we conclude that gender, race, age, IGE scores, pruritus and body surface area affected were comparable at baseline among the treatment groups for the FMITT population Age was analyzed using a general linear model with treatment and site as factors. Pruritus and body surface area affected were analyzed using a general linear model with treatment as a factor. Gender, Race and IGE scores were analyzed using a Chi-square test.

Table 16 Demographic Characteristics in the FMITT Population: ALT 0417-01-01 (Tacrolimus 0.03%)

	Total N=716	Tacrolimus 0.03% N=240	Protopic®0.03% N=240	Placebo N=236	p-value
Gender					
Female	452	145	157	150	0.5176
Male	264	95	83	86	
Race					
Black	322	116	106	100	0.2596
White	348	104	122	122	
Other [a]	46	20	12	14	
Age (years)					
Mean (STD)	28.58 (17.99)	28.13 (17.68)	28.83 (18.84)	28.78 (17.47)	0.7289
Median	23.5	23.5	21	24	
Range	8-83	8-83	8-82	8-80	

[a] The "other" races were "Asian", "American Indian or Alaska Native", "Native Hawaiian or other Pacific Islander" or "Other".

Table 17 Summary of the Total Individual Clinical Signs and Symptoms Scores at Baseline per Body Region for the FMITT Population: ALT 0417-01-01 (Tacrolimus 0.03%)

	Total N=716	Tacrolimus 0.03% N=240	Protopic®0.03% N=240	Placebo N=236	p-value[a]
Head and Neck					
Mean (Std)	5.35 (4.90)[b]	5.58 (4.91)[b]	4.99 (4.93)	5.49 (4.85)	0.7657
Median	5	5	4.5	5.0	
Range	0-18	0-18	0-18	0-18	
Upper Extremities					
Mean (Std)	9.62 (4.16)	9.44 (4.23)	9.62 (4.15)	9.81 (4.11)	0.3582
Median	10.0	10	10.0	11.0	
Range	0-18	0-18	0-18	0-18	
Trunk					
Mean (Std)	6.43 (4.90)	6.28 (4.89)	6.40 (5.01)	6.61 (4.82)	0.4729
Median	7.0	7.0	6.0	7.0	
Range	0-18	0-17	0-18	0-18	
Lower Extremities					
Mean (Std)	8.95 (4.9)	8.74 (5.09)	9.15 (4.85)	8.97 (4.77)	0.6344
Median	10.0	9	10.0	10.0	
Range	0-18	0-18	0-18	0-18	

[a] p-values were obtained from using a general linear model with treatment and site as factors.
[b] Subject (b) (6) in the test treatment group had missing Erythema, Induration/Papulation, Lichenification, Scaling, Oozing/Crusting, and Excoriation for the Head and Neck so the mean, std, median and range was calculated based on 715 subjects for the total values and 239 subjects in the Tacrolimus group.

Table 18 Frequency and Percentage of the Investigator's Global Evaluation at Baseline for the FMITT Population: ALT 0417-01-01 (Tacrolimus 0.03%)

IGE Score[a]	Grade	Total N=716	Tacrolimus 0.03% N=240	Protopic®0.03% N=240	Placebo N=236	p-value[b]
3	Moderate	639 (89.25%)	212 (88.33%)	216 (90.00%)	211 (89.41%)	0.8366
4	Severe	77 (10.75%)	28 (11.67%)	24 (10.00%)	25 (10.59%)	

[a] p-values were obtained using a Chi-square test.
[b] No subject had an IGE score of 0,1 or 2 (Grade Clear, Almost Clear or Mild) respectively.

The percentage of the IGE scores at baseline for the FMITT population is illustrated in Figure 2. The figure shows that the IGE scores at baseline are comparable among all of the treatment groups in the FMITT population.

Figure 3 **Percent of the IGE Scores at Baseline for the FMITT Population: ALT 0417-01-01 (Tacrolimus 0.03%)**

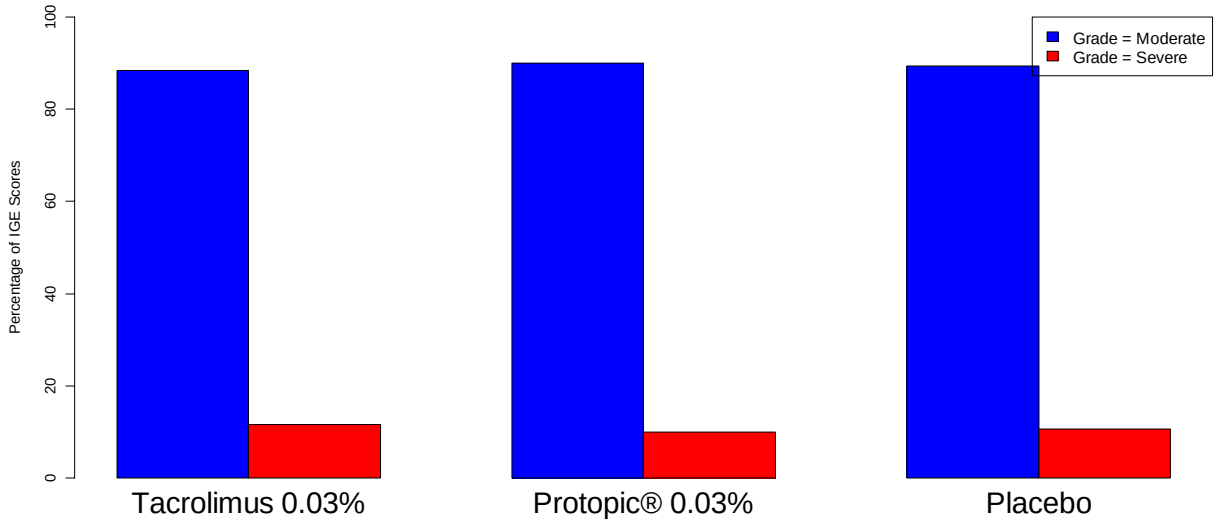


Table 19 **Summary of the Pruritus Scores at Baseline for the FMITT: ALT 0417-01-01 (Tacrolimus 0.03%)**

Pruritus (Itching)	Total N=716	Tacrolimus 0.03% N=240	Protopic ®0.03% N=240	Placebo N=236	p-value[a]
Mean (Std)	2.43 (0.65)	2.38 (0.70)	2.47 (0.62)	2.45 (0.63)	0.2507
Median	3.0	2.0	3.0	3.0	
Range	0-3	0-3	0-3	1-3	

[a] p-values were obtained from using a general linear model with treatment as a factor.

Table 20 **Frequency and Percentage of the Overall Pruritus Scores at Baseline for the FMITT Population: ALT 0417-01-01 (Tacrolimus 0.03%)**

Pruritus Score	Grade	Total N=716	Tacrolimus 0.03% N=240	Protopic ®0.03% N=240	Placebo N=236
0	None	3 (0.42%)	2 (0.83%)	1 (0.42%)	0 (0%)
1	Mild	55 (7.68%)	25 (10.42%)	13 (5.42%)	17 (7.20%)
2	Moderate	288 (40.22%)	94 (39.17%)	99 (41.25%)	95 (40.25%)
3	Severe	370 (51.68%)	119 (49.58%)	127 (52.92%)	124 (52.54%)

Table 21 Summary of % Total Body Surface Area Affected at Baseline for the FMITT Population: ALT 0417-01-01 (Tacrolimus 0.03%)

% Body Surface Area	Total N=716	Tacrolimus 0.03% N=240	Protopic ®0.03% N=240	Placebo N=236	p-value[a]
Mean (STD)	21.36 (16.53)	22.04 (18.57)	20.81 (15.12)	21.24 (15.73)	0.7094
Median	15	15	15	15	
Range	10-90	10-90	10-80	10-90	

[a] p-values were obtained from using a general linear model with treatment as factor

Demographic and baseline characteristics for the FPP population were similar to those of the FMITT population.

3.2.4 Statistical methodologies (Tacrolimus Ointment 0.03%)

Statistical analysis methods

Efficacy Analysis

All treatment arms should be similar for signs/symptoms scores at the enrollment visit. The active treatments should be more distinguishable from placebo as the study progresses. The efficacy analyses for the proportion of subjects with treatment success were carried out by using Fisher's exact test (two-sided) for each active treatment versus placebo with two-sided significance level of $\alpha = 0.05$.

Equivalence Analysis

Based on the usual method used in the Office of Generic Drugs (OGD) for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within -0.20 to 0.20 in order to establish equivalence. The overall success rates at visit 4 in the FPP populations were used as the primary outcomes for the clinical equivalence analysis.

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -0.20$

or $p_T - p_R > 0.20$

versus

H_A : $-0.20 \leq p_T - p_R \leq 0.20$

where

p_T = success rate of test treatment and p_R = success rate of reference treatment.

Let

n_T = sample size of test treatment, n_R = sample size of reference treatment,

and

$$se = (\hat{p}_T(1-\hat{p}_T)/n_T + \hat{p}_R(1-\hat{p}_R)/n_R)^{1/2}$$

where

$\hat{p}_T$ = observed success rates for the test treatment and

$\hat{p}_R$ = observed success rates for reference treatment.

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using the Wald test with Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$
$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

3.2.5 Results and conclusions (Tacrolimus Ointment 0.03%)

3.2.5.1 Sponsor's analysis results (Tacrolimus Ointment 0.03%)

Table 22 below summarizes the results of the sponsor's analyses. Based on these results the sponsor concluded that the equivalence test passed for the SPP for the proportion of subjects with treatment success at Visit 4 (Day 28 (±3 Days)). Also, that the two active treatments are statistically significantly better than the Placebo in the SMITT population. It is important to note that the definition of clinical success, defined by the sponsor as an endpoint was the proportion of subjects in each treatment group who had an IGE rating of "Clear" or "Almost Clear" for atopic dermatitis.

Table 22 Efficacy and Equivalence Analyses for the Proportion of Subjects with Treatment success at Visit 4 (Day 28(±3 Days)) per Sponsor: ALT 0417-01-01 (Tacrolimus 0.03%)

Sponsor's Population	Test[a] % successes (No. of successes /total)	Reference[a] % successes (No. of successes /total)	Placebo[a] % successes (No. of successes /total)	p-value[b] for Test vs. Placebo	p-value[b] for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
SPP	54.42 (123/226)	54.62 (130/238)	37.72 (86/228)			-8.236%, 7.842%	Yes
SMITT	51.02 (150/294)	52.96 (152/287)	32.42 (95/293)	<0.001	<0.001		

[a] The rate of success equals the number of successes divided by the total number, then multiplied by 100.
[b] The p-values are from Fisher's exact test (two-sided).

A last-observation-carried-forward (LOCF) approach was used for missing efficacy data in the SMITT population and for SPP subjects who discontinued due to lack of treatment effect.

3.2.5.2 Reviewer's results (Tacrolimus Ointment 0.03%)

Efficacy and equivalence analysis results

Table 23 summarizes the results of the efficacy and equivalence analysis for the proportion of subjects with treatment success at the end of treatment Visit 4 (Day 28 (±3 Days)) for the FMITT and FPP populations respectively. Based on these results we conclude that the equivalence test passed for the FPP population for the proportion of subjects with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the Investigator's Global Assessment of Disease Severity) at the end of treatment Visit 4 (Day 28 (±3 Days)). Also, using Fisher's exact test (two-sided) we conclude that the two active treatments are statistically significantly better than the Placebo in the FMITT population.

Table 23 Efficacy and Equivalence Analyses for the Proportion of Subjects with Treatment success1 at Visit 4 (Day 28 (±3 Days)) for the FDA Populations: ALT 0417-01-01 (Tacrolimus 0.03%)

Population	Test[a] % successes (No. of successes /total)	Reference[a] % successes (No. of successes /total)	Placebo[a] % successes (No. of successes /total)	p-value[b] for Test vs. Placebo	p-value[b] for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
FPP	54.40 (99/182)	53.03 (105/198)	37.50 (66/176)			-7.584, 10.314	Yes
FMITT	50.83 (122/240)	52.50 (126/240)	32.20 (76/236)	< 0.001	< 0.001		

[a]The rate of success equals the number of successes divided by the total number, then multiplied by 100.
[b]The p-values are from Fisher's exact test (two-sided).

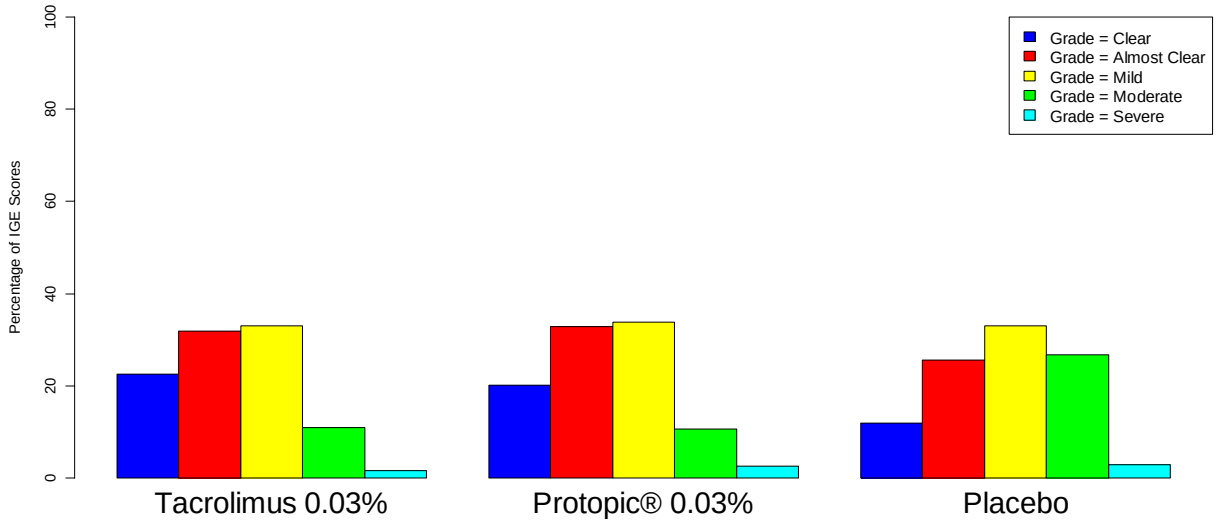
The frequency of the IGE scores at Visit 4 (Day 28 (±3 Days)) for the FPP population is summarized in Table 24. A similar table for the FMITT population is found in Appendix 2, Table 33.

Table 24 Frequency and Percentage of the IGE Scores at Visit 4 (Day 28 (± 3 Days)) for the FPP Population: ALT 0417-01-01 (Tacrolimus 0.03%)

IGE Score	Grade	Total N=556	Tacrolimus 0.03% N=182	Protopic® 0.03% N=198	Placebo N=176
0	Clear	102 (18.35%)	41 (22.53%)	40 (20.20%)	21 (11.93%)
1	Almost Clear	168 (30.22%)	58 (31.87%)	65 (32.83%)	45 (25.57%)
2	Mild	185 (33.27%)	60 (32.97%)	67 (33.84%)	58 (32.95%)
3	Moderate	88 (15.83%)	20 (10.99%)	21 (10.61%)	47 (26.70%)
4	Sever	13 (2.34%)	3 (1.65%)	5 (2.53%)	5 (2.84%)

The percentage of the IGE scores at Visit 4 (Day 28 (±3 Days)) for the FPP population is illustrated in the Figure 4. The figure shows that the IGE scores at Visit 4 (Day 28 (±3 Days)) are comparable for the Test versus the Reference drug and that both are better than Placebo in the FPP population.

Figure 4 **Percent of the IGE Scores at Visit 4 (Day 28 (±3 Days)) for the FPP Population: ALT 0417-01-01 (Tacrolimus 0.03%)**



The frequency of the overall pruritus scores at Visit 4 (Day 28 (±3 Days))for the FPP population is summarized in Table 25. A similar table for the FMITT population is found in Appendix 2, Table 34.

Table 25 **Frequency and Percentage of the Overall Pruritus Scores at Visit 4 (Day 28 (±3 Days)) for the FPP Population: ALT 0417-01-01 (Tacrolimus 0.03%)**

Pruritus Score	Grade	Total N=554[a]	Tacrolimus 0.03% N=182	Protopic® 0.03% N=198	Placebo N=176
0	None	181 (32.67%)	69 (37.91%)	70 (35.71%)	42 (23.86%)
1	Mild	239 (43.14%)	82 (45.05%)	84 (42.86%)	73 (41.48%)
2	Moderate	96 (17.33%)	24 (13.19%)	31 (15.82%)	41 (23.30%)
3	Severe	38 (6.86%)	7 (3.85%)	11 (5.61%)	20 (11.36%)

[a]Two subjects (b) (6) in the reference treatment group had missing pruritus values ant Visit 4.

The summary of the total body surface area affected at Visit 3 (Day 28 (±3 Days)) for the FPP population is summarized in Table 26. A similar table for the FMITT population is found in Appendix 2, Table 35.

Table 26 Summary of % Total Body Surface Area Affected at Visit 3 (Day 28 (±3 Days)) for the FPP Population: ALT 0417-01-01 (Tacrolimus 0.03%)

% Body Surface Area	Total N=556	Tacrolimus 0.03% N=182	Protopic® 0.03% N=198	Placebo N=176	p-value[a]
Mean (STD)	10.82 (13.31)	10.20 (14.99)	9.61 (10.47)	12.84 (14.14)	0.0175
Median	8	6	7	10	
Range	0-90	0-90	0-60	0-70	

[a] p-values were obtained from using a general linear model with treatment and site as factors

4 Conclusions Conclusions

4.1 Comments on the Sponsor's Analyses

Site Pooling:

In both studies the sponsor decided to pool sites that enrolled a small number of subjects according to the following algorithm:

Step 1: If the site had the smallest cell count (treatment-by-site) of fewer than 3 subjects in the SMITT population, then the site was merged with a site that had the next smallest cell count into a new pooled site within the same geographic region. This procedure was repeated until the new pooled site had at least 3 subjects in the SMITT population for each treatment group. If several sites within the same geographic region had the same cell count of subjects, then the sites were ordered by site number, and those with the lowest site number were pooled first.

Step 2: Step 1 was repeated within each geographic region, until all new pooled sites had at least 3 subjects in the SMITT population for each treatment group.

Step 3: Analyses were completed using the newly created pooled sites.

Sites for which there were no SMITT subjects were excluded from site pooling.

The geographical regions for each site were defined as follows:

Region	**Site**
Latin America	47, 48, 49
Midwest	6, 21, 24, 27,33, 44, 51
Northeast	2, 10, 11, 17, 23, 30, 34, 36, 50
Southeast	5, 7, 8, 9, 12, 18, 25, 39, 40
Southwest	1, 3, 4, 13
West	20, 22, 28, 31, 35, 38, 41, 42, 43, 45

In our analyses reported in this review, sites were not pooled. When we explored pooling the sites according to the sponsor's algorithm, the results were not substantially different.

Packaging Error:

There was a potential for a packaging error. The potentially incorrectly dosed subjects were excluded from the PP population, but were included in the MITT population using an "Analyzed as Randomized" approach if the subject met all MITT criteria. For all safety analyses, these potentially incorrectly dosed subjects were "Analyzed as Dosed". Table 38 and Table 39 in Appendix 3 list the subjects that were misdosed for study ALT 0416-01-01 (Tacrolimus 0.1%) and study ALT 0417-01-01 (Tacrolimus 0.03%) respectively. This was acceptable to the medical reviewer.

4.2 Conclusions

4.2.1 Study ALT 0416-01-01: Bioequivalence Study for Tacrolimus Ointment 0.1% Strength

The equivalence test did pass for the FPP population for the proportion of subjects with treatment success at Visit 3 (Day 14 (-1/+3 Days)) where the treatment success was defined as the proportion of subjects in each treatment group who had an IGE rating of "Clear" or "Almost Clear" for atopic dermatitis. Also, the two active treatments are statistically significantly better than the Placebo in the FMITT.

4.2.2 Study ALT 0417-01-01: Bioequivalence Study for Tacrolimus Ointment 0.03% Strength

The equivalence test did pass for the FPP population for the proportion of subjects with treatment success at Visit 4 (Day 28 (±3 Days)) where the treatment success was defined as the proportion of subjects in each treatment group who had an IGE rating of "Clear" or "Almost Clear" for atopic dermatitis. Also, the two active treatments are statistically significantly better than the Placebo in the FMITT.

_____	_____
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HFD-700 Lillian Patrician OB

5 References

Joseph L. Fleiss, Bruce Levin, and MyungHee Cho Paik. (1981). Statistical Methods for Rates and Proportions (2nd edition). New York: Wiley-Interscience.

Schuirmann, D. J. (2008) One-Sided Tests and Confidence Bounds for the Difference between Probabilities for Matched Pairs Dichotomous Data. Presented at the Spring Meetings of the Eastern North American Region (ENAR) of the International Biometric Society, March 17, 2008 in Crystal City, VA.

Clopper, C. and Pearson, S. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413.

6 Appendix 1

The frequency and percentage of the IGE scores at Visit 3 (Day 14 (-1/+3 Days)) for the FMITT population in Study ALT 0416-01-01 (Tacrolimus 0.1 %) are summarized in Table 27 below:

Table 27 Frequency and Percentage of the IGE Scores at Visit 3 (Day 14 (-1/+3 Days)) for the FMITT Population for Study ALT 0416-01-01 (Tacrolimus 0.1 %)

IGE Score	Grade	Total N=671	Tacrolimus 0.1% N=228	Protopic® 0.1% N=232	Placebo N=211
0	Clear	73 (10.88%)	23 (10.09%)	34 (14.66%)	16 (7.58%)
1	Almost Clear	235 (35.02%)	90 (39.47%)	91 (39.22%)	54 (25.59%)
2	Mild	213 (31.74%)	75 (32.89%)	69 (29.74%)	69 (32.70%)
3	Moderate	135 (20.12%)	38 (16.67%)	32 (13.79%)	65 (30.81%)
4	Sever	15 (2.24%)	2 (0.88%)	6 (2.59%)	7 (3.32%)

The frequency and percentage of the overall pruritus scores IGE scores at Visit 3 (Day 14 (-1/+3 Days)) for the FMITT population in Study ALT 0416-01-01 (Tacrolimus 0.1 %) are summarized in Table 28 below:

Table 28 Frequency and Percentage of the Overall Pruritus Scores at Visit 3 (Day 14 (-1/+3 Days)) for the FMITT Population for Study ALT 0416-01-01 (Tacrolimus 0.1 %)

Pruritus Score	Grade	Total N=671	Tacrolimus 0.1% N=228	Protopic® 0.1% N=232	Placebo N=211
0	None	199 (29.66%)	70 (30.70%)	76 (32.76%)	53 (25.12%)
1	Mild	279 (41.58%)	105 (46.05%)	99 (42.67%)	75 (35.55%)
2	Moderate	127 (18.93%)	42 (18.42%)	35 (15.09%)	50 (23.70%)
3	Sever	66 (9.84%)	11 (4.82%)	22 (9.48%)	33 (15.64%)

The summary of the total body surface area affected at Visit 3 (Day 14 (-1/+3 Days)) for the FMITT population in Study ALT 0416-01-01 (Tacrolimus 0.1 %) are summarized in Table 29 below:

Table 29 Summary of % Total Body Surface Area Affected at Visit 3 (Day 14 (-1/+3 Days)) for the FMITT Population for Study ALT 0416-01-01 (Tacrolimus 0.1 %)

% Body Surface Area	Total N=671	Tacrolimus 0.1% N=228	Protopic® 0.1% N=232	Placebo N=211	p-value[a]
Mean (STD)	14.21 (15.87)	13.81 (15.74)	13.22 (15.55)	15.72 (16.33)	0.3360
Median	10	10	10	11	
Range	0-99	0-90	0-90	0-99	

[a] p-values were obtained from using a general linear model with treatment and site as factors

Table 30 below provides a listing of the subjects that were excluded from SMITT to form FMITT based on the FDA Medical and Statistical reviewers for ALT 0416-01-01 (Tacrolimus 0.1 %).

Table 30 Listing of Subjects Excluded from SMITT to form FMITT based on the FDA's reviewers for Study ALT 0416-01-01 (Tacrolimus 0.1 %)

Obs	SITE	SUBJID	Treatment	Reason for Exclusion
1	25	(b) (6)	Tacrolimus Ointment 0.1%	Use of the exclusionary medication valaciclovir with no washout period prior to study entry
2	12		Tacrolimus Ointment 0.1%	Use of the exclusionary medications acyclovir and hydroxyzine with no washout period prior to study entry
3	3		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
4	3		Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
5	1		Tacrolimus Ointment 0.1%	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
6	4		Tacrolimus Ointment 0.1%	Use of the exclusionary medications acyclovir and amoxicillin with no washout period prior to study entry and during the study
7	7		Tacrolimus Ointment 0.1%	Use of the exclusionary medication loratadine with no washout period prior to study entry
8	5		Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
9	5		Tacrolimus Ointment 0.1%	Use of the exclusionary medication loratadine with no washout period prior to study entry
10	18		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
11	27		Tacrolimus Ointment 0.1%	Use of the exclusionary medication desloratadine with no washout period prior to study entry
12	21		Tacrolimus Ointment 0.1%	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
13	31		Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
14	3		Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
15	3		Tacrolimus Ointment 0.1%	Use of the exclusionary medications cetirizine and diphenhydramine with no washout period prior to study

				entry
16	1	(b) (6)	Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
17	1		Tacrolimus Ointment 0.1%	Exclusionary medical condition psoriasis
18	5		Tacrolimus Ointment 0.1%	Use of the prohibited concomitant medication doxycycline during the study. Also, the use of the exclusionary medication diphenhydramine without washout period.
19	7		Tacrolimus Ointment 0.1%	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
20	38		Tacrolimus Ointment 0.1%	Use of the exclusionary medication chlorpheniramine with no washout period prior to study entry
21	35		Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
22	35		Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
23	49		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
24	49		Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
25	44		Tacrolimus Ointment 0.1%	Use of cetirizine and diphenhydramine
26	47		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
27	47		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
28	47		Tacrolimus Ointment 0.1%	Use of the exclusionary medications cetirizine and diphenhydramine with no washout period prior to study entry
29	20		Tacrolimus Ointment 0.1%	Does not satisfy one of the Inclusion/Exclusion Criteria based on the medical reviewer
30	25		Protopic Ointment 0.1%	Use of the exclusionary medication advil PM with no washout period prior to study entry
31	1		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
32	4		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
33	4		Protopic Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
34	7		Protopic Ointment 0.1%	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
35	9		Protopic Ointment 0.1%	Use of the exclusionary medication desloratadine with no washout period prior to study entry
36	5		Protopic Ointment 0.1%	Use of the exclusionary medication acetaminophen, chlorphenamine and phenylephrine with no washout period prior to study entry
37	18		Protopic Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
38	6		Protopic Ointment 0.1%	Use of the exclusionary medication fexofenadine and pseudoephedrine with no washout period prior to study entry
39	21		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
40	3		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
41	20		Protopic Ointment 0.1%	Use of the exclusionary medication levocetirizine with

				no washout period prior to study entry
42	38	(b) (6)	Protopic Ointment 0.1%	Exclusionary medical condition telangiectasias
43	35		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
44	43		Protopic Ointment 0.1%	Use of the exclusionary medication acyclovir cetirizine with no washout period prior to study entry
45	49		Protopic Ointment 0.1%	Use of the exclusionary medications cetirizine and loratadine cetirizine with no washout period prior to study entry
46	49		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
47	44		Protopic Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
48	47		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
49	47		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
50	12		Placebo	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
51	3		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
52	3		Placebo	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
53	1		Placebo	Use of the exclusionary medications fexofenadine, pseudoephedrine and Vitamin D supplements with no washout period prior to study entry
54	4		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
55	4		Placebo	Use of the exclusionary medication actifed that contains triprolidine with no washout period prior to study entry
56	4		Placebo	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
57	22		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
58	22		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
59	24		Placebo	Use of the exclusionary medications trimethoprim and diphenhydramine with no washout period prior to study entry
60	5		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
61	18		Placebo	Use of the exclusionary medication hydroxyzine with no washout period prior to study entry
62	17		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
63	27		Placebo	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
64	6		Placebo	Use of the exclusionary medication unknown antihistamine with no washout period prior to study entry
65	31		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
66	3		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
67	1		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry

68	1	(b) (6)	Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
69	1		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
70	4		Placebo	Use of the exclusionary medication Tylenol PM with no washout period prior to study entry
71	6		Placebo	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
72	7		Placebo	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
73	20		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
74	20		Placebo	Use of the exclusionary medication Vitamin D supplements with no washout period prior to study entry
75	31		Placebo	Exclusionary medical condition Alzheimer's
76	38		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
77	35		Placebo	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
78	42		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
79	43		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
80	43		Placebo	Use of the exclusionary medication amoxicillin and clavulanate prior to the study entry without enough wash out period
81	45		Placebo	Does not satisfy one of the Inclusion/Exclusion Criteria based on the medical reviewer
82	45		Placebo	Use of clindamycin and benzoyl peroxide, loratadine and pseudoephedrine
83	49		Placebo	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
84	49		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
85	47		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
86	47		Placebo	Use of the exclusionary medication desloratadine with no washout period prior to study entry
87	20		Placebo	Does not satisfy one of the Inclusion/Exclusion Criteria based on the medical reviewer

[a] Subjects (b) (6) were already excluded from SPP but not SMITT. The medical monitor disagreed with the investigator's assessment of inclusion/exclusion. These subjects were excluded from the FMITT (They are already excluded from the FPP).

Table 31 below provides a listing of the subjects that were excluded from the SPP to form the FPP population based on the FDA Medical and Statistical reviewers for ALT 0416-01-01 (Tacrolimus 0.1 %).

Table 31 Listing of Subjects Excluded from FPP based on the FDA's reviewers for Study ALT 0416-01-01 (Tacrolimus 0.1 %)

Obs	SITE	SUBJID	Treatment	Reason for Exclusion
1	25	(b) (6)	Tacrolimus Ointment 0.1%	Use of the exclusionary medication valaciclovir with no washout period prior to study entry
2	12		Tacrolimus Ointment 0.1%	Use of the exclusionary medications acyclovir and hydroxyzine with no washout period prior to study entry
3	3		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
4	3		Tacrolimus Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
5	1		Tacrolimus Ointment 0.1%	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
6	1		Tacrolimus Ointment 0.1%	Use of the exclusionary medication amoxicillin with no washout period prior to study entry and during the study
7	4		Tacrolimus Ointment 0.1%	Use of the exclusionary medications acyclovir and amoxicillin with no washout period prior to study entry and during the study
8	7		Tacrolimus Ointment 0.1%	Use of the exclusionary medication loratadine with no washout period prior to study entry
9	5		Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
10	5		Tacrolimus Ointment 0.1%	Use of the exclusionary medication loratadine with no washout period prior to study entry
11	18		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
12	27		Tacrolimus Ointment 0.1%	Use of the exclusionary medication desloratadine with no washout period prior to study entry
13	21		Tacrolimus Ointment 0.1%	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
14	31		Tacrolimus Ointment 0.1%	Use of the exclusionary medication diphenhydramine with no washout period prior to study entry
15	3		Tacrolimus Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
16	3		Tacrolimus Ointment 0.1%	Use of the exclusionary medications cetirizine and diphenhydramine with no washout period prior to study entry
17	1		Tacrolimus Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
18	1		Tacrolimus Ointment 0.1%	Exclusionary medical condition psoriasis
19	5		Tacrolimus Ointment 0.1%	Use of the exclusionary medication fluconazole with no washout period prior to study entry and during the study
20	7		Tacrolimus Ointment 0.1%	Use of the exclusionary medication fexofenadine

				cetirizine with no washout period prior to study entry
21	38	(b) (6)	Tacrolimus Ointment 0.1%	Use of the exclusionary medication chlorpheniramine with no washout period prior to study entry
22	35		Tacrolimus Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
23	35		Tacrolimus Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
24	49		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
25	49		Tacrolimus Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
26	44		Tacrolimus Ointment 0.1%	Use of the exclusionary medications cetirizine and diphenhydramine with no washout period prior to study entry
27	47		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
28	47		Tacrolimus Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
29	47		Tacrolimus Ointment 0.1%	Use of the exclusionary medications cetirizine and diphenhydramine with no washout period prior to study entry
30	25		Protopic Ointment 0.1%	Use of the exclusionary medication advil PM with no washout period prior to study entry
31	10		Protopic Ointment 0.1%	Use of the exclusionary medication Theraflu with no washout period prior to study entry and during the study
32	1		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
33	4		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
34	4		Protopic Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
35	7		Protopic Ointment 0.1%	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
36	9		Protopic Ointment 0.1%	Use of the exclusionary medication desloratadine with no washout period prior to study entry
37	5		Protopic Ointment 0.1%	Use of the exclusionary medication acetaminophen, chlorphenamine and phenylephrine with no washout period prior to study entry
38	18		Protopic Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
39	6		Protopic Ointment 0.1%	Use of the exclusionary medication fexofenadine and pseudoephedrine with no washout period prior to study entry
40	21		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
41	3		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with

				no washout period prior to study entry
42	20	(b) (6)	Protopic Ointment 0.1%	Use of the exclusionary medication levocetirizine with no washout period prior to study entry
43	38		Protopic Ointment 0.1%	Medical Condition during the study: telangiectasias
44	35		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
45	39		Protopic Ointment 0.1%	Use of the exclusionary medication Theraflu with no washout period prior to study entry and during the study
46	43		Protopic Ointment 0.1%	Use of the exclusionary medication acyclovir cetirizine with no washout period prior to study entry
47	49		Protopic Ointment 0.1%	Use of the exclusionary medications cetirizine and loratadine cetirizine with no washout period prior to study entry
48	49		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
49	44		Protopic Ointment 0.1%	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
50	47		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
51	47		Protopic Ointment 0.1%	Use of the exclusionary medication cetirizine with no washout period prior to study entry
52	12		Placebo	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
53	8		Placebo	Use of the exclusionary medication fluconazole with no washout period prior to study entry and during the study
54	3		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
55	3		Placebo	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
56	1		Placebo	Use of the exclusionary medications fexofenadine, pseudoephedrine and Vitamin D supplements with no washout period prior to study entry
57	4		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
58	4		Placebo	Use of the exclusionary medication actifed that contains triprolidine with no washout period prior to study entry
59	4		Placebo	Use of the exclusionary medication fexofenadine cetirizine with no washout period prior to study entry
60	22		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
61	22		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
62	24		Placebo	Use of the exclusionary medications trimethoprim and diphenhydramine with no washout period prior to study entry
63	5		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry

64	18	(b) (6)	Placebo	Use of the exclusionary medication hydroxyzine with no washout period prior to study entry
65	17		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
66	27		Placebo	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
67	6		Placebo	Use of the exclusionary medication unknown antihistamine with no washout period prior to study entry
68	31		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
69	3		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
70	1		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
71	1		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
72	1		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
73	4		Placebo	Use of the exclusionary medication Tylenol PM with no washout period prior to study entry
74	6		Placebo	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
75	7		Placebo	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
76	20		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
77	20		Placebo	Use of the exclusionary medication Vitamin D supplements with no washout period prior to study entry
78	31		Placebo	Medical Condition during the study: Alzheimer's
79	38		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
80	35		Placebo	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
81	42		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry
82	43		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
83	43		Placebo	Use of the exclusionary medication amoxicillin and clavulanate prior to the study entry without enough wash out period
84	45		Placebo	Use of clindamycin and benzoyl peroxide, loratadine and pseudoephedrine
85	49		Placebo	Use of the exclusionary medication of diphenhydramine with no washout period prior to study entry
86	49		Placebo	Use of the exclusionary medication cetirizine with no washout period prior to study entry
87	47		Placebo	Use of the exclusionary medication loratadine with no washout period prior to study entry

88	47	(b) (6)	Placebo	Use of the exclusionary medication desloratadine with no washout period prior to study entry
89	31		Placebo	Use of the exclusionary medication amoxicillin with no washout period prior to study entry and during the study

Table 32 provides a listing of subjects that were included in the FPP but were excluded from the SPP.

Table 32 Listing of Subjects Included to the FPP based on the FDA's reviewers for Study ALT 0416-01-01 (Tacrolimus 0.1 %)

Obs	SITE	SUBJID	Treatment	Reason for Inclusion
3	30	(b) (6)	Protopic Ointment 0.1%	Subject had Visit 3 data and had no reason to be excluded from FPP. It was excluded from the Sponsor's PP population because it did not have Visit 2 data which is not the test-of-cure visit.

7 Appendix 2

The frequency and percentage of the IGE scores at Visit 4 (Day 28 (±3 Days)) for the FMITT population in Study ALT 0417-01-01 (Tacrolimus 0.03 %) are summarized in Table 33 below:

Table 33 Frequency and Percentage of the IGE Scores at Visit 4 (Day 28 (±3 Days)) for the FMITT Population for Study ALT 0417-01-01 (Tacrolimus 0.03 %)

IGE Score	Grade	Total N=716	Tacrolimus 0.03% N=240	Protopic® 0.03% N=240	Placebo N=236
0	Clear	118 (16.48%)	51 (21.25%)	45 (18.75%)	22 (9.32%)
1	Almost Clear	206 (28.77%)	71 (29.58%)	81 (33.75%)	54 (22.88%)
2	Mild	238 (33.24%)	77 (32.08%)	77 (32.08%)	84 (35.59%)
3	Moderate	131 (18.30%)	35 (14.58%)	32 (13.33%)	64 (27.12%)
4	Sever	23 (3.21%)	6 (2.50%)	5 (2.08%)	12 (5.08%)

The frequency and percentage of the overall pruritus scores scores at Visit 4 (Day 28 (±3 Days)) for the FMITT population in Study ALT 0417-01-01 (Tacrolimus 0.03 %) are summarized in Table 34 below:

Table 34 Frequency and Percentage of the Overall Pruritus Scores at Visit 4 (Day 28 (±3 Days)) for the FMITT Population for Study ALT 0417-01-01 (Tacrolimus 0.03 %)

Pruritus Score	Grade	Total N=714	Tacrolimus 0.03% N=239	Protopic® 0.03% N=239	Placebo N=236
0	None	212 (29.69%)	82 (34.31%)	80 (33.47%)	50 (21.19%)
1	Mild	305 (42.72%)	109 (45.61%)	103 (43.10%)	93 (39.41%)
2	Moderate	134 (18.77%)	34 (14.23%)	40 (16.74%)	60 (25.42%)
3	Sever	63 (8.82%)	14 (5.86%)	16 (6.69%)	33 (13.98%)

[a]Subjects (b) (6) in the test treatment group and 42-1022 in the reference treatment group had missing pruritus values at Visit 4 (Day 25-31)

The summary of the total body surface area affected at Visit 4 (Day 28 (±3 Days)) for the FMITT population in Study ALT 0417-01-01 (Tacrolimus 0.03 %) are summarized in Table 35 below:

Table 35 Summary of % Total Body Surface Area Affected at Visit 4 (Day 28 (±3 Days)) for the FMITT Population for Study ALT 0417-01-01 (Tacrolimus 0.03 %)

% Body Surface Area	Total N=715	Tacrolimus 0.03% N=239	Protopic®0.03% N=240	Placebo N=236	p-value[a]
Mean (STD)	11.76 (14.26)	11.77 (16.76)	9.60 (10.27)	13.94 (14.73)	0.3360
Median	8	6	7	10	
Range	0-90	0-90	0-60	0-70	

Table 36 below provides a listing of subjects that were excluded from the SMITT population to form the FMITT population based on the FDA Medical and Statistical reviewers for ALT 0417-01-01 (Tacrolimus 0.03 %).

Table 36 Listing of Subjects Excluded from SMITT to form FMITT based on the FDA's reviewers for Study ALT 0417-01-01 (Tacrolimus 0.03 %)

Obs	SITE	SUBJID	Treatment	Reason for Exclusion
1	14	(b) (6)	Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
2	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
3	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
4	10		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
5	18		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
6	18		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
7	18		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
8	17		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study

9	12	(b) (6)	Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine, loratadine, amoxicillin and clavulanate) with no washout period and continued to use the prohibited concomitant medication during the study
10	12		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Tacrolimus) with no washout period
11	28		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
12	3		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
13	3		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
14	3		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
15	5		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
16	16		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine and Diphenhydramine) with no washout period
17	4		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
18	4		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
19	20		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
20	15		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
21	25		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
22	25		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
23	30		Tacrolimus Ointment 0.03%	Exclusionary medical condition (folliculitis)
24	2		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with

		(b) (6)		
				no washout period and continued to use the prohibited concomitant medication during the study
25	2		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine and Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
26	21		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
27	13		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication with no washout period (Cetirizine) and prohibited Medication during the study (amoxicillin)
28	13		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
29	31		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine and Pseudoephedrine) with no washout period and continued to use the prohibited concomitant medication during the study
30	17		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
31	17		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
32	33		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
33	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
34	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
35	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
36	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
37	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Hydroxyzine) with no washout period and continued to use the prohibited concomitant medication during the study
38	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with

		(b) (6)		
				no washout period and continued to use the prohibited concomitant medication during the study
39	37		Tacrolimus Ointment 0.03%	Exclusionary medical condition (dyschromia and xerosis)
40	37		Tacrolimus Ointment 0.03%	Prohibited concomitant (fluconazole) medication during the study with exclusionary medical condition (ichen simplex chronicus)
41	3		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
42	48		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Desloratadine) with no washout period and continued to use the prohibited concomitant medication during the study
43	48		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
44	51		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Levocetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
45	34		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Benzoyl Peroxide and Certirizine) with no washout period and continued to use the prohibited concomitant medication during the study
46	34		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine) with no washout period
47	32		Tacrolimus Ointment 0.03%	Inclusion/Exclusion Criteria not met
48	37		Tacrolimus Ointment 0.03%	Prohibited concomitant medication (Azithromycin, Loratadine, Pseudoephedrine and Tamiflu) during the study with exclusionary medical condition (dyschromia)
49	37		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
50	37		Tacrolimus Ointment 0.03%	Exclusionary medical condition (contact dermatitis)
51	12		Tacrolimus Ointment 0.03%	Exclusionary medical condition (recurrent hives)
52	57		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Tamiflu) with no washout period and continued to use the prohibited concomitant medication during the study
53	38		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Clindamycin and Benzoyl Peroxide) with no washout period
54	55		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (acyclovir) with no washout period and continued to use the prohibited concomitant medication during the study
55	27		Protopic Ointment 0.03%	Prohibited concomitant medication (Dimetapp Cold & Cough) during the study with exclusionary medical condition (lichen nitidus)

56	18	(b) (6)	Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
57	18		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
58	18		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
59	18		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
60	17		Protopic Ointment 0.03%	Use of Exclusionary Medication (Periactin) with no washout period and continued to use the prohibited concomitant medication during the study
61	12		Protopic Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
62	12		Protopic Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
63	6		Protopic Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
64	3		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
65	3		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
66	3		Protopic Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
67	3		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
68	5		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
69	15		Protopic Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the

		(b) (6)		study
70	15		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout
71	25		Protopic Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
72	30		Protopic Ointment 0.03%	Use of Exclusionary Medication (Ketoconazole) with no washout period
73	2		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine and Pseudoephedrine) with no washout period and continued to use the prohibited concomitant medication during the study
74	2		Protopic Ointment 0.03%	Use of Exclusionary Medication (Levocetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
75	13		Protopic Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
76	13		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
77	13		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
78	32		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
79	42		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine and Pseudoephedrine) with no washout period and continued to use the prohibited concomitant medication during the study
80	4		Protopic Ointment 0.03%	Use of Exclusionary Medication (Acyclovir) with no washout period and continued to use the prohibited concomitant medication during the study
81	10		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
82	17		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
83	19		Protopic Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
84	19		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the

		(b) (6)		
				prohibited concomitant medication during the study
85	25		Protopic Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine) with no washout period
86	27		Protopic Ointment 0.03%	Medical Condition during (Common variable benign skin lesion) the study and the use of Exclusionary Medication (Fexofenadine) with no washout period
87	42		Protopic Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
88	36		Protopic Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
89	36		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
90	36		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
91	37		Protopic Ointment 0.03%	Exclusionary medical condition (Dyschromia and Xerosis)
92	37		Protopic Ointment 0.03%	Exclusionary medical condition (Xerosis)
93	37		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cephalexin) with no washout period and continued to use the prohibited concomitant medication during the study
94	38		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
95	48		Protopic Ointment 0.03%	Medical Condition (common variable immune deficiency) during the study and the use of Exclusionary Medication (Cetirizine) with no washout period
96	48		Protopic Ointment 0.03%	Use of Exclusionary Medication with no washout period and prohibited Medication during the study (Amoxicillin and Cetirizine)
97	34		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
98	34		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
99	37		Protopic Ointment 0.03%	Exclusionary medical condition (Ichythyosis Vulgaris)
100	37		Protopic Ointment 0.03%	Use of Exclusionary Medication (Terbinafine Oral, Griseofulvin) with no washout period and continued to use the prohibited concomitant

		(b) (6)		medication during the study with exclusionary medical condition (Tinea Corporis)
101	48		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
102	27		Placebo	Use of Exclusionary Medication (Ketoconazole) with no washout period
103	27		Placebo	Use of Exclusionary Medication (Tylenol Allergy that contains chlorpheniramine) with no washout period and continued to use the prohibited concomitant medication during the study
104	14		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
105	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period
106	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
107	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
108	10		Placebo	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
109	10		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
110	10		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
111	18		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
112	18		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
113	17		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
114	12		Placebo	Use of Exclusionary Medication (Amoxicillin) with no washout period with exclusionary medical condition (Recurrent Hives)
115	9		Placebo	Use of Exclusionary Medication (Acyclovir and Hydroxyzine) with no washout period and

		(b) (6)		
				continued to use the prohibited concomitant medication during the study
116	28		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
117	6		Placebo	Use of Exclusionary Medication (Brompheniramine) with no washout period and continued to use the prohibited concomitant medication during the study
118	3		Placebo	Use of Exclusionary Medication (Cetirizine, Loratadine and Pseudoephedrine) with no washout period and continued to use the prohibited concomitant medication during the study
119	3		Placebo	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
120	4		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
121	4		Placebo	Use of Exclusionary Medication with no washout period and prohibited Medication during the study (Azithromycin and Diphenhydramine)
122	15		Placebo	Use of Exclusionary Medication (Fexofenadine) with no continued to use the prohibited concomitant medication during the study
123	23		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
124	2		Placebo	Use of Exclusionary Medication (Cetirizine and Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
125	2		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
126	2		Placebo	Use of Exclusionary Medication (Cetirizine and Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
127	2		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
128	13		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
129	13		Placebo	Use of Exclusionary Medication (Advair and Loratadine) with no washout period and continued to use the prohibited concomitant medication

		(b) (6)		
				during the study
130	32		Placebo	Inclusion/Exclusion Criteria not met
131	32		Placebo	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
132	42		Placebo	Use of Exclusionary Medication (Loratadine and Pseudoephedrine) with no washout period and continued to use the prohibited concomitant medication during the study
133	5		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
134	2		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
135	10		Placebo	Use of Exclusionary Medication (Cetirizine and Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
136	17		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
137	19		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
138	19		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
139	19		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
140	25		Placebo	Use of Exclusionary Medication with no washout period
141	40		Placebo	Use of Exclusionary Medication (Loratadine and Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
142	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
143	36		Placebo	Use of Exclusionary Medication (Loratadine and Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
144	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the

		(b) (6)		study
145	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
146	37		Placebo	Exclusionary medical condition (Dyschromia and Xerosis)
147	37		Placebo	Use of Exclusionary Medication (Ketoconazole) with no washout period
148	37		Placebo	Use of Exclusionary Medication (Fexofenadine, Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study with exclusionary medical condition (Folliculitis)
149	37		Placebo	Use of Exclusionary Medication (Bactrim) with no washout period and continued to use the prohibited concomitant medication during the study
150	38		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period
151	3		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
152	48		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
153	48		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
154	48		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
155	51		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
156	52		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
157	34		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
158	34		Placebo	Use of Exclusionary Medication (Chlorpheniramine) with no washout period and continued to use the prohibited concomitant medication during the study

Table 37 below provides a listing of subjects that were excluded from the SPP population to form the FPP population based on the FDA Medical and Statistical reviewers for ALT 0417-01-01 (Tacrolimus 0.03 %).

Table 37 Listing of Subjects Excluded from SPP to form FPP based on the FDA's reviewers for Study ALT 0417-01-01 (Tacrolimus 0.03 %)

Obs	SITE	SUBJID (b) (6)	Treatment	Reason for the Excludion
1	14		Tacrolimus Ointment 0.03%	Prohibited concomitant medication during the study - doxycycline
2	14		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
3	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
4	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
5	10		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
6	18		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
7	18		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
8	18		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
9	12		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine, loratadine, amoxicillin and clavulanate) with no washout period and continued to use the prohibited concomitant medication during the study
10	12		Tacrolimus Ointment 0.03%	Prohibited concomitant medication during the study - Nyquil
11	28		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
12	3		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
13	3		Tacrolimus Ointment 0.03%	Prohibited concomitant medication during the study - Theraflu
14	5		Tacrolimus Ointment 0.03%	Prohibited concomitant medication during the study - azelastine
15	4		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
16	4		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study

		(b) (6)		
17	15		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
18	25		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
19	30		Tacrolimus Ointment 0.03%	Medical Condition during the study:folliculitis
20	2		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
21	2		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine and Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
22	13		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication with no washout period (Cetirizine) and prohibited Medication during the study (amoxicillin)
23	13		Tacrolimus Ointment 0.03%	Prohibited concomitant medication during the study - Symbicort
24	17		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
25	17		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine)with no washout period and continued to use the prohibited concomitant medication during the study
26	33		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
27	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
28	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study concomitant
29	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
30	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Hydroxyzine) with no washout period and continued to use the prohibited concomitant medication during the study
31	36		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
32	37		Tacrolimus Ointment 0.03%	Medical Condition during the study:dyschromia and xerosis
33	37		Tacrolimus Ointment 0.03%	Prohibited concomitant medication during the study - acyclovir and doxycycline
34	37		Tacrolimus Ointment 0.03%	Use of fluconazole and Medical Condition - lichen simplex chronicus
35	3		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study

36	51	(b) (6)	Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Levocetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
37	34		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Benzoyl Peroxide and Certirizine) with no washout period and continued to use the prohibited concomitant medication during the study
38	34		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
39	37		Tacrolimus Ointment 0.03%	Prohibited concomitant medication (Azithromycin, Loratadine, Pseudoephedrine and Tamiflu) during the study with exclusionary medical condition (dyschromia)
40	37		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
41	37		Tacrolimus Ointment 0.03%	Medical Condition during the study: contact dermatitis
42	12		Tacrolimus Ointment 0.03%	Medical Condition during the study:recurrent hives
43	57		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Tamiflu) with no washout period and continued to use the prohibited concomitant medication during the study
44	38		Tacrolimus Ointment 0.03%	Use of Exclusionary Medication (Clindamycin and Benzoyl Peroxide) with no washout period
1	27		Protopic Ointment 0.03%	Prohibited concomitant medication (Dimetapp Cold & Cough) during the study with exclusionary medical condition (lichen nitidus)
2	36		Protopic Ointment 0.03%	Prohibited concomitant medication during the study - azithromycin
3	18		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
4	18		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
5	17		Protopic Ointment 0.03%	Use of Exclusionary Medication (Periactin) with no washout period and continued to use the prohibited concomitant medication during the study
6	12		Protopic Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
7	6		Protopic Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
8	6		Protopic Ointment 0.03%	Prohibited concomitant medication during the study - cefdinir
9	3		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
10	3		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study

11	3	(b) (6)	Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
12	5		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
13	15		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
14	30		Protopic Ointment 0.03%	Use of Exclusionary Medication (Ketoconazole) with no washout period
15	2		Protopic Ointment 0.03%	Use of Exclusionary Medication (Levocetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
16	13		Protopic Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
17	13		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
18	13		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
19	13		Protopic Ointment 0.03%	Prohibited concomitant medication during the study - loratadine
20	32		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
21	42		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine and Pseudoephedrine) with no washout period and continued to use the prohibited concomitant medication during the study
22	4		Protopic Ointment 0.03%	Use of Exclusionary Medication (Acyclovir) with no washout period and continued to use the prohibited concomitant medication during the study
23	10		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
24	17		Protopic Ointment 0.03%	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
25	19		Protopic Ointment 0.03%	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
26	19		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
27	25		Protopic Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
28	27		Protopic Ointment 0.03%	Medical Condition during (Common variable benign skin lesion) the study and the use of Exclusionary Medication (Fexofenadine) with no washout period

29	36	(b) (6)	Protopic Ointment 0.03%	Use of Exclusionary Medication (Diphenhydramine and Loratadine)with no washout period and continued to use the prohibited concomitant medication during the study
30	36		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
31	36		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
32	37		Protopic Ointment 0.03%	Medical Condition during the study:dyschromia and xerosis
33	37		Protopic Ointment 0.03%	Medical Condition during the study:xerosis
34	38		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
35	3		Protopic Ointment 0.03%	Prohibited concomitant medication during the study - bactrim
36	48		Protopic Ointment 0.03%	Medical Condition (common variable immune deficiency) during the study and the use of Exclusionary Medication (Cetirizine) with no washout period
37	48		Protopic Ointment 0.03%	Prohibited concomitant medication during the study - amoxicillin
38	34		Protopic Ointment 0.03%	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
39	37		Protopic Ointment 0.03%	Medical Condition during the study:ichythyosis vulgaris
40	37		Protopic Ointment 0.03%	Use of Exclusionary Medication (Terbinafine Oral, Griseofulvin) with no washout period and continued to use the prohibited concomitant medication during the study with exclusionary medical condition (Tinea Corporis)
41	27		Placebo	Use of Exclusionary Medication (Ketoconazole) with no washout period
42	27		Placebo	Use of Exclusionary Medication (Tylenol Allergy that contains chlorpheniramine) with no washout period and continued to use the prohibited concomitant medication during the study
43	14		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
44	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
45	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
46	10		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
47	10		Placebo	Prohibited concomitant medication during the study - Nyquil

48	18	(b) (6)	Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
49	17		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
50	12		Placebo	Use of Exclusionary Medication (Amoxicillin) with no washout period with exclusionary medical condition (Recurrent Hives)
51	9		Placebo	Use of Exclusionary Medication (Acyclovir and Hydroxyzine) with no washout period and continued to use the prohibited concomitant medication during the study
52	28		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
53	6		Placebo	Use of Exclusionary Medication (Brompheniramine) with no washout period and continued to use the prohibited concomitant medication during the study
54	5		Placebo	Prohibited concomitant medication during the study - diphenhydramine
55	5		Placebo	Prohibited concomitant medication during the study - mupirocin and zinc oxide
56	4		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the
57	4		Placebo	Use of Exclusionary Medication with no washout period and prohibited Medication during the study (Azithromycin and Diphenhydramine)
58	15		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
59	23		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
60	2		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
61	2		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
62	13		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
63	13		Placebo	Use of Exclusionary Medication (Advair and Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
64	32		Placebo	Prohibited concomitant medication during the study - penicillin
65	32		Placebo	Use of Exclusionary Medication (Diphenhydramine and Loratadine)with no washout period and continued to use the prohibited concomitant medication during the study

66	42	(b) (6)	Placebo	Use of Exclusionary Medication (Loratadine and Pseudoephedrine) with no washout period and continued to use the prohibited concomitant medication during the study
67	4		Placebo	Prohibited concomitant medication during the study - doxycycline
68	5		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
69	2		Placebo	Prohibited concomitant medication during the study - levocetirizine
70	10		Placebo	Use of Exclusionary Medication (Cetirizine and Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
71	17		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
72	19		Placebo	Use of Exclusionary Medication (Fexofenadine) with no washout period and continued to use the prohibited concomitant medication during the study
73	19		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
74	25		Placebo	Use of Exclusionary Medication (Diphenhydramine) with no washout period and continued to use the prohibited concomitant medication during the study
75	27		Placebo	Prohibited concomitant medication during the study - Nyquil
76	40		Placebo	Use of Exclusionary Medication (Diphenhydramine) with no washout period
77	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
78	36		Placebo	Use of Exclusionary Medication (Diphenhydramine) with no washout period
79	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
80	36		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
81	37		Placebo	Medical Condition during the study:dyschromia and xerosis
82	37		Placebo	Prohibited concomitant medication during the study - acyclovir and erythromycin
83	37		Placebo	Use of Exclusionary Medication (Ketoconazole) with no washout period
84	37		Placebo	Use of Fexofenadine, Diphenhydramine and Medical condition --Folliculitis
85	3		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study

86	48	(b) (6)	Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
87	48		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
88	48		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
89	51		Placebo	Use of Exclusionary Medication (Loratadine) with no washout period and continued to use the prohibited concomitant medication during the study
90	52		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
91	34		Placebo	Use of Exclusionary Medication (Cetirizine) with no washout period and continued to use the prohibited concomitant medication during the study
92	34		Placebo	Use of Exclusionary Medication (Chlorpheniramine) with no washout period and continued to use the prohibited concomitant medication during the study

8 Appendix 3

Table 38 and Table 39 list the subjects that were misdosed for study ALT 0416-01-01 (Tacrolimus 0.1%) and study ALT 0417-01-01 (Tacrolimus 0.03%) respectively. They were analyzed as randomized.

Table 38 Listing of Subjects who were misdosed for Study ALT 0416-01-01 (Tacrolimus 0.1 %)

Obs	SITE	SUBJID	Randomized as	Misdosed With
1	25	(b) (6)	Tacrolimus Ointment 0.1%	Placebo
2	25		Tacrolimus Ointment 0.1%	Placebo
3	20		Tacrolimus Ointment 0.1%	Placebo
4	20		Tacrolimus Ointment 0.1%	Placebo
5	20		Tacrolimus Ointment 0.1%	Placebo
6	4		Tacrolimus Ointment 0.1%	Placebo
7	30		Tacrolimus Ointment 0.1%	Placebo
8	30		Placebo	Placebo
9	18		Tacrolimus Ointment 0.1%	Placebo
10	11		Tacrolimus Ointment 0.1%	Placebo
11	11		Tacrolimus Ointment 0.1%	Placebo

Table 39 Listing of Subjects who were misdosed/potentially misdosed for Study ALT 0417-01-01 (Tacrolimus 0.03 %)

Obs	SITE	SUBJID	Randomized as	Misdosed With
1	36	(b) (6)	Placebo	Tacrolimus Ointment 0.03%
2	18		Placebo	Tacrolimus Ointment 0.03%
3	17		Placebo	Tacrolimus Ointment 0.03%
4	12		Placebo	Tacrolimus Ointment 0.03%
5	28		Placebo	Tacrolimus Ointment 0.03%
6	6		Placebo	Tacrolimus Ointment 0.03%
7	7		Placebo	Tacrolimus Ointment 0.03%
8	3		Placebo	Tacrolimus Ointment 0.03%
9	3		Placebo	Tacrolimus Ointment 0.03%
10	5		Placebo	Tacrolimus Ointment 0.03%
11	8		Placebo	Tacrolimus Ointment 0.03%
12	20		Placebo	Tacrolimus Ointment 0.03%
13	15		Placebo	Tacrolimus Ointment 0.03%
14	25		Placebo	Tacrolimus Ointment 0.03%
15	23		Placebo	Tacrolimus Ointment 0.03%
16	23		Placebo	Tacrolimus Ointment 0.03%
17	23		Placebo	Tacrolimus Ointment 0.03%
18	23		Placebo	Tacrolimus Ointment 0.03%
19	32		Placebo	Tacrolimus Ointment 0.03%
20	32		Placebo	Tacrolimus Ointment 0.03%
21	32		Placebo	Tacrolimus Ointment 0.03%
22	32		Placebo	Tacrolimus Ointment 0.03%
23	32		Placebo	Tacrolimus Ointment 0.03%
24	32		Placebo	Tacrolimus Ointment 0.03%

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/s/

FAIROUZ T MAKHLOUF
08/02/2013

STELLA C GROSSER
08/02/2013

YI TSONG
08/21/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200744Orig1s000

BIOEQUIVALENCE REVIEWS

Clinical Review of ANDA 200744
Bioequivalence Study with Clinical Endpoints

Drug Product:	Tacrolimus Ointment, 0.1% and 0.03%
Drug Class:	Non-Steroidal Anti-Inflammatory Skin Agents (40207700)
Chemical Name:	[3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*, 15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17, 18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10, 12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,monohydrate
ANDA:	200744
ANDA Sponsor:	Fougera Pharmaceuticals Inc
Reference Listed Drug:	Protopic
NDA:	050777 (0.03% and 0.1%)
RLD Sponsor:	Astellas
Reviewer:	Sarah H. Seung, Pharm.D. Clinical Reviewer Division of Clinical Review Office Generic Drugs
Secondary Reviewer:	John R Peters, MD Director, Division of Clinical Review Office of Generic Drugs
Tertiary Reviewer:	Dale P. Conner, Pharm.D. Director, Division of Bioequivalence I Office of Generic Drugs Center for Drug Evaluation and Research
Materials Reviewed:	Statistical Review finalized on 8/21/2013 by Fairouz Makhlouf, Ph.D. OSI Review finalized on 1/9/2013 by Young M. Choi, Ph.D.
Guidance/Draft Guidance:	Draft Guidance on Tacrolimus Ointment/Topical, 0.03%, and Draft Guidance on Tacrolimus Ointment/Topical, 0.1%
Date Posted:	March 2012 (0.03% and 0.1%)
Date of Original Submission:	4/8/2010
Addenda to submission:	9/8/2010; 11/18/2010; 2/29/2012
Date of Completion:	9/25/2013
Conclusion:	Recommend Approval

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Review of Bioequivalence Studies with Clinical Endpoints for ANDA 200744

1 Executive Summary

On 8/8/10, Fougera Pharmaceuticals Inc (formerly Nycomed US Inc. and Altana inc.; the "sponsor") submitted an abbreviated new drug application (ANDA) for Tacrolimus Ointment, 0.1%. On 11/9/10, the sponsor submitted an amendment to add the 0.03% strength to the ANDA. In support for the ANDA, the sponsor conducted two clinical endpoint bioequivalence studies. Both studies were double-blinded, randomized, multi-center, parallel-group, placebo controlled for the treatment of atopic dermatitis. The first study (ALT 0416-01-01, "Study 0416"), conducted between 1/28/08 to 8/12/09, compared the 0.1% strength of their proposed test product (Tacrolimus Ointment) to the reference listed drug (RLD), Astellas' Protopic® (Tacrolimus ointment), 0.1% (Reference). The second study (ALT 0417-01-01, "Study 0417"), conducted between 1/10/08 to 9/11/09, compared the 0.03% strength of their proposed test product (Tacrolimus Ointment) to the reference listed drug (RLD), Astellas' Protopic® (Tacrolimus ointment), 0.03% (Reference). In both studies, the test and reference products were also compared to placebo (the vehicle ointment).

During the course of these studies (on 10/21/08), a packaging/dosing error, which affected both studies, was discovered. Flow charts detailing the chain of events and subsequent actions taken by the sponsor are provided in the Appendix of this review. A summary is provided below:

> A package weight discrepancy in shipping documentation for Ecuador for Study 0416 triggered an inspection of the shipment by Ecuadorian Customs. The shipment was returned to the sponsor. Ten kits from the shipment were tampered with by the Ecuadorian Customs, including one tube (for Kit 0090) which was punctured. The sponsor's Project Management unblinded the punctured tube and discovered that the unblinded tube did not match the lot numbers provided for Study 0416. The sponsor stated that the sponsor's "Project Management securely maintains the randomization code and makes no decisions regarding clinical study conduct." Further investigation revealed that lot numbers for Study 0416 (Lot Z432, Test Tacrolimus Ointment, 0.1%) was potentially intermingled with lot numbers for Study 0417 (Lot Z034, Placebo). On 10/28/08, enrollment for both studies was suspended. At that point, 438 patients (out of 793 total) were enrolled in Study 0416 and 483 patients (out of 900 total) were enrolled in Study 0417. However, patients already enrolled into these studies continued to use the study medications.
>
> An outside third party packaging vendor (b) (4) was contracted to evaluate the unused and used study supplies for both studies. During the evaluation of the unused kits, (b) (4) discovered more tubes of Z432 (Tacrolimus Ointment, 0.1%) in the placebo treatment arm for Study 0417 (the

0.03% study). After a new randomization code was generated and new clinical kits created, enrollment was restarted in March 2009 for both studies. (b) (4) also unblinded the used kits. (b) (4) provided the results of the used study supplies evaluation to the sponsor in the form of "blinded" memos on the morning of 10/9/09 for Study 0416 and on 7/14/09 for Study 0417. The memos confirmed that for Study 0416 (0.1% study), 1 patient was confirmed to be midosed and 9 patients were considered potentially mis-dosed due to at least 1 tube of study drug not returned. For Study 0417 (0.03% study), 5 patients were confirmed to be mis-dosed and 19 patients were considered potentially mis-dosed. On the afternoon of 10/9/09 for Study 0416 and on 7/17/09 for Study 0417, (b) (4) provided a final "unblinded" results in the form of a memo to a single unblinded statistician at (b) (4) These memos included the patients numbers of those patients who were mis-dosed and those who were potentially mis-dosed. On the day that the databases was soft locked, the single unblinded statistician at (b) (4), who received the "unblinded" memo moved the mis-dosed/potentially mis-dosed patients to a different group for evaluation. The databases were hard locked later that same day.

As a result of the packaging/dosing error, a safety monitoring study (ALT 0417-01-02, "Study 0417-01-02") was conducted between 11/16/09 to 4/15/11 to follow-up on those patients who were confirmed to be and potentially mis-dosed. Only 5 subjects enrolled into this study.

On 8/8/13, the Division of Clinical Review (DCR) issued a "Clinical Bioequivalence Deficiency (Easily Correctable)" to the sponsor requesting more information, particularly regarding the packaging/dosing error. The sponsor submitted their response on 8/23/13.

The sponsor submitted enough evidence to assure that the integrity of the study data was not impacted by the packaging error and the unblinding of the used study medication kits.

1.1 Approval Recommendation

The data submitted to ANDA 200744, using the primary endpoint of the proportion of patients in the per-protocol population in each group with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, based on a 4-point scale, within all treatment areas) based on the Investigator's Global Assessment at the end of treatment (i.e., week 2 visit for Study 0416 and week 4 visit for Study 0417), are adequate to demonstrate bioequivalence of the sponsor's Tacrolimus Ointment, 0.03% and 0.1% with the RLD, Astellas' Protopic® (Tacrolimus Ointment), 0.03% and 0.1%, respectively. Therefore, from a clinical bioequivalence perspective, the test products are recommended for approval.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

Tacrolimus Ointment, 0.03% and 0.1% is a non-steroidal anti-inflammatory skin agents indicated as second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults (and children for the 0.03% strength

only) who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable. The sponsor conducted two clinical endpoint bioequivalence studies to establish the bioequivalence of their proposed Tacrolimus Ointment, 0.03% and 0.1% to the RLD, Protopic®, 0.03% and 0.1%, respectively, in the treatment of atopic dermatitis. Both studies were double-blinded, randomized, multi-center, parallel-group, placebo controlled. The first study (Study 0416), enrolling 793 patients, was conducted in patients at least 18 years of age with moderate to severe atopic dermatitis, where each patient applied the study medication twice-daily for 2 weeks. The second study (Study 0417), enrolling 900 patients, was conducted in patients at least 8 years of age with moderate to severe atopic dermatitis, where each patient applied the study medication twice-daily for 4 weeks. All patients were randomized to receive either the sponsor's product (Test), Protopic® (Reference) or Placebo.

1.2.2 Comparative Efficacy

The recommended primary endpoint of the studies is the proportion of patients in the per-protocol population in each group with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, based on a 4-point scale, within all treatment areas) based on the Investigator's Global Assessment at the end of treatment. For Study 0416 (0.1% strength) the end of treatment is at the week 2 visit and for Study 0417 (0.03% strength) the end of treatment is at the week 4 visit. To meet the bioequivalence criteria, 90% CI of the test - reference difference between products for the primary endpoint must be within the limits of [-0.20, 0.20], in the per-protocol population.

The FDA's statistical analysis shows the 90% CI of the test - reference difference between products for the primary endpoint in the proportion of patients in the per-protocol population in each group with treatment success were (-15.023%, 3.048%) for Study 0416 (0.1% strength) and (-7.584%, 10.314%) for Study 0417 (0.03% strength), which are within the established bioequivalence limits of [-0.20, 0.20].

The proportion of patients with treatment success for the Test and Reference products were demonstrated by the FDA's analysis to be superior to placebo in both studies.

1.2.3 Comparative Safety

The safety data submitted in this ANDA confirmed that the test product did not cause any worse adverse events compared to the reference product in the topical treatment of atopic dermatitis. A brief summary is provided below.

Study #	Total (N)	Test (n)	RLD (n)	Placebo (n)	Comment
Study 0416 (0.1% strength)	793	269	260	264	Tacrolimus concentration levels within levels observed during RLD PK studies.

Patients with at least one AEs	65 (8.2%)	17 (6.3%)	25 (9.6%)	23 (8.7%)	• p=0.202 (test vs. RLD) • No SAEs or deaths were reported in any group
Discontinued study drug due to above AE	14 (1.8%)	1 (0.4%)	9 (3.5%)	4 (1.5%)	p=0.02 (test vs. RLD)
Study 0417 (0.03% strength)	899	302	297	300	Tacrolimus concentration levels within levels observed during RLD PK studies.
Patients with at least one AEs	163 (18.1%)	52 (17.2%)	53 (17.8%)	55 (19.9%)	• p=0.840 (test vs. RLD) • No deaths were reported in any group
SAE	2	1	0	1	p=1.000 (test vs. RLD)
Discontinued study drug due to above AE	19 (1.9%)	5 (1.7%)	3 (1.0%)	11 (4.0%)	p=0.725 (test vs. RLD)
Study 0417-01-02 (0.03% strength follow-up)	5	NA	NA	NA	One year follow-up study.
Patients with at least one AEs	4 (80.0%)	NA	NA	NA	

2 Clinical Review

2.1 Introduction and Background

2.1.1 Summary of Drug Information

Drug Established Name	Tacrolimus Ointment, 0.03% and 0.1%
Drug Class	Non-Steroidal Anti-Inflammatory Skin Agents (40207700)
Reference Listed Drug	Protopic
RLD Applicant	Astellas
RLD # (NDA/ANDA)	050777 (0.03% and 0.1%)
Date of RLD Approval	12/8/00 (0.03% and 0.1%)
RLD Approved Indication(s)	Both 0.03% and 0.1% approved for adults Only 0.03% approved for children aged 2-15 years Indicated as second-line therapy for the short-term and non-

	continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.
RLD Recommended Dosing Regimens	**Adult (0.03% and 0.1%) & Pediatric - 2 to 15 years (0.03% only)** • Apply a thin layer of PROTOPIC (tacrolimus) Ointment to the affected skin twice daily. The minimum amount should be rubbed in gently and completely to control signs and symptoms of atopic dermatitis. Stop using when signs and symptoms of atopic dermatitis resolve. • If signs and symptoms (e.g. itch, rash, and redness) do not improve within 6 weeks, patients should be re-examined by their healthcare provider to confirm the diagnosis of atopic dermatitis. • Continuous long-term use of topical calcineurin inhibitors, including PROTOPIC Ointment should be avoided, and application should be limited to areas of involvement with atopic dermatitis. The safety of PROTOPIC Ointment under occlusion, which may promote systemic exposure, has not been evaluated. PROTOPIC Ointment should not be used with occlusive dressings.

2.1.1.1 Description of the reference drug, including pertinent safety or dosing considerations

Tacrolimus, the active ingredient in this product, is a macrolide immunosuppressant that is produced by *Streptomyces tsukubaensis*. Although the mechanism of action of tacrolimus in atopic dermatitis is unknown, tacrolimus is known to inhibit t-lymphocyte activation by first binding to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited.

Black Box Warning:

WARNING

Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including PROTOPIC Ointment. Therefore:

- Continuous long-term use of topical calcineurin inhibitors, including PROTOPIC Ointment, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- PROTOPIC Ointment is not indicated for use in children less than 2 years of age. Only 0.03% PROTOPIC Ointment is indicated for use in children 2-15 years of age.

2.1.1.2 Brief Discussion about the Indication

Atopic dermatitis (AD) is a chronic, pruritic eczematous disease that nearly always begins in childhood and follows a remitting/flaring course that could continue throughout life. The disease often moderates with age, but patients carry a life-long skin sensitivity to irritants. AD is divided into three phases: infant, childhood and adult, and the disease characteristics vary with age. Infants have facial and patchy or generalized body eczema while adolescents and adults have eczema in flexural areas and on the hands. AD starts with itching and it is the scratching that creates most of the characteristic patterns of the disease. Several patterns and types of lesions may be produced by exposure to external stimuli or may be precipitated by scratching. Acute inflammation begins with erythematous papules and erythema. Subacute dermatitis is associated with erythematous, excoriated, scaling papules. Chronic dermatitis is the result of scratching over an extended period causing thickened skin, accentuated skin markings (lichenification) and fibrotic papules. Inflammation resolves slowly, leaving the skin in a dry, scaly, compromised condition called xerosis. All types of reactions can coexist in the same individual.

2.1.2 Regulatory Background

2.1.2.1 Regulatory History

The Reference Listed Drug (RLD), Protopic Ointment (NDA 050777) was approved on 12/8/2000.

For information on the early regulatory history of the RLD, refer to the protocol review of P05-056 by Carol Y. Kim, Pharm.D. finalized on 2/28/2006 (\\cdsnas\ogds11\Firmsnz\NOVUM\LTRS&REV\05056P.0905.mor.doc) .
Since the finalization of P05-056 protocol review, in January, 2006, the FDA approved updated labeling with boxed warning about a possible risk of cancer and a Medication Guide (FDA-approved patient labeling) was distributed to help ensure that patients using Protopic are aware of this concern. The new labeling also clarifies that Protopic is recommended for use as second-line treatments.

During the FDA Pediatric Advisory Committee (PAC) meetings on 3/22/2010 and 5/16/2011, the committee recommended that FDA continue to monitor the occurrence of cancer cases in pediatric patients using Topical Calcineurin Inhibitors: Elidel and Protopic and return to the committee again with an updated literature review and an analysis from the registry on cancer cases at 5 years. Once sufficient data becomes available from the 10 year sponsor registries, FDA will provide another update to the PAC.

2.1.2.2 INDs, Protocols, or Control Documents submitted by Sponsor

On 12/3/04, the sponsor submitted a Control Document for a protocol (OGD# 04-1145; P04-056) then several amendments to OGD# 04-1145 and P04-056 on 12/10/04, 3/18/05 and 5/31/05 for this drug product. The sponsor proposed to conduct a clinical endpoint bioequivalence study for the 0.1% strength and an in vitro testing for the 0.03% strength. On 11/30/05 and 1/19/06, the sponsor submitted a meeting request to discuss their clinical endpoint bioequivalence study. The meeting request was later withdrawn on 4/27/07.

On 1/3/06, OGD forwarded comments to the sponsor. OGD's comments to the sponsor included recommendations to conduct a clinical endpoint BE study for the 0.03% strength and to enroll patients with moderate to severe atopic dermatitis with at least 20% body surface area (BSA) affected, as defined by the criteria of Hanifin and Rajka.

On 2/7/06, the sponsor submitted a response to our 1/31/06 comments with several disagreements. On 2/22/06, OGD responded to the sponsor with comments reinforcing the original recommendations from 1/3/06.

On 9/20/06, the sponsor sent an email to OGD proposing to add an interim assessment to potentially adjust the sample size for their clinical endpoint BE study for Tacrolimus Ointment. Prior to OGD's response, the sponsor (now acquired by Nycomed) submitted a second email (on 6/27/08) proposing to use an alpha-based statistical approach. The two email inquiries were converted to Control Documents (OGD #06-1411).

On 7/11/08, the sponsor submitted a protocol (P08-080) for the 0.03% strength.

On 4/8/10, the sponsor submitted their ANDA (200744) for Tacrolimus Ointment, 0.1%.

On 11/18/10, the sponsor submitted a New Strength Amendment for the 0.03% strength. Subsequently, on 2/24/12, P08-080 (the protocol for the 0.03% strength) was administratively closed upon the sponsor's request because the ANDA was already submitted.

On 3/23/12, two Draft Guidance on Tacrolimus Ointment/Topical, 0.03% and 0.1% were posted on the FDA website. On the same date, the sponsor (now acquired by Fougera, formerly Nycomed and Altana) was contacted and informed that their previous two email inquiries (OGD #06-1411) were closed due to the submission of the ANDA and due to the posting of the two Draft Guidance on Tacrolimus Ointment/Topical, 0.03% and 0.1%.

Reviewer's Comments:

- *In a subsequent amendment (dated 9/8/10) to ANDA 200744, the sponsor stated that no interim analysis was performed. Plans for an Interim Analysis was removed from their protocol in "Protocol Amendment 3." The sponsor stated that "after conducting an updated literature review (May-July 2009) it was determined that assumptions made for sample size calculations were appropriate and Nycomed decided to remove the plan for an Interim Analysis."*

- *Comments forwarded to the sponsor in the 1/3/06 correspondence are consistent with the recommendations found in the Draft Guidance on Tacrolimus Ointment/Toipcal, 0.03% and 0.1% except for the list of signs and symptoms for assessment. The 1/3/06 correspondence included two additional signs (excoriation and oozing/crusting) not found in the Draft Guidance.*

2.1.2.3 INDs, Protocols, or Control Documents submitted by other sponsors

Several protocols and controls have been submitted by other sponsors for this drug product.

There are 4 protocols from other sponsors in the Office of Generic Drug database (as of 9/11/13):

Protocol No	Drug Name	Firm	Letter Date	Completed Date	Comments
04-044	Tacrolimus 0.03%	(b) (4)			
05-056	Tacrolimus				
06-047	Tacrolimus 0.1%				
11-021	Tacrolimus				

There are 15 Controlled Correspondence Documents from other sponsors listed in the OGD database (as of 9/11/13):

Control No	Title	Description	Status	Doc Date	From
04-1084	Tacrolimus Ointment	(b) (4)			
05-0979	Tacrolimus Ointment				
06-0139	Tacrolimus				
06-0851	Tacrolimus Ointment				
06-0929	Tacrolimus Ointment				

07-0273	Tacrolimus	(b) (4)
07-1535	Tacrolimus	
08-0336	Tacrolimus Ointment	
09-0356	Non proportional Tacrolimus BE recommendation	
11-0336	Tacrolimus ointment	
12-0999	Tacrolimus Ointment	

2.1.2.4 Other ANDA submissions for same product

(b) (4)

2.1.3 Other Relevant Information

The FDA has posted a *Draft Guidance on Tacrolimus Ointment/Topical, 0.03%, (March 2012)* and *Draft Guidance on Tacrolimus Ointment/Topical, 0.1%, (March 2012)* on the FDA website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296989.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296988.pdf, respectively.

Reviewer's Comments:

The sponsor's protocol (P04-056) were submitted to OGD prior to the posting of these Draft Guidances. OGD comments regarding the protocol (and all subsequent correspondences with the sponsor) were forwarded to the sponsor prior to the posting of these Draft Guidances. As previously mentioned, comments forwarded to the sponsor in the 1/3/06 correspondence are consistent with the recommendations found in the Draft Guidance on Tacrolimus Ointment/Topical, 0.03% and 0.1% except for the list of signs and symptoms for assessment. The 1/3/06 correspondence included two additional signs (excoriation and oozing/crusting) not found in the Draft Guidance.

2.2 Description of Clinical Data and Sources

2.2.1 Clinical Endpoint Bioequivalence Study for Tracolimus Ointment 0.1% Strength

Protocol Number	ALT 0416-01-01
Study Title	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.1% to PROTOPIC® (Tacrolimus) Ointment 0.1% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis
Contract Research Organization(s)	*Clinical Trial Management and Clinical Monitoring*: Symbio, LLC (Symbio) (b) (4)
Study Period	
(date of first enrollment):	28 January 2008
(date of last completed):	12 August 2009

Study Centers, Principal Investigators and Enrollment

This was a multicenter study conducted at 39 sites in the United States and 3 sites in Latin America.

Site Number	Principal Investigator & Study Center	Number Enrolled	Number in Sponsor's Per-Protocol Population
Site #1	Jeffrey Adelglass, MD Research Across America Plano, TX	43	36
Site #2	Elizabeth A. Arthur, MD Spa, LLC Rochester, NY	5	4
Site #3	Suzanne Bruce, MD Suzanne Bruce and Associates The Center for Skin Research Houston, TX	19	18
Site #4	Alicia Bucko, D.O. Academic Dermatology Associates Albuquerque, NM	42	35
Site #5	Robert Call, MD Specialists, Inc. Richmond, VA	45	25
Site #6	Michelle Chambers, MD Radiant Research Columbus, OH	40	32
Site #7	Zoe Diana Draelos, MD Dermatology Consulting Services High Point, NC	50	45

Site Number	Principal Investigator & Study Center	Number Enrolled	Number in Sponsor's Per-Protocol Population
Site #8	Charles F. Fogarty, MD Spartanburg Medical Research Spartanburg, SC	30	23
Site #9	Joseph Fowler, MD Dermatology Specialists, PSC Louisville, KY	15	10
Site #10	Ellen H. Frankel, MD Clinical Partners, LLC Johnston, RI	18	15
Site #11	Sandra Gawchik, MD Asthma and Allergy Research Associates Upland, PA	17	13
Site #12	Michael Gold, MD Tennessee Clinical Research Center Nashville, TN	10	9
Site #13	Terry Jones, MD J & S Studies, Inc. College Station, TX	17	16
Site #14	None enrolled	0	0
Site #15	None enrolled	0	0
Site #16	None enrolled	0	0
Site #17	Jerry Bagel, MD Windsor Dermatology East Windsor, NJ	4	2
Site #18	Jonathan Kantor, MD (Robert G. Brown, MD) North Florida Dermatology Associates Research Department Jacksonville, FL	39	29
Site #19	None enrolled	0	0
Site # 20	Walter K. Nahm, MD University Clinical Trials, Inc. San Diego, CA Walter K. Nahm, MD, Inc. San Diego, CA	67	52
Site #21	Anjuli Nayak, MD Sneeze, Wheeze & Itch Associates, LLC Normal, IL	5	3
Site #22	Phoebe Rich, MD Oregon Dermatology & Research Center Portland, OR	9	9
Site #23	Ronald Savin, MD The Savin Center New Haven, CT	4	2
Site #24	Kimball Silverton, DO Silverton Skin Institute Grand Blanc, MI	2	1
Site #25	Panos E. Vasiloudes, MD Academic Alliance in Dermatology Tampa, FL	14	9
Site #26	None enrolled	0	0

Site Number	Principal Investigator & Study Center	Number Enrolled	Number in Sponsor's Per-Protocol Population
Site #27	John Winder, MD Toledo Center for Clinical Research Sylvania, OH	4	4
Site #28	Paul Yamauchi, MD, PhD Dermatology Institute and Skin Care Center Inc. Santa Monica, CA	19	13
Site #29	None enrolled	0	0
Site #30	Pinkas E. Lebovits, MD Pinkas E. Lebovits, MD, PC New York, NY	62	45
Site #31	T. Joseph Raoof, MD T. Joseph Raoof, MD, Inc. Encino, CA	62	46
Site #32	None enrolled	0	0
Site #33	Robert Haber, MD Haber Dermatology & Cosmetic Surgery South Euclid, OH	2	0
Site #34	John DiGiovanna, MD Dermatopharmacology Division - Rhode Island Hospital Providence, RI	2	2
Site #35	Alan Goldsobel, MD Allergy & Asthma Associates of Santa Clara Valley Research Center San Jose, CA	11	11
Site #36	David Hassman, DO Comprehensive Clinical Research Berlin, NJ	7	3
Site #37	None enrolled	0	0
Site #38	Karl Heine, MD Karl Heine Dermatology Henderson, NV	18	15
Site #39	Jo Lynne Herzog. MD Birmingham Radiant Research Birmingham, AL	18	15
Site #40	Cheryl Hull, MD Hull Dermatology, PA Village on the Creeks Rogers, AR	3	2
Site #41	Cindy Lamerson, MD Nevada Center for Dermatology Reno, NV	3	1
Site #42	Robert Matheson, MD Oregon Medical Research Center, PC Portland, OR	10	10
Site #43	Isaac Melamed, MD 1st Allergy and Clinical Research Center Centennial, CO	8	6
Site #44	Jeffrey K. Moore, MD Deaconess Clinic Downtown Evansville, IN	4	3
Site #45	William P Werschler, MD Premier Clinical Research Spokane, WA	13	5

Site Number	Principal Investigator & Study Center	Number Enrolled	Number in Sponsor's Per-Protocol Population
Site #46	None enrolled	0	0
Site #47	Charles McKeever, MD Hospital Punta Pacifica, Suite 5-12 Blvd. Pacifica y Via Punta Darien Panama City, Panama	14	14
Site #48	Nelly Paz, MD Centro Orquídea Blanca 10 Calle 17-18 Ave no. 9 San Pedro Sula, Honduras	2	2
Site #49	Daisy Blanco, MD Instituto Dermatológico Calle Federico Velásquez Esq. Albert Thomas Ensanche Maria Auxiliadora Santo Domingo, Republica Dominicana	11	10
Site #50	Lawrence C. Parish, MD Paddington Testing Co., Inc. Philadelphia, PA	24	21
Site #51	George Murakawa, MD Somerset Skin Centre Troy, MI	1	0

2.2.2 Clinical Endpoint Bioequivalence Study for Tacrolimus Ointment 0.03% Strength

Protocol Number	ALT 0417-01-01
Study Title	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.03% to PROTOPIC® (Tacrolimus) Ointment 0.03% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis
Contract Research Organization(s)	*Clinical Trial Management and Clinical Monitoring*: Symbio, LLC (Symbio) (b) (4)
Study Period	
(date of first enrollment):	10 January 2008
(date of last completed):	11 September 2009

Study Centers, Principal Investigators and Enrollment

This was a multicenter study conducted at 47 sites in the US and 4 sites in Latin America.

Site Number	Principal Investigator & Study Center	Number Enrolled	Number in Sponsor's Per-Protocol Population
Site #1	Alicia Barba, MD International Dermatology Research, Inc. Miami, FL	8	6

Site Number	Principal Investigator & Study Center	Number Enrolled	Number in Sponsor's Per-Protocol Population
Site #2	Warner W. Carr, MD Southern California Research Mission Viejo, CA	23	10
Site #3	Suzanne Bruce, MD Suzanne Bruce and Associates The Center for Skin Research Houston, TX	33	25
Site #4	Alicia Bucko, D.O Academic Dermatology Associates Albuquerque, NM	36	27
Site #5	Robert Call, MD Commonwealth Clinical Research Specialists, Inc. Richmond, VA	37	30
Site #6	Charles F. Fogarty, MD Spartanburg Medical Research Spartanburg, SC	21	16
Site #7	Ellen H. Frankel, MD Clinical Partners, LLC Johnston, RI	16	9
Site #8	Sandra Gawchik, MD Asthma and Allergy Research Associates Upland, PA	20	17
Site #9	Michael Gold, MD Tennessee Clinical Research Center Nashville, TN	14	13
Site #10	Alan B. Goldsobel, MD Allergy & Asthma Associates of Santa Clara Valley Research Center San Jose, CA	24	22
Site #11	Kimberly Grande, MD The Skin Wellness Center, PC Clinical Research Division Knoxville, TN	1	1
Site #12	Duane J. Harris, MD Intermountain Clinical Research Draper, UT	11	8
Site #13	Michael P. Husseman, MD REGS: Wee Care Pediatrics, Bountiful, UT SITE: Layton, UT	30	24
Site #14	Michael Jarratt, MD DermResearch, Inc. Austin, TX	16	14
Site #15	Steven Kempers, MD Minnesota Clinical Study Center Fridley, MN	19	14
Site #16	Mark S. Lee, MD Progressive Clinical Research San Antonio, TX	6	4
Site #17	Mark Ling, MD, PhD MedaPhase, Inc. Newnan, GA	18	13

Site Number	Principal Investigator & Study Center	Number Enrolled	Number in Sponsor's Per-Protocol Population
Site #18	Robert Matheson, MD Oregon Medical Research Center, PC Portland, OR	36	25
Site #19	John H. Tu, MD, MS Skin Search of Rochester, Inc. Rochester, NY	26	22
Site # 20	Eugene Monroe, MD Advanced Healthcare, SC Clinical Research Center Milwaukee, WI	4	2
Site #21	Anjuli Nayak, MD Sneeze, Wheeze & Itch Associates, LLC Normal, IL	4	3
Site #22	Kimball Silverton, DO Silverton Skin Institute Grand Blanc, MI	5	4
Site #23	David R. Hassman, DO Comprehensive Clinical Research Berlin, NJ	32	15
Site #24	None enrolled	0	0
Site #25	Daniel M. Stewart, DO Michigan Center for Skin Care Research Clinton Township, MI	20	14
Site #26	Leonard Swinyer, MD Dermatology Research Center, Inc. Salt Lake City, UT Leonard Swinyer, MD, PC Salt Lake City, UT	3	0
Site #27	Panos E. Vasiloudes, MD Academic Alliance in Dermatology Tampa, FL	8	8
Site #28	Patricia P. Westmoreland, MD Palmetto Clinical Trial Services, LLC Simpsonville, SC	14	12
Site #29	None enrolled	0	0
Site #30	Dow Stough, MD Burke Pharmaceutical Research Hot Springs, AR	15	13
Site #31	Pranav B. Sheth, MD University Dermatology Consultants, Inc. Dermatology Research Center Cincinnati, OH	3	2
Site #32	Lawrence C. Parish, MD Paddington Testing Co., Inc. Philadelphia, PA	107	82
Site #33	Manuel Briones, MD Franciso Bolona #610 Decima Oeste 1er Piso Officina #105 Ciudadela Kennedy Guayaquil, Ecuador	2	2

Site Number	Principal Investigator & Study Center	Number Enrolled	Number in Sponsor's Per-Protocol Population
Site #34	Charles McKeever, MD Hospital Punta Pacifica, Suite 5-12 Blvd. Pacifica y Via Punta Darien Panama City, Panama	34	32
Site #35	Nelly Paz, MD Centro Orquídea Blanca 10 Calle 17-18 Ave no. 9 San Pedro Sula, Honduras	2	2
Site #36	Daisy Blanco, MD Instituto Dermatológico Calle Federico Velásquez Esq. Albert Thomas Ensanche Maria Auxiliadora Santo Domingo, Republica Dominicana	28	23
Site #37	Tory Sullivan, MD, PA Miami Dermatology Research Institute, LLC North Miami Beach, FL	45	40
Site #38	Jeffrey Adelglass, MD Research Across America, Plano, TX REGS TO: RAA, Dallas, TX	41	32
Site #39	None enrolled	0	0
Site #40	Michelle Chambers, MD Radiant Research Columbus, OH	20	12
Site #41	None enrolled	0	0
Site #42	Zoe Diana Draelos, MD Dermatology Consulting Services High Point, NC	22	20
Site #43	None enrolled	0	0
Site #44	None enrolled	0	0
Site #45	JoLynne Herzog, MD Birmingham Radiant Research Birmingham, AL	11	7
Site #46	Cindy Lamerson, MD Nevada Center for Dermatology Reno, NV	1	0
Site #47	Pinkas E. Lebovits, MD Pinkas E. Lebovits, MD, PC New York, NY	12	11
Site #48	Isaac Melamed, MD 1st Allergy and Clinical Research Center Centennial, CO	15	9
Site #49	Stephen Shewmake, MD Centre For Health Care Medical Associates Poway, CA	2	2
Site #50	Jeffrey K. Moore, MD Deaconess Clinic Downtown Evansville, IN	3	3
Site #51	William P. Werschler, MD Premier Clinical Research Spokane, WA	8	6

Site Number	Principal Investigator & Study Center	Number Enrolled	Number in Sponsor's Per-Protocol Population
Site #52	Terry Jones, MD J & S Studies, Inc. College Station, TX	4	3
Site #53	George Murakawa, MD Somerset Skin Centre Troy, MI	4	3
Site #54	Iltefat Hamzavi, MD Hamzavi Dermatology Fort Gratiot, MI	1	0
Site #55	T. Joseph Raoof, MD T. Joseph Raoof, MD, Inc. Encino, CA	23	14
Site #56	Serena Mraz, MD Solano Clinical Research, A Division of Dow Pharmaceutical Sciences, Inc. Vallejo, CA	3	2
Site #57	Walter Nahm, MD University Clinical Trials Inc. San Diego, CA 92123 Walter K. Nahm, MD, PhD, Inc. San Diego, CA	15	14

2.2.3 Safety Monitoring Study

Protocol Number	ALT 0417-01-02
Study Title	A Safety Monitoring Extension to ALT 0417-01-01, a Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.03% to PROTOPIC® (Tacrolimus) Ointment 0.03% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis
Contract Research Organization(s)	*Study Monitoring, Quality Assurance, Data Management, Statistical Analysis, and preparation of integrated clinical/statistical report* : Symbio (b) (4)
Study Period	
(date of first enrollment):	16 November 2009
(date of last completed):	15 April 2011

Study Centers, Principal Investigators and Enrollment

This was a multicenter study conducted at 14 sites in the US and 1 site in Dominican Republic.

Site Number	Principal Investigator & Study Center	Number Enrolled
Site #1	Suzanne Bruce, MD Suzanne Bruce and Associates The Center for Skin Research Houston, TX	0

Site Number	Principal Investigator & Study Center	Number Enrolled
Site #2	Robert Call, MD Commonwealth Clinical Research Specialists, Inc. Richmond, VA	0
Site #3	Charles F. Fogarty, MD Spartanburg Medical Research Spartanburg, SC	0
Site #4	Ellen H. Frankel, MD Clinical Partners, LLC Johnston, RI	0
Site #5	Sandra Gawchik, MD Asthma and Allergy Research Associates Upland, PA	0
Site #6	Duane J. Harris, MD Intermountain Clinical Research Draper, UT	0
Site #7	Steven Kempers, MD Minnesota Clinical Study Center Fridley, MN	0
Site #8	Mark Ling, MD, PhD MedaPhase, Inc. Newnan, GA	0
Site #9	Robert Matheson, MD Oregon Medical Research Center, PC Portland, OR	0
Site # 10	Eugene Monroe, MD Advanced Healthcare, SC Clinical Research Center Milwaukee, WI	0
Site #11	David R. Hassman, DO Comprehensive Clinical Research Berlin, NJ	1
Site #12	Daniel M. Stewart, DO Michigan Center for Skin Care Research Clinton Township, MI	1
Site #13	Patricia P. Westmoreland, MD Palmetto Clinical Trial Services, LLC Simpsonville, SC	0
Site #14	Lawrence C. Parish, MD Paddington Testing Co., Inc. Philadelphia, PA	2
Site #15	Daisy Blanco, MD Instituto Dermatológico Calle Federico Velásquez Esq. Albert Thomas Ensanche Maria Auxiliadora Santo Domingo, Republica Dominicana	1

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

Original Submission:

April 8, 2010 (Study 0416-01-01 for the 0.1% strength)

Study Amendments:

1. September 9, 2010 (eCTD Sequence 0001; Resubmission/After Refuse to Receive) - Revised Datasets and additional information for Study 0416-01-01 for the 0.1% strength
2. November 19, 2010 (eCTD Sequence 0005; New Strength Amendment) – Study report for the 0.03% strength (Study 0417-01-01) submitted
3. February 29, 2012 (eCTD Sequence 0015; Gratuitous Bioequivalence Amendment) - safety monitoring report (Study 0417-01-02) for error in packaging for 0.03% strength study
4. May 4, 2012 (eCTD Sequence 0017; Clinical Bioequivalence Amendment/Response to Information Request) – Information regarding the trough tacrolimus concentrations submitted.
5. August 23, 2013 (eCTD Sequence 0024; Clinical Bioequivalence Amendment/Response to DCR's Easily Correctable Deficiency finalized on 8/8/13)

Office of Scientific Investigation (OSI) Report:

Memorandum finalized on January 9, 2013 by Young Moon Choi, Ph.D.

FDA Statistical Review:

Statistical Review finalized on August 21, 2013 by Fairouz Makhlouf, Ph.D.

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

2.3.2.1 Office of Scientific Investigations (OSI) Report:

OSI Review finalized on January 9, 2013 by Young M. Choi, Ph.D.

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states:

"The protocol and informed consent form (ICF) [for Study ALT 0416-01-01 and Study ALT 0417-01-01], and assent form [for Study ALT 0417-01-01] were reviewed and approved in writing by a central or local Institutional Review Board (IRB) prior to enrollment of any patients into the study…. The investigator ensured that the IRB complied with the requirements set forth in Title 21 of the United States (US) Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR), Part 56."

"This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and current Good Clinical Practices (GCPs) and in compliance with local regulatory requirements and 21 CFR 312."

Deficiency (8/8/13 ECD Item A.1 and B.1):

When the potential mis-packaging was initially discovered, did the study participants stop study medication use?

Response

The potential mis-packaging was discovered on 10/21/08. Symbio LLC, the Contract Research Organization that managed the study, notified all sites of a hold on study enrollment via fax on 10/28/08 and all sites provided confirmation of receipt. Study participants dosing at the time of the enrollment hold did not discontinue study medication use.

Blinded adverse event listings were reviewed for subjects entered into the database. No unexpected trends were observed.

Reviewer assessment

In the case of Study 0416-01-01 for the 0.1% strength, there was a potential for patients in the test group to be dosed with the placebo. Thus, the packaging error did not create a safety concern for these patients. However, in the case of Study 0417-01-01 for the 0.03% strength, there was a potential for patients (which included pediatrics) in the placebo group to be dosed with the 0.1% strength of the test product. Given that the 0.1% strength is approved in the adult population, it is acceptable that the adult patients continued using the mis-packaged medication. However, the 0.1% strength is not approved in the pediatric population. Thus, the pediatric patients enrolled into the placebo group may have been placed at increased risk. From an ethical perspective, pediatric subjects enrolled and taking study medications should have discontinued the study medications once the packaging error was discovered. Fortunately there were no untoward events reported and so this data can be considered in the analysis.

2.3.4 Evaluation of Financial Disclosure

The sponsor certified (Form FDA 3454) that the principal investigators and sub-investigators involved in Study 0416 and Study 0417 did not have any financial arrangements, significant payments, proprietary interest or equity interest to report.

2.4 Review of a Clinical Endpoint Bioequivalence Study

2.4.1 Brief Statement of Conclusions

Based on the FDA's statistical analysis, these studies appear to demonstrate bioequivalence of the test product with the reference product. The proportion of patients with treatment success for the Test and Reference products were demonstrated by the FDA's analysis to be superior to placebo in both studies.

2.4.2 General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's clinical endpoint bioequivalence studies (ALT 0416-01-01 and ALT 0417-01-01) was reviewed to evaluate the bioequivalence of the test product and the reference product. The primary endpoint was the proportion of patients in the per-protocol population in each group with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, based on a 4-point scale, within all treatment areas) based on the Investigator's Global Assessment of Disease Severity, at the end of treatment (i.e., week 2 visit/Day 15 for Study ALT 0416 and week 4 visit/Day 28 for Study ALT 0417). The sponsor's proposed primary parameter was evaluated for bioequivalence and secondary parameters were considered as supportive information. In addition, the sponsor's safety monitoring study (ALT 0417-01-02) was reviewed to evaluate the safety concerns of those patients mis-dosed with the 0.1% strength of the test material instead of the 0.03% placebo.

2.4.3 Detailed Review of Bioequivalence Study with Clinical Endpoints for Tracolimus Ointment 0.1% Strength (Study ALT 0416-01-01)

2.4.3.1 Protocol Review

Sponsor's protocol #:	ALT 0416-01-01
Title	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.1% to PROTOPIC® (Tacrolimus) Ointment 0.1% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis
Objectives	The objectives of this study were to compare the safety and efficacy profiles of Nycomed US Inc.'s tacrolimus ointment, 0.1% to those of Astellas Pharma US, Inc.'s PROTOPIC® (tacrolimus) Ointment 0.1% and to demonstrate the superior efficacy of the two active ointments over that of the Nycomed US Inc. Vehicle (placebo) in the treatment of atopic dermatitis.

2.4.3.1.1 Study Design

Overall Study Design and Plan

This was a randomized, double-blind, vehicle-controlled, parallel-group study conducted in patients at least 18 years of age with moderate to severe atopic dermatitis and ≥ 10% body surface area (BSA) affected. Approximately 792 patients were to be enrolled in order to obtain 465 per-protocol (PP) patients (155 patients in each active treatment group and 155 patients in the Vehicle group).

At the Baseline Visit (Visit 1/Day 1), informed consent was obtained prior to any study-related procedures. The investigator then performed an assessment of the patient's signs and symptoms of atopic dermatitis and a global evaluation of its severity. The patient's assessment of pruritus was recorded. The investigator also recorded the patient's medical history and prior and

concomitant medications, and performed a physical examination. Females of childbearing potential were required to have a negative urine pregnancy test at the Baseline Visit.

Eligible patients were then randomized in a 1:1:1 ratio to one of the three study formulations (Test product, Reference product, or Placebo). Patients were instructed to apply the study medication topically twice-daily (morning and evening, after washing with non-medicated, non-irritating soap) approximately 12 hours apart for two weeks (14 days). Patients returned to the office for follow up evaluations at Day 4 (-0, +2 days/Visit 2) and Day 14 (-1, +3 days/Visit 3). A blood sample was drawn for the assay of tacrolimus concentration at Visit 2. The signs and symptoms of the target sites were assessed and the investigator's evaluations were recorded at Visit 2 and Visit 3. The patient's concomitant medications were assessed and recorded, along with any adverse events (AEs). Patients returned at each visit with the study medication and patient diaries. Compliance with study medication applications were assessed via the patient diary, and at Visit 3, all study medication was collected.

The study schedule is depicted in **Error! Reference source not found.**.

Efficacy variables included the Investigator's Global Evaluation (IGE) and individual clinical signs and symptoms (ie, erythema, induration/papulation, lichenification, scaling, oozing/crusting, and excoriation) per body region (head and neck, trunk, upper extremities, and lower extremities), pruritus scores, and the percent of the total body surface area affected with atopic dermatitis (% BSA). Safety variables included adverse events (AEs).

The primary endpoint was the proportion of patients in the per-protocol population with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the IGE at the end of treatment (Day 14/Visit 3).

Procedures and Observations:

A summary of the study procedures performed at each visit is given in Table 1.1.

Table 1.1: Study Schedule (per sponsor)*

Visit Number	Visit 1 Baseline	Visit 2	Visit 3 End of Study/ Early Termination	Unscheduled Visit
Visit Day	**Day 1**	**Day 4 (-0, +2 Days)**	**Day 14 (-1, +3 Days)**	
Screening/Consent	X			
Demographics	X			
Medical History	X			
Physical Examination[1]	X			
Urine Pregnancy Test[2]	X			
Inclusion/Exclusion Criteria Review	X			
Assessment of Diagnosis of Atopic Dermatitis	X			
Assessment of Signs and Symptoms of Target Lesions	X	X	X	X
Pruritus Assessment	X	X	X	X
Blood Draw		X		
Investigator's Global Evaluation	X	X	X	X
Adverse Event Reporting		X	X	X
Concomitant Medication Review	X	X	X	X
Drug Dispensing, if applicable	X	X		If applicable
Patient Instruction/Compliance Review	X	X	X	X
Drug Return, Accountability		X	X	If applicable

* From Sponsor's April 8, 2010 submission, Final Report Version 1.0 ALT 0416-01-01 Table 9.1.
[1] Physical examinations included vital signs (height, weight, body temperature, pulse, respiration rate, and blood pressure).
[2] Performed on females of childbearing potential only and completed at the site prior to enrollment into the study.

Reviewer Comments:

The Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012) recommends that the End of Study visit be on Study Day 15. The sponsor used Study Day 14 as the End of Study visit. Since the same difference in date is very minimal and was applied to all study arms, this discrepancy should not have any clinical significance.

Study Population:

Inclusion Criteria:

1. Had a definite clinical diagnosis of moderate to severe atopic dermatitis with ≥ 10% BSA affected.
2. Had, according to the Hanifin and Rajka Criteria, at least two of the following: itching, chronic relapsing course, typical morphology and distribution of lesions (ie, flexural lichenification and linearity in adults; facial and extensor involvement during infancy and childhood), or familial and/or personal history of other atopic disorders (ie, asthma, allergic rhinoconjunctivitis, atopic dermatitis).
3. Had a Baseline Investigator's Global Evaluation (IGE) of at least moderate (score ≥ 3 on a 5-point scale).
4. Had moderate to severe atopic dermatitis for which the use of alternative, conventional therapies was deemed inadvisable because of potential risks, or were not adequately responsive or are intolerant of alternative, conventional therapies.

5. Were male or female, and at least 18 years of age.
6. If female and of childbearing potential (a female who was not postmenopausal for greater than 2 years and had not had a tubal ligation or a hysterectomy), had a negative urine pregnancy test and was willing to use an acceptable form of birth control during the study.
7. Patients must have provided a study specific Institutional Review Board (IRB) approved written informed consent for this study.
8. Were willing and able to understand and comply with the requirements of the study, apply the study medication as instructed, return for the required treatment period visits, comply with therapy prohibitions, and complete the study.
9. Agreed to adhere to protocol-specified requirements and concomitant therapy restrictions during the study, including discontinuation of non-medicated topical agents such as creams, lotions and emollients (to treatment area); topical antihistamines; topical antimicrobials; topical or systemic corticosteroids; light treatments (ultraviolet A [UVA], UVB); non-steroid immunosuppressants; and other investigational drugs. Patients were willing not to apply any treatments 24 hours before each study visit.
10. Were willing to avoid constant sun exposure and the use of tanning booths or other UV light sources during their participation in the study.
11. Were in good health, as confirmed by medical history and physical examination, and free from any clinically significant disease, other than atopic dermatitis, that might interfere with the study evaluations.

Reviewer Comments:

Although the Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012) and the Division of Dermatologic and Dental Products (DDDP) generally recommends a BSA of at least 20% for moderate to severe atopic dermatitis, OGD informed the sponsor in our March 22, 2006 comments to P04-056 that patients with minimum of 10% baseline BSA involvement may be enrolled as long as the baseline % BSA is similar among the treatment arms and the median baseline % BSA is >20% in all treatment groups. Based on the sponsor's baseline dermatological characteristics analysis of the ITT population (see ***Error! Reference source not found.****), the median baseline % BSA is 15.0% in all treatment groups. The FDA statistician confirmed that the baseline % BSA in the FDA's mITT and PP populations are similar among the treatment arms (p = 0.9766) and the median baseline % BSA in the FDA's mITT population is 15% for Test and Placebo, and 16% for Reference (see* ***Error! Reference source not found.****). Given that the mean baseline % BSA is >20% in all treatment groups and the baseline % BSA is similar among the treatment groups, it is acceptable that the median baseline % BSA is <20% in all treatment groups.*

Table 1.2: ***Summary of % Total Body Surface Area Affected at Baseline for the FMITT Population: Tacrolimus 0.1% (per FDA Statistician)***

% Body Surface Area	Total N=671	Tacrolimus 0.1% N=228	Protopic®0.1% N=232	Placebo N=211	p-value[a]
Mean (STD)	22.34 (17.65)	22.38 (17.69)	22.56 (18.28)	22.05 (16.97)	0.6687
Median	15	15	16	15	
Range	10-99	10-99	10-97	10-99	

[a] p-values were obtained from using a general linear model with treatment and site as factors

- *Even though the Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012) recommends that patients have been treated with a bland emollient for at least 7 days, OGD did not convey this recommendation to the sponsor in any of the previous communications. In addition, this criterion omission applies to all patients. Thus, it is acceptable.*
- *All other inclusion criteria are acceptable.*

Exclusion Criteria:

1. Were pregnant, nursing, or planning a pregnancy within the study participation period.
2. Had clinically infected atopic dermatitis at Baseline.
3. Had a skin disorder other than atopic dermatitis that may interfere with the study evaluations (ie, Netherton's Syndrome, psoriasis, topical fungal infections, ichthyosis, etc.).
4. Had pigmentation, extensive scarring, or pigmented lesions in the proposed treatment areas, which could interfere with the rating of efficacy parameters.
5. Had known or suspected history of a clinically significant systemic disease (ie, immunological deficiencies, human immunodeficiency virus [HIV]), unstable or not controlled medical disorders (ie, unstable diabetes, unstable hypertension), life-threatening disease, or current malignancies, or any significant medical condition likely to compromise participation in the study or the outcome of assessments, or to place the patient at risk.
6. Had been treated with systemic or photo antipsoriatic therapies/drugs (ie, acitretin, UVA/UVB, PUVA, oral retinoids, MMF, thioguanine, hydroxyurea, sirolimus, azathioprine, 6-MP, tanning booths, nonprescription UV light sources) within four weeks prior to study entry.
7. Had taken systemic corticosteroids (ie, oral or intravenous) within the past four weeks. Inhaled or intranasal corticosteroids were allowed if the patient was on a stable dose at study entry.
8. Had been treated with non-steroidal immunosuppressive medication (ie, cyclosporine, methotrexate) for any indication within four weeks prior to study entry.
9. Had been treated with any marketed or investigational biologic treatment for psoriasis or atopic disease (eg, alefacept, efalizumab, infliximab, adalimumab, etanercept, etc.) within the past three months or five half-lives of the biologic, whichever is longer. Vaccinations were not considered an exclusionary biologic treatment.
10. Had been treated with any topical anti-psoriatic (eg, salicylic acid, anthralin, tar, calcipotriene, etc.), any topical corticosteroid medications, and/or topical tacrolimus, or any topical retinoid (eg, tazarotene) within two weeks prior to study entry.

11. Had applied topical antimicrobials, topical antihistamines, or other medicated topical agents to the affected areas within the past seven days.
12. Had applied any non-medicated topical agents (including creams, ointments, gels, lotions, and emollients) in the areas to be treated within the previous 24 hours.
13. Had a known hypersensitivity to any of the following (in any dosage form): tacrolimus, macrolides (ie, erythromycin), or any excipient of the ointment.
14. Consumed excessive amounts of alcohol, abuse drugs, or had any condition that would compromise compliance, in the investigator's opinion, with the protocol.
15. Had been treated with an investigational drug or investigational device within a period of 30 days prior to study entry.
16. Had been previously enrolled in this study.

Reviewer Comments:

- *Enrollment of patients with stable diabetes is contrary to the Draft Guidance. However, OGD did not comment on it when submitted in the protocol by Altana (P04-056). In addition, the number of enrolled patients with diabetes was evenly distributed amongst the treatment arms (Test 13; Reference 15; Placebo 14). Therefore, it is acceptable that patients with stable diabetes were enrolled into this study.*
- *Sponsor deleted "patients who have taken astemizole within the past six (6) weeks" from their original protocol P04-056. Astemizole has been taken off the US market since June 1999. Therefore, it is acceptable to delete this criterion.*
- *Per the Draft Guidance, patients who used the following within 14 days of baseline should not have been enrolled into the study: 1) systemic antibiotics, 2) calcipotriene or other vitamin D preparations, or 3) retinoids. Although these exclusions were not forwarded to the sponsor in response to their submitted protocol (P04-056), use of these medications would confound the results of the study. Therefore, any patients who used the above mentioned items should be excluded from the FDA mITT and PP populations.*
- *Per the Draft Guidance, antihistamine use within 7 days prior to baseline should be an exclusion criteria. In the protocol submitted by Altana (P04-056) patients who took H1 and H2 antihistamines (e.g. Claritin, Zyrtec) within the past 7 days was an exclusion criterion, but has been deleted in this study. Any patient who used an antihistamine within 7 days prior to the baseline visit should be excluded from the FDA mITT and PP populations.*

Criteria for removal from the study:

Patients could have been removed from the study for any of the following reasons:

1. Patient withdrew his or her consent for any reason.
2. Patient's condition worsened to the degree that the investigator felt it was unsafe for the patient to continue in the study.
3. Patient's study drug was unblinded.
4. There was a significant protocol violation.
5. A concomitant therapy was reported or required that was liable to interfere with the results of the study.
6. Patient was lost to follow-up.
7. Patient became pregnant.

8. Administrative reasons.
9. An AE occurred for which the patient desired to discontinue treatment or the investigator determined that it was in the patient's best interest to be discontinued.

Reviewer Comments:

The sponsor's criteria for patient removal from the study is acceptable.

Prior and Concomitant Therapy:

Medications deemed exclusionary for study entry were also not permitted at any point during the study; however, the use of some treatments was permitted during study participation.

1. Antihistamines and inhaled or intranasal corticosteroids were allowed if the patient was on a stable dose at study entry and remained on a stable dose throughout the study period.
2. Vaccinations were not considered an exclusionary biologic treatment.
3. The use of sunscreen was also allowed during study participation.
4. Non-medicated topical agents such as creams, lotions, and emollients (to treatment area) were allowed as long as they were not applied within 24 hours before each study visit.

Reviewer Comments:

- *This reviewer disagrees that antihistamines should be allowed during the study period. Antihistamine use should be prohibited during the study period even if the patient was on a stable dose at study entry and remained on a stable dose throughout the study period. Those patients who used an antihistamine during the study have been excluded from the FDA analysis.*
- *The other items listed above are acceptable.*

Precautions/Restrictions:

The following precautions were taken during the study:

1. Patients were instructed to avoid common triggers for atopic dermatitis, such as exposure to decreased humidity (dry climates), very high or very low outside temperatures, wool, acrylic, dust mites, pet dander, harsh soaps, detergents, chlorinated water, and pollen. Also, on an individual level, patients were instructed to avoid excessive sweating, anxiety, and stress, which can also exacerbate the condition.
2. Patients were instructed to avoid long, hot baths.
3. Patients were instructed to be aware of foods that could cause an outbreak and to avoid those known foods (ie, fresh fruit, juices, seafood, meats, and egg protein).
4. Patients were instructed to minimize or avoid natural or artificial sunlight exposure.
5. Patients were instructed to avoid scratching, picking, rubbing, brushing, or otherwise traumatizing their lesions.
6. Patients were instructed not to bathe, shower, wash, or swim sooner than four hours after the application of study medication.
7. Patients were instructed to wash their hands after application, unless their hands were also being treated.
8. Patients were instructed not to allow the study medication to come in contact with their

eyes, mouth, or mucous membranes.

9. Patients were instructed to ensure that the skin was completely dry prior to study medication application.
10. No occlusive bandages, dressings, or wraps were allowed to cover the treated skin.

Reviewer Comments:

The sponsor's precautions and restrictions are acceptable.

Treatments:

Patients were randomly assigned to one of the following 3 study formulations:

Test (A)	Tacrolimus Ointment, 0.1% Manufacturer: Nycomed US Inc. Lot # Z432 Manufacture Date: 8/2007
Reference (B)	Protopic® (tacrolimus) Ointment 0.1% Manufactured: Astellas Pharma US, Inc Lot # 26181 Expiration: 9/2009
Placebo (C)	Vehicle of Test product Manufacturer: Nycomed US Inc. Lot # Z033 Manufacture Date: 6/2007

Patients were instructed to cleanse their skin with warm water and a non-medicated, non-irritating soap and dry their skin and hands thoroughly prior to application of the study medication. Patients were told to gently massage a thin layer of study medication lightly and evenly to all affected areas that the investigator diagnosed as atopic dermatitis. Similarly, patients were instructed to apply a thin layer of study medication to the other affected areas and then wash their hands after applying the ointment.

Compliance:

Patients were instructed to apply the medication twice daily for 14 days. Patients applied their first application of study medication in the office under the supervision of the third-party dispenser. Patients were instructed to apply the second application early in the evening, approximately 12 hours after the first application, or, if not enough time had lapsed between applications, the next application occurred the following morning. Compliance was determined from the patient Study Drug Diary card, which the patient was instructed to use to record all applications made and all applications missed. The number of applications missed was totaled by the study staff and recorded on the compliance page of the patient's CRF. All study medication was to be returned to the study site at each visit or early termination.

The compliance rate was calculated as:

$$\text{Compliance Rate} = \frac{\text{Total Number of Applications Taken}}{} \times 100\%$$

(Date of Last Application – Date of First Application + 1) × 2

Randomization:

A third-party dispenser assigned a patient number to each patient. The patient number corresponded to a computer-generated randomization schedule that assigned the number to one of the three study treatment groups. The randomization scheme was generated so that the Test product, Reference product, and Placebo were assigned in a 1:1:1 ratio. The patient numbers were assigned sequentially in the order in which patients enrolled at each study site.

Due to the discovery of a packaging error, enrollment into the study was suspended on 10/28/08. At that point, 438 patients (out of 793 total) were enrolled. After an outside third party packaging vendor (b) (4) evaluated the unused kits, a new randomization code was generated and new clinical kits were created. Enrollment was restarted in March 2009.

Deficiency (8/8/13 ECD Item A.5):

Provide contact information for (b) (4), who is listed as having generated the first set of randomization schedule.

Response

The contact information for (b) (4), which provided the randomization schedule for kits 0001 through 1011 (Packaging 1), has the following contact information:

(b) (4)

Reviewer assessment

Acceptable.

Deficiency (8/8/13 ECD Item A.6):

Clarify if (b) (4) also generated the second set of randomization schedule. If not, who generated the second set of randomization schedule. Provide their contact information.

Response

The randomization schedule for kits 2000 through 2773 (Packaging 2) was generated by (b) (4)

Reviewer assessment

Acceptable.

Deficiency (8/8/13 ECD Item A.7):

At what point in the study timeline did the Project Management (PM) Department of Nycomed receive a copy of the randomization code? Who had access to the randomization code maintained in the PM Department?

Response

The Project Management (PM) representative received the randomization code prior to the start of enrollment for subjects in that series and maintained such until database lock.

This responsibility was transferred to other Project Management representatives over the course of the study due to changes in staffing. However access continued to remain controlled and limited to PM only. Project Management made no decisions regarding conduct of these clinical studies.

Reviewer assessment

Acceptable. When a sponsor does not package the test materials, the sponsor can generate the randomization code and thus would have a copy of the randomization code. Therefore, it is acceptable that the sponsor's Project Management representative, who is not part of the Clinical Operations, has a copy of the randomization code.

Deficiency (8/8/13 ECD Item A.10):

Provide contact information for the outside unblinding/packaging vendor, (b) (4)

Response

(b) (4)

Reviewer assessment

Acceptable.

Reviewer Comments:

During the OSI inspections of the clinical sites, no issues were noted regarding the appropriate maintenance of a sealed/blinded randomization code.

Blinding:

All study medication was supplied in 100-gram tubes. Each patient's treatment unit consisted of one kit box of study medication as follows:

- Kit Boxes 0001 to 1011 contained five 100-gram tubes of study medication (first randomization)
- Kit Boxes 2000 to 2773 contained three 100-gram tubes of study medication (second randomization)

From the first series of kits randomized, it was determined that patients were using on average one to three tubes of study medication. Therefore, with the second packaging, three tubes were provided per kit.

The outer label of the box did not contain any information that could have identified the treatment group to which the patient was assigned, but did identify to which patient the kit had been assigned. The study medication was blinded by covering the tubes with an adhesive material. The labels on the tubes included the name of the sponsor, the study protocol number, patient number, a blank space for recording patient initials, and directions for use and storage. In addition, the labels included the following warning statements: "For dermatological use. Keep out of reach of children. Not for oral, ophthalmic or intravaginal use," and "Caution: New Drug Limited by Federal (or United States) law to investigational use."

Each tube carried a two-part label, of which each section included all of the above information, as well as a blank space for entering the patient's initials. The tear-off portion of each tube label carried the identity of the study medication contained in the tube. The identity of the study medication on the tear-off label was covered with an occluding layer that could have been removed (i.e., scratched off) if the investigator needed to know which treatment the patient received in order to make decisions regarding medical management.

The tear-off portion of the label had an adhesive backing to facilitate attachment to the Study Drug Label page. The individual boxes were numbered sequentially and study medication was to be dispensed as such. A copy of each patient's Study Drug Label page was collected at the end of the study in order to verify the adherence of the blind.

In order to nullify any remaining differences in product packaging, an third-party study medication dispenser who was not performing the clinical evaluations dispensed and received study medication. The investigator performing the clinical evaluations did not dispense or retrieve study medication.

The outside third party packaging vendor (b) (4) unblinded the unused kits and used study kits from the first randomization. (b) (4) provided the results of the used study supplies evaluation to the sponsor's Clinical Operations ("Clin Ops") Department in the form of a "blinded" memos on the morning of 10/9/09. The memos confirmed that 1 patient was confirmed to be misdosed and 9 patients were considered potentially mis-dosed due to at least 1 tube of study drug not returned. On the afternoon of 10/9/09, (b) (4) provided a final "unblinded" results in the form of a memo to a single unblinded statistician at (b) (4)

(b) (4) The memo included the patients numbers of those patients who were mis-dosed and those who were potentially mis-dosed. In addition, after the hard database lock, an "unblinded" memo was sent to Clin Ops.

Deficiency (8/8/13 ECD Item A.2):

When were the used study medication kits sent to (b) (4) *for unblinding?*

Response

The used study medication kits (defined as kits that were assigned to enrolled study subjects) from kit series 0001-1011 were sent to (b) (4) on 9/3/09. (b) (4) began unblinding these used kits on 9/9/09.

Reviewer assessment

Acceptable. The used study medication kits were sent to (b) (4) *after the last subject visit.*

Deficiency (8/8/13 ECD Item A.3):

Were the used study medication kits sent to (b) (4) *for unblinding after the study participants completed the study?*

Response

Yes. The Last Subject Last Visit was conducted on 8/12/09. (b) (4) began unblinding the used kits (of the 0001-1011 series with the potential packaging issue) on 9/9/09. Study integrity was maintained by utilizing a third party outside vendor to conduct all unblinding procedures.

Reviewer assessment

Acceptable

Deficiency (8/8/13 ECD Item A.8):

Who packaged the study medications for this study? Provide their contact information.

Response

The packaging of kits 0001 through 1011 (Packaging 1) was conducted at the Fougera Pharmaceuticals Inc. Hicksville facility by the production staff.

Fougera Pharmaceuticals Inc.
55 Cantiague Rock Road
Hicksville, NY 11801
631-454-7677
Gary Price- Associate Director, Quality Systems

The packaging of kits 2000 through 2773 (Packaging 2) was conducted at (b) (4).

(b) (4)

Reviewer assessment

Acceptable.

Deficiency (8/8/13 ECD Item A.9):

Clarify if new study medication kits were assembled for the second set of randomization or if the unblinded, unused study kids were re-blinded for the second set of randomization.

Response

The unused, sealed kits from Packaging 1 (kits 0001 through 1011) were returned to the Fougera Distribution Center in Arizona using insulated shipper boxes, with temptales (temperature monitoring devices) included in each box. Once returned, all unused kits were shipped in bulk to (b) (4) The kits were sorted into Test, Reference and Vehicle groups and then systematically unblinded to determine if there were any packaging errors included in the unused kits. Once sorted by treatment arm, a second randomization code generated by (b) (4) was applied to these same tubes creating kits 2000 through 2773.

Reviewer assessment

Acceptable

Deficiency (8/8/13 ECD Item A.11):

Clarify how many of the used study kits from the first randomization code was unblinded by (b) (4) *Provide a list of all the used study kits that were unblinded by* (b) (4)

Response

A 'used kit' is defined as a kit of study medication assigned to an enrolled study subject. A total of 438 used kits from the first randomization code were unblinded by (b) (4) Please refer to ALT 0416-01-01 Used Unblinded Kits for a detailed list of these kits.

Reviewer assessment

A total of 793 patients were enrolled and randomized to receive study medication kits, which means that (b) (4) *unblinded 55.23% (438 out of 793) of the medication kits from this study.*

Deficiency (8/8/13 ECD Item A.12):

Provide a copy of the "blinded" memo that was sent from (b) (4) *to "Clin Ops" the morning of 10/9/09.*

Response

Please refer to ALT 0416-01-01 Blinded (b) (4) Memo to Clin Ops 10-9-09.

Reviewer assessment

A copy of the memo is provided in the response. In the memo, the patient numbers are blackened out such that the patient identity can't be determined. No other patient identifiers are included in the memo. Acceptable.

Deficiency (8/8/13 ECD Item A.13):

Provide a copy of the "unblinded" memo that was sent from (b) (4) *the afternoon of 10/9/09.*

Response

Please refer to ALT 0416-01-01 Unblinded (b) (4) 10-9-09

Reviewer assessment

A copy of the memo is provided in the response. This "unblinded" memo is the same as the "blinded" memo from (b) (4) *to "Clin Ops" except the patient numbers are not blackened out. Acceptable.*

Deficiency (8/8/13 ECD Item A.14):

Provide a copy of the "unblinded" memo that was sent to "Clin Ops" on 11/5/09.

Response

Please refer to ALT 0416-01-01 Unblinded (b) (4) Memo to Clin Ops 11-5-09. (b) (4) discovered an inadvertent error in the initial 10/9/09 blinded memo. The 11/5/09 version of the memo was updated to correct this error.

Reviewer assessment

A copy of the memo is provided in the response. The sponsor explained elsewhere in the study report that Patient (b) (6) *was inadvertently included in the memo as potentially misdose. Details of this error can be found in Section 2.4.3.2.2* Statistical and Analytical Issues *of this review. Acceptable.*

Reviewer Comments:

The sponsor's blinding appears appropriate. The sponsor submitted enough evidence to assure that the integrity of the study data was not impacted by the packaging error and the unblinding of the used study medication kits.

2.4.3.1.2 Endpoints/Variables

Efficacy Measures

Clinical Signs and Symptoms Assessment: The patient's body was divided into the following four body regions: head and neck, trunk, upper extremities, and lower extremities. Target sites that exhibit the signs and symptoms of atopic dermatitis were chosen and assessed at all visits. Up to four target sites were to be selected on each patient, one in each of the four body regions, depending upon how many body regions in which atopic dermatitis is present. These target sites were to demonstrate the most typical atopic dermatitis involvement in that body region. It was not required that atopic dermatitis be present in all four body regions as long as the patient exhibited atopic dermatitis involvement in at least 10% of their total BSA. The target sites' locations were recorded on an anatomical diagram in the patients source documentation (Protocol Appendix III) so as to ensure consistent reporting at every visit.

At each visit, the same investigator, to the greatest extent possible, assessed the signs and symptoms (erythema, induration/papulation, lichenification, scaling, oozing/crusting, and excoriation) of the patient's atopic dermatitis at each target site and evaluated the presence and severity using the definitions below:

1. Erythema (defined as redness; residual hyperpigmentation, hypopigmentation, pigmented macules, or diffuse slight pink coloration were not included as erythema)

Score	Grade	Definition
0	None	No erythema present
1	Mild	Slight erythema, very light-pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red

2. Induration/papulation (defined as inflammation; swelling)

Score	Grade	Definition
0	None	No elevation
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation

3. Lichenification (defined as thickening upper layers of skin)

Score	Grade	Definition
0	None	No lichenification
1	Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2	Moderate	Definite thickening of the skin with skin marking exaggerated so that they form a visible criss-cross pattern
3	Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern

4. Scaling (defined as flakes or shedding of the stratum corneum)

Score	Grade	Definition
0	None	No evidence of scaling
1	Mild	Occasional fine, flaky scale predominates
2	Moderate	Coarse scale predominates
3	Severe	Thick, coarse, crusted scale predominates

5. Oozing/crusting (defined as seeping of tissue fluid; dried blood or tissue fluids)

Score	Grade	Definition
0	None	No evidence of oozing/crusting
1	Mild	Evidence of exudation
2	Moderate	Serous brown, yellow, or green exudations and/or drying of the discharge
3	Severe	Many dry scabs and/or exudations

6. Excoriation (defined as the loss of the top layer of the skin caused by scratching)

Score	Grade	Definition
0	None	No evidence of excoriation
1	Mild	Scant evidence of excoriation with no signs of deeper skin damage (erosion, crust)
2	Moderate	Several linear marks on the skin with some showing evidence of deeper skin injury (erosion, crust)
3	Severe	Many erosive or crusty lesions

7. Pruritus Assessment: Patients evaluated their overall itching/scratching/discomfort in the preceding 24 hours based on the following scale:

Score	Grade	Definition
0	None	None
1	Mild	Occasional, slight itching/scatching
2	Moderate	Constant or intermittent itching/scratching/discomfort that does not disturb sleep
3	Severe	Bothersome itching/scratching/discomfort that disturbs sleep

Reviewer Comments:

- *The sponsor's scales for individual signs and symptoms assessment are acceptable. The* Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012) *only list 4 signs and symptoms: Erythema, Induration/Papulation, Lichenification, and Pruritus. In our 3/22/06 comments, OGD informed the sponsor that EXCORIATION should be included in the signs and symptoms for assessment and that it is acceptable to include SCALING. Although oozing/crusting is not mentioned in the Draft Guidance or the sponsor's original protocol (P04-056), it is acceptable to include in the signs and symptoms for assessment (given that these signs and symptoms are not part of the primary endpoint and not part of the inclusion assessment/criteria.). The sponsor's list of signs and symptoms is acceptable. Recommend adding EXCORIATION and SCALING to the Draft Guidance list also.*
- *The* Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012) *does not mention if the assessment of the signs and symptoms should be limited to target sites or if should be based on all affected areas. Given that the signs and symptoms scores are secondary endpoints and the IGE evaluation (the primary endpoint) is on the "overall assessment of patient's atopic dermatitis," it is acceptable that the signs and symptoms assessment is limited to target sites.*

Investigator's Global Evaluation: The investigator made an independent global evaluation for overall assessment of the patient's atopic dermatitis. The same investigator, to the greatest extent possible, was to perform the Investigator's Global Evaluation (IGE) at each visit. This assessment incorporated evaluations for erythema, induration/papulation, amount of involvement, and a general clinical assessment.

The IGE was evaluated using the following scale:

Score	Grade	Definition
0	Clear	Minor, residual discoloration, no erythema or induration/papulation, no oozing/crusting
1	Almost Clear	Trace, faint pink erythema with almost no induration/population and no oozing/crusting
2	Mild	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation, possibly with some oozing/crusting
4	Severe	Deep/bright red erythema with severe induration/papulation with oozing/crusting

Reviewer Comments:

The sponsor's IGE scale is in accordance with the Investigator's Global Assessment of Disease Severity as found in the Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012) *and is acceptable.*

Clinical Laboratory Test: A blood sample was drawn for the assay of tacrolimus concentration (Visit 2 only) after the study medication was weighed. The blood samples were not to be taken from areas treated with study medication.

Safety Measures

Whether the adverse event (AE) was observed by the investigator or study coordinator, or reported independently by the patient, all AEs were recorded on the patient's CRF and in the appropriate source documentation at the site. The investigator assessed each AE in terms of the duration and frequency of each event, the action taken, the relationship to the study medication, the degree of severity (intensity), the seriousness, and the outcome.

Primary Endpoint:

The sponsor's primary efficacy endpoint was the proportion of patients in each treatment group who had an IGE rating of "Clear" or "Almost Clear" for atopic dermatitis (success).

Reviewer Comments:

The FDA recommended primary endpoint of this study is the proportion of patients in the per-protocol population with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the Investigator's Global Assessment of Disease Severity (which is the same as the sponsor's IGE) at the end of treatment (week 2 visit; study day 15). The sponsor's primary endpoint is in accordance with the Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012) *and is acceptable.*

Secondary Endpoints:

The secondary efficacy endpoints included

1. the mean change from baseline in the total individual clinical signs and symptoms (ie, erythema, induration/papulation, lichenification, scaling, oozing/crusting, and excoriation) per body region (ie, head and neck, trunk, upper extremities, and lower extremities),
2. the mean change from baseline in pruritus, and
3. the mean change from baseline in the % BSA.

Reviewer's Comments:

The sponsor's secondary endpoints are considered supportive information. A formal analysis from the FDA statistician of the secondary endpoints has not been requested.

2.4.3.1.3 Statistical analysis plan

The statistical analysis plan (SAP) used for the sponsor's analyses is provided in Appendix 16.1.9 of the sponsor's study report.

Patient Populations:

The sponsor's efficacy analyses were performed on the modified Intent-to-Treat and Per-Protocol populations. Safety analyses were performed on the Intent-to-Treat population.

Intent-to-Treat (ITT) Population

The sponsor's ITT population includes any individual who:

1. was enrolled into the study, randomized, and
2. received at least one application of study medication.

Reviewer's Comments:

The sponsor's definition for the ITT population is acceptable.

Modified Intent-to-Treat (mITT) Population

The sponsor's mITT population includes any ITT patient who:

1. met all inclusion and no exclusion criteria and
2. had at least one post-baseline IGE score.

Reviewer's Comments:

The sponsor's definition for the mITT population is acceptable.

Per-Protocol (PP) Population

The sponsor's PP population includes any mITT patient who:

1. was consistent with the protocol,
2. had not taken any concomitant medications that could potentially affect study evaluations and did not have any other significant protocol violations,
3. had at least seven days of treatment and one of the following:
   a. returned for Visit 3/End of Study Visit within visit windows, had a study drug compliance rate between 80-120%, and had data on the IGE at Visit 3, or
   b. met PP criteria up to the time of early study discontinuation due to worsening disease or lack of improvement, had a study drug compliance rate of at least 80%, and had at least one post-baseline value for the IGE (note: these patients were included as treatment failures), and
4. definitively dosed with the correct study medication as per the randomization.

For the purpose of determining the PP status of a patient, a study protocol violation was defined as any patient or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy. Additionally, any patient who developed a skin infection in one or more target areas was to be discontinued from the study and subsequently excluded from the PP population.

Reviewer's Comments:

- *Per the* Draft Guidance on Tacrolimus Ointment/Topical, 0.1% (March 2012)*, the currently recommended PP population should include patients who "did not miss the scheduled applications for more than 3 consecutive days." However, during the review of the sponsor's P04-056 protocol, which was prior to the posting of this Draft Guidance, this criteria for the PP population was not communicated to the sponsor. Therefore, the sponsor's submitted PP population definition is acceptable.*

- *In Listing 16.2.1 of the sponsor's study report, compliance rate is listed as 85-120%. A review of the datasets indicates that the sponsor used 85-120% as the compliance rate. Given that 80-120% is acceptable and 85-120% is more stringent, the use of 85-120% by the sponsor in their analyses is acceptable.*

General Considerations

The sponsor's equivalence analysis was conducted on both the mITT and PP populations: the equivalence analyses for the End of Study Visit results in the PP population were considered definitive with that for the mITT population as supportive. The sponsor's superiority analyses were conducted on both the mITT and PP populations: the superiority analyses for the end of treatment results in the mITT population were considered definitive with those for the PP population as supportive.

All statistical tests used a significance level of 0.05 (= 0.05), unless otherwise noted.

Since there was a potential for a packaging error, the potentially incorrectly dosed patients were excluded from the sponsor's PP population, but were included in the sponsor's mITT population using an "Analyzed as Randomized" approach if the patient met all mITT criteria. For all safety analyses, these potentially incorrectly dosed patients were "Analyzed as Dosed."

Deficiency (8/8/13 ECD Item A.4)

Clarify if the definitely mis-dosed patient (Patient (b) (6)) used only the mis-packaged tube or if that patient also used any correctly packaged tubes from the medication kits.

Response

Patient (b) (6) was randomized to the Test treatment group. The case report form indicates that the subject was dispensed and returned three 100-gram tubes. The case report form does not indicate how many tubes were used by the subject.

After the packaging error discovery, (b) (4) accounted for the following: (1) number of tubes per kit, (2) number of tubes that were of the incorrect lot and (3) whether or not the foil seal on the incorrect tubes was broken (indicating that it was used). Foil seals on tubes with the correct lot number were not evaluated. The number of correct tubes used by the subject (foil seal broken) cannot be definitively determined.

(b) (4) determined that of the three tubes dispensed, only one tube was vehicle, and this vehicle tube had a broken foil seal indicating it had been used. The subject was also dispensed 2 tubes of test product. However, it cannot be determined if the subject actually used these tubes or only the placebo tube. On Day 4 the case report form indicated that the subject used 51 grams of product over 8 applications. The subject completed the study reporting 25 applications. At this rate it is likely that the subject used at least some product from a test lot tube.

The subject was excluded from PP and in included in MITT as test (analyzed as randomized) for efficacy analyses. The subject was analyzed in a separate group called potential incorrect dose for safety analyses of the ITT population.

Reviewer assessment

Given that Patient [redacted] is excluded from the PP population, the use of both the mis-packaged and correctly packaged tubes should not impact the results. The use of both tubes would affect the safety data. However, the sponsor separated out this patient (with the other potentially mis-dosed patients) into a separate group of their own for the safety analysis. Therefore, it is acceptable that it cannot be determined definitively whether or not the patient used only the mis-packaged tube or correctly packaged tube.

Reviewer's Comments:

This reviewer agrees that the definitely mis-dosed patient (Patient [redacted]) and the potentially mis-dosed patients (Patients [redacted]) should be excluded from the PP population but included in the mITT population as "analyzed as randomized" unless there is a reason for exclusion from the mITT population.

Missing values or Dropouts:

For the analyses of efficacy, a last-observation-carried-forward (LOCF) approach was used by the sponsor for missing efficacy results in the mITT population. In the PP population, the LOCF approach was used only by the sponsor for patients who discontinued due to treatment failure or lack of efficacy (improvement) for their subsequent visits after discontinuation. If Visit 2 was missing, the Early Termination efficacy results were used by the sponsor to replace the missing Visit 2 efficacy results if Visit 3/Early Termination occurred on Day 10 or earlier.

Reasons for premature termination were compared by the sponsor among treatment groups and, if there were sufficient numbers of patients in each category, the frequency of reasons was compared by the sponsor using Pearson's Chi-square test, or Fisher's exact test, if more appropriate.

For demographic and baseline characteristics, each variable was analyzed by the sponsor using all available data. Patients with missing data were excluded only from analyses for which data were not available.

Reviewer's Comments:

The sponsor's statistical plan for missing values and dropouts is acceptable.

Site Pooling

According to the sponsor, in order to maintain an unbiased statistical analyses that could result from sites that enrolled a smaller number of patients, site pooling was used for sites with one or more mITT patients. After sorting the site by the smallest cell count (treatment-by-site) within each geographic region, the following algorithm for site pooling was used by the sponsor for all analyses:

- Step 1: If the site had the smallest cell count (treatment-by-site) of fewer than 3 patients in the mITT population, then the site was merged with a site that had the next smallest cell count into a new pooled site within the same geographic region. This procedure was repeated until the new pooled site had at least 3 patients in the mITT population for each treatment group. If several sites within the same geographic region had the same cell count of patients, then the sites were ordered by site number, and those with the lowest site number were pooled first.
- Step 2: Step 1 was repeated within each geographic region, until all new pooled sites had at least 3 patients in the mITT population for each treatment group.
- Step 3: Analyses were completed using the newly created pooled sites.

Sites for which there were no mITT patients were excluded from site pooling.

The geographical regions for each site were defined as follows:

Region	**Site**
Latin America	47, 48, 49
Midwest	6, 21, 24, 27,33, 44, 51
Northeast	2, 10, 11, 17, 23, 30, 34, 36, 50
Southeast	5, 7, 8, 9, 12, 18, 25, 39, 40
Southwest	1, 3, 4, 13
West	20, 22, 28, 31, 35, 38, 41, 42, 43, 45

Reviewer's Comments:

The FDA statistician did not utilize site pooling in their analysis. The FDA statistician states that "[w]hen we explored pooling the sites according to the sponsor's algorithm, the results were not substantially different."

Baseline Comparability

The comparability of treatment groups with regard to patient demographic and baseline characteristics was evaluated by the sponsor to identify differences among treatment groups that were not eliminated by randomization. The comparison was performed on the ITT, mITT, and PP populations.

The sponsor summarized each categorical variable (i.e., gender, ethnicity, race, IGE) by frequencies (N) and percentages (%) within each treatment group. The Cochran-Mantel-Haenszel (CMH) procedures were used to test the comparability of treatment groups, adjusting by study site.

Continuous variables (i.e., age, height, weight, and % BSA) were summarized by the sponsor using descriptive statistics, including the number of patients, mean, standard deviation (SD), median, and range (minimum [min], maximum [max]). The comparability of treatment groups was examined by a two-way analysis of variance (ANOVA) using treatment and study site as factors when normality and homogeneity assumptions were supported, or by the nonparametric ANOVA using Friedman's test when they were not.

Primary Endpoint Analysis:

The sponsor's primary efficacy endpoint was the proportion of patients in each treatment group who had an IGE rating of "Clear" or "Almost Clear" ("success") for atopic dermatitis at Visit 3 (End of Study). The significance level used for the final primary analyses was 0.05.

The difference between the active treatment (Test and Reference) groups in the proportion of patients with success at Visit 3 (End of Study) was evaluated by the sponsor using a two-sided 90% confidence interval (CI). This interval was constructed by Wald's method with Yates' continuity correction based on the data pooled from all study sites. The equivalence of the Test and Reference products was established if the confidence bounds of the 90% CI were contained within the limits of –0.20 to 0.20.

The sponsor compared the difference between each active treatment (Test and Reference) group in the proportion of patients with success at Visit 3 (End of Study) with that of the placebo group using independent, continuity-corrected Z-tests. The active treatment was considered superior to the Placebo if the proportion of patients with success in the active treatment group was significantly greater ($p < 0.05$) than that for patients in the placebo group.

Reviewer's Comments:

To establish bioequivalence, the 90% confidence interval of the test - reference difference between products for the primary endpoint (success proportion) must be contained within [-0.20, +0.20] for dichotomous variables (success versus failure), using the PP population. The sponsor's analysis for bioequivalence is acceptable.

As a parameter for determining adequate study sensitivity, the test and reference products should both be statistically superior to placebo control ($p<0.05$, two-sided) for the primary endpoint using the mITT population and LOCF. The sponsor's analysis for bioequivalence is acceptable.

Changes to the Planned Analyses

There was one amendment to the sponsor's original planned analyses, dated 6/20/08: Amendment 1 is dated 9/23/09. Due to the packaging error (discovered on 10/21/08, prior to database lock on 10/9/09) and the need to replace patients who received the incorrect assignment and those who potentially received the incorrect assignment, additional patients were enrolled to meet the new sample size. The sponsor's protocol and SAP were updated to reflect the changes to the analyses due to this error, as well as address any statistical concerns that could have resulted from the new sample size.

The following updates to the original SAP were implemented with Amendment 1:
General grammar, formatting, and spelling errors were corrected.

- Additional references to ALTANA Inc were removed and replaced with Nycomed US Inc.
- The number of subjects to be enrolled and the number of enrolling sites were increased due to a packaging error that might have occurred that led to the need for an increased sample size.

- The PP population was updated to exclude any subject who could have been incorrectly dosed due to the packaging error.
- General considerations for treatment-by-site interaction affects were updated to include an algorithm for site pooling for those sites with fewer than 3 subjects per treatment group in the mITT population.
- Information regarding the interim analysis was deleted since it was decided that an interim analysis would no longer be conducted.
- The statistical significance level for the primary endpoint of success rate was changed from 0.001 in the interim analysis and 0.049 for the final analysis to 0.05 overall.
- Due to the potential for subjects to have been dosed with incorrect study medication, analyses group definitions were updated as follows:

    - The efficacy analyses performed on the PP and mITT populations excluded potentially incorrectly dosed subjects from the PP population but included potentially incorrectly dosed subjects in the mITT population so that they were "analyzed as randomized."
    - The safety analysis performed on the ITT population included potentially incorrectly dosed subjects so that they were "analyzed as dosed."

- The frequency and percentages of AEs were updated to be tabulated by treatment groups (Test, Reference, and Vehicle), plus a group that included subjects who were potentially incorrectly dosed; SOC; PT; intensity; and relationship to study medication.
- Tables and listings were updated as needed to account for the changes in the text portion of the SAP.

Reviewer's Comments:

Based on the sponsor's investigation of the packaging error, patients who were randomized to receive the test product may have received Placebo. According to the sponsor's report, 1 patient (Patient (b) (6)) was confirmed to be mis-dosed and 9 patients (Patients (b) (6)) were considered potentially mis-dosed.

2.4.3.2 Study Conduct

2.4.3.2.1 Changes to the Conduct of the Study

There were three amendments to the sponsor's original protocol, dated 11/5/07: Amendment 1 is dated 2/20/08, Amendment 2 is dated 6/24/08, and Amendment 3 is dated 8/04/09.

The following updates were implemented with Amendment 1:

- Exclusion Criterion #10 was updated to include a washout period for topical tacrolimus use.
- The concomitant and prohibited medications table was updated to include the topical tacrolimus washout period, as well as other washout periods specified in exclusion criteria that were not previously included in this table.

- The Sponsor name was updated from ALTANA Inc (ALTANA) to Nycomed US Inc. throughout the document since Nycomed acquired ALTANTA Inc's parent company (ALTANA Pharma AG).

The following updates were implemented with Amendment 2:

- General spelling and grammatical errors were corrected.
- The clinical signs and symptoms assessment text was updated to clarify that a subject was required to have 10% BSA affected by atopic dermatitis in order to be enrolled in the trial, but that the 10% could have been present in as few as one or as many as four separate body regions, and that a target site was selected from each applicable body region in which atopic dermatitis was present.
- The planned interim analysis and monitoring were updated to be based on assumed success rates rather than conditional power in order to provide for a statistically robust evaluation of the underlying sample size assumptions for the placebo and active treatment response rates.
- The statistical significance level for the primary endpoint of success rate was changed from 0.05 overall to 0.001 in the interim analysis and 0.049 for the final analysis.

The following updates were implemented with Amendment 3:

- Additional references to ALTANA Inc were removed and replaced with Nycomed US Inc.
- The number of subjects to be enrolled was increased due to a packaging error that might have occurred that led to the need for an increased sample size.
- Efficacy and safety analyses were updated to account for the potentially incorrectly dosed subjects.
- Information regarding the interim analysis was deleted since it was decided that an interim analysis would no longer be conducted.
- The statistical significance level for the primary endpoint of success rate was changed from 0.001 in the interim analysis and 0.049 for the final analysis to 0.05 overall.
- General formatting errors with heading numbers were corrected, as well as general spelling and grammatical errors.
- Information regarding the packaging of study medication was updated because subjects, on average, used less study medication than initially anticipated when the study began; therefore, when more kits were processed to account for the additional subject enrollment, three tubes of study medication were included per kit, rather than the original five tubes of study medication per kit.
- The PP population was updated to exclude any subject who could have been incorrectly dosed due to the packaging error.
- Protocol appendices were updated as necessary.

Reviewer's Comments:

The first patient was enrolled on 1/28/08. All of the sponsor's protocol amendments were implemented after the first patient was enrolled.

2.4.3.2.2 Statistical and Analytical Issues

During the course of the study and prior to database lock on 10/9/09, the following statistical and analytical issues were noted by the sponsor:

- There was a potential packaging error associated with some of the study medication kits (eg, patients may have received treatment with the Vehicle treatment and not according to the randomization code) was noted; therefore, the efficacy analyses performed on the PP and mITT populations excluded potentially incorrectly dosed patients from the PP population but included potentially incorrectly dosed patients in the mITT population so that they were "analyzed as randomized" and the safety analysis performed on the ITT population included potentially incorrectly dosed patients so that they were "analyzed as dosed."
- A treatment-by-site interaction effect was suspected; therefore, general considerations for treatment-by-site interaction affects were updated to include an algorithm for site pooling for those sites with fewer than 3 patients per treatment group in the mITT population.

After database lock on 10/9/08, the following statistical and analytical issues were noted:

- Patient (b) (6) in the Reference group was erroneously noted as having discontinued due to an AE; however, this patient competed the study on (b) (6) and the listings and tables in the sponsor's study report reflect this error.
- It was noted after database lock that two patients in the Reference group had incorrect data recorded for race. Patient (b) (6) should have been recorded as "Asian" but was erroneously captured as "American Indian." Patient (b) (6) should have been recorded as "White" but was erroneously captured as "American Indian." These errors were not updated in the sponsor's database, but were corrected in the sponsor's study report for Listing 16.2.2 and Table 14.1.3 (ITT patients), Table 14.1.4 (mITT patients), and Table 14.1.5 (PP patients) to reflect the true value as specified above.
- Additionally, Patien (b) (6) (Reference group) had height recorded as 73 cm and weight recorded as 158.3 kg in the database when height should have been captured as 158.3 cm and weight should have been captured as 73 kg. Patient (b) (6) (Vehicle group) had height recorded as 66 cm in the database, but height should have been captured as 63 inches.
- Patient (b) (6) (Placebo group) was originally included in the memo documenting the potential mis-dosing of patients. This was a transcription error and the patient should have not been considered potentially mis-dosed. This patient was included in error in the Potential Incorrect dose group; however, since this patient was "analyzed as randomized" in the demographic, baseline, and efficacy summaries and "analyzed as dosed" in the safety summaries, this error did not affect the outcome of any statistical analyses.

Reviewer's Comments:

- *See "Reviewer's Comments" under "General Considerations" in Section 2.4.3.1.3* Statistical analysis plan.
- *According to the CRF, Patient (b) (6) did discontinue the study medication ((b) (6) due to an AE of "skin burning". The patient's study diary confirms that the first dose was applied on (b) (6) and the last dose of study medication was applied on (b) (6), which is less than the required 7 days of treatment needed for inclusion in the PP population. Even*

though the patient did return for all 3 visits and was evaluated, this patient should remain excluded from the FDA's PP population. This error should have no impact on the results.

- *Patient (b) (6) is noted to have other reasons for exclusion from the PP population (i.e., Did Not Have At Least 7 Days Of Treatment; Out Of Window For Visit 3; Did Not Have 85%-120% Compliance Rate; Did Not Have Data On IGE At Visit 3;and Study Medication and Diary Not Returned;Missed dose(s)). Even though the patient was erroneously listed in the potentially mis-dosed list, this patient would have been excluded from the PP population for these other reasons. In addition, as the sponsor stated, since this patient was included in the mITT population as "analyzed as randomized", this patient would still have stayed in the same treatment arm. Thus, this error has no impact on the results and no change to the FDA PP or mITT population are necessary.*
- *The other errors noted after the database lock do not cause any change in the study results and no change to the FDA PP or mITT population are necessary.*

2.4.3.2.3 Patient Disposition:

As shown in **Error! Reference source not found.**, a total of 793 patients were enrolled into the study and randomized to one of the three treatment groups: 269 patients in the Test group, 260 patients in the Reference group, and 264 patients in the Placebo group. No patients were excluded from the sponsor's ITT population. Overall, 758 patients (95.6%) were included in the sponsor's mITT population and 616 patients (77.7%) were included in the sponsor's PP population.

Of the 793 patients who were randomized to study treatment, 727 patients (91.7%) completed the study and 66 patients (8.3%) discontinued prematurely. The most common reason for discontinuation, regardless of treatment group, was patient withdrew consent (28 patients, 3.5%).

Few patients (2 patients total, 0.3%) were discontinued from the study because their condition worsened to the degree that it was unsafe to continue in the study: 1 patient (0.4%) each in the Test and Placebo groups. Overall, a total of 12 patients (1.5%) were discontinued from the study due to an AE: 9 patients (3.5%) in the Reference group and 3 patients (1.5%) in the Placebo group. This includes 1 patient (Patient (b) (6) in the Reference group) who was erroneously noted as having discontinued due to an AE; this patient completed the study on (b) (6) AEs leading to discontinuation were recorded as follows: allergic dermatitis, application site irritation, application site pruritus, application site rash, atopic dermatitis, headache, influenza, and skin burning sensation.

Table 1.3: Patient Disposition: ALT 0416-01-01/Tacrolimus 0.1% (per sponsor)[*]

	Test	Reference	Placebo	Total	p-value[3]
Patients enrolled	269	260	264	793	
Patients randomized[1]	269 (100%)	260 (100%)	264 (100%)	793 (100%)	
Patients completed study[2]	249 (92.6%)	242 (93.1%)	236 (89.4%)	727 (91.7%)	
Patients discontinued from study[2]	20 (7.4%)	18 (6.9%)	28 (10.6%)	66 (8.3%)	
Reason discontinued:					
Patient withdrew consent	9 (3.3%)	4 (1.5%)	15 (5.7%)	28 (3.5%)	0.180
Patient's condition worsened to the degree that it was unsafe to	1 (0.4%)	0	1 (0.4%)	2 (0.3%)	1.000

continue in the study					
Patient's drug code was unblinded	1 (0.4%)	1 (0.4%)	0	2 (0.3%)	1.000
Significant protocol violation	1 (0.4%)	0	2 (0.8%)	3 (0.4%)	1.000
Lost to follow-up	8 (3.0%)	5 (1.9%)	7 (2.7%)	20 (2.5%)	0.435
Adverse event	0	9 (3.5%)	3 (1.1%)	12 (1.5%)	0.002
Patients included in ITT population[1]	269 (100%)	260 (100%)	264 (100%)	793 (100%)	
Patients included in mITT population[2]	257 (95.5%)	252 (96.9%)	249 (94.3%)	758 (95.6%)	
Patients included in PP population	210 (78.1%)	211 (81.2%)	195 (73.9%)	616 (77.7%)	

* From Sponsor's April 8, 2010 submission, Final Report Version 1.0 ALT 0416-01-01 Tables 10.1 and 11.1.
ITT=Intent-to-treat; mITT=modified intent-to-treat; PP=per-protocol
[1] The denominator was the number of patients enrolled.
[2] The denominator was the number of patients randomized.
[3] The p-value for treatment group comparisons (Test and Reference) used Pearson's chi-square test or Fisher's exact test, if appropriate.

Reviewer's Comments:

The two patients who were discontinued from the study due to worsening condition were both appropriately included/excluded from the sponsor's mITT and PP populations.

2.4.3.2.4 Protocol Violations:

Patients with protocol violations were excluded from the sponsor's PP population. As seen in **Error! Reference source not found.**, a total of 3 patients (0.4%) were discontinued from the study due to a significant protocol violation: 1 patient (0.4%) in the Test group and 2 patients (0.8%) in the Placebo group. An additional 2 patients (1 patient each in the Test and Reference groups) were excluded from the PP population due to a significant protocol violation.

Deficiency (8/8/13 ECD Item A.15)

Clearly specify the protocol violations for the 3 patients who were discontinued from the study due to a significant protocol violation and for the additional 2 patients who were excluded from the PP population for significant protocol violations.

Response

Subject Number	Protocol Violation
(b) (6)	***Unblinded study medication***; Did not have any post baseline IGE; Did not have at least 7 days of treatment; Out of window for Visit 3; Did not have 85%-120% compliance rate; Did not have data on IGE at Visit 3 Additional information: Subject unblinded their study medication; lot # was potentially exposed; Study medication returned to third party dispenser, maintaining the blind for the investigator
	Unblinded study medication; Did not have 85%-120% compliance rate Additional information: Subject's girlfriend unblinded study medication on (b) (6); lot # was potentially exposed; Study medication returned to third party dispenser, maintaining the blind for the investigator

Subject Number	Protocol Violation
(b) (6)	***Did not have at least 7 days of treatment***; Out of window for Visit 3; Did not have 85%-120% compliance Rate Additional information: Subject was sent a certified letter and contacted site as soon as she received the letter. Early termination visit was done, however subject did not return both study medication and diary, so total number of applications cannot be determined.
	Subject non-compliant- only applied 8 doses- Did not have at least 7 days of treatment; Out of window for Visit 3 Additional information: This subject was a no show for Visit 2; Patient brought in for Visit 3 (3 days out of window) for a final evaluation and to return study drug/diary even though he was non-compliant with medication
	Subject reported breast feeding during study participation; Subject was discontinued early and unblinded; Did not meet Inclusion/Exclusion criteria Additional information: Scratch off portion of clinical label intentionally unblinded

Reviewer's assessment

Based on the protocol violations for the above patients, the sponsor appropriately excluded them from the PP population. These patients should remain excluded from the FDA PP population.

Patients with minor protocol deviations were not excluded from the sponsor's PP analyses if they met all other criteria for that population.

Patients who did not meet all inclusion criteria and none of the exclusion criteria were excluded from the sponsor's mITT and PP populations. Overall, 9 patients fell into this category for exclusion in the mITT and PP populations: Patients (b) (6) in the Test group; Patient (b) (6) in the Reference group; and Patients (b) (6) (b) (6) in the Placebo group. Additionally, the medical monitor disagreed with the investigator's assessment of inclusion/exclusion criteria for the following patients: (b) (6) (Test group), (b) (6) (b) (6) (Placebo group), and (b) (6) (Placebo group). These patients were excluded from the sponsor's PP population and included in the sponsor's mITT population.

Due to a potential packaging error, 10 patients in the Test group were potentially mis-dosed with study medication not per the randomization code. For demographic, baseline, and efficacy summaries and analyses, these patients were analyzed according to the randomization schedule, ie, "analyzed as randomized."

As seen in Table 1.3, a total of 2 patients (0.3%) were discontinued from the study due to unblinding study medication; 1 patient each (0.4%) in the Test and Reference groups. An additional 19 patients were found to have unblinded study medication but were not discontinued due to this reason; 5 patients in the Test group, 2 patients in the Reference group, and 12 patients in the Placebo group. Patients whose drug code was unblinded were excluded from the sponsor's PP population.

Reviewer's Comments:

The following changes are recommended:

Exclude from FDA mITT and PP populations	
Used exclusionary medication prior to and during study	
Patient Number	**Violation**
(b) (6)	acetaminophen, chlorphenamine and phenylephrine
	Actifed
	acyclovir
	cetirizine
	Advil PM
	Chlorpheniramine
	clindamycin and benzoyl peroxide
	desloratadine
	diphenhydramine
	fexofenadine
	fexofenadine and pseudoephedrine
	hydroxyzine
	levocetirizine
	Loratadine
	loratadine and pseudoephedrine
	trimethoprim
	Tylenol PM
	valaciclovir
	Vitamin D supplements
	amoxicillin and clavulanate
	diphenhydramine
	unknown antihistamine
	psoriasis
	Alzheimer's
	telangiectasia, post inflammatory hyperpigmentation and melasma
Exclude from FDA PP population	
Used exclusionary medication during study	
(b) (6)	amoxicillin
	doxycycline

(b) (6)	fluconazole
	Theraflu
Exclude from FDA mITT population	
disagreed with the investigator's assessment of inclusion/exclusion criteria	
(b) (6)	
Include in FDA PP population	
Visit 3 data available	
(b) (6)	Sponsor excluded for not having Visit 2 data. No other reason for PP population exclusion.

This reviewer notes the following: two patients (b) (6) *were noted to have discontinued the study early for worsening condition. Patient* (b) (6) *did not have any post-baseline data and is appropriately excluded from the sponsor's mITT and PP populations. Patient* (b) (6) *is included in the sponsor's mITT and PP population. Patient* (b) (6) *should remain included in the FDA's mITT and PP populations.*

Table 1.4 provide the FDA's summary of patient disposition.

Table 1.4: Number of Subjects in the Sponsor's and FDA's ITT, MITT and PP Populations: ALT 0416-01-01/Tacrolimus 0.1% (per FDA Statistician)

	Sponsor				FDA			
	Test	**Reference**	**Placebo**	**Total**	**Test**	**Reference**	**Placebo**	**Total**
Enrolled and Randomized	**269**	**260**	**264**	**793**	**269**	**260**	**264**	**793**
Total ITT population	**269**	**260**	**264**	**793**	**269**	**260**	**264**	**793**
Total exclusion from ITT population	0	0	0	0	0	0	0	0
Total MITT population	**257**	**252**	**249**	**758**	**228**	**232**	**211**	**671**
Total exclusion from MITT population	12	8	15	35	41	28	53	122
Reason for exclusion from MITT								
Did Not Have Any Post baseline IGE	10	7	9	26	10	7	9	26
Did Not Meet Inclusion/Exclusion Criteria	2	1	6	9	31	21	44	96
Total PP population	**210**	**211**	**195**	**616**	**181**	**190**	**157**	**528**
Total Exclusion from PP population	59	49	69	177	88	70	107	265
Reason for exclusion from PP								
Excluded from MITT	12	8	15	35	41	28	53	122
Diary Not Returned	1	1	1	3	1	1	1	3
Inappropriate Washout Period	0	3	0	3	0	3	0	3
Lost To Follow-Up	1	0	0	1	1	0	0	1
Sponsor and Medical Monitor disagrees with Inclusion/Exclusion Criteria	1	0	0	1	--	--	--	--
Misdosed	1	0	0	1	1	0	0	1
Potentially Misdosed	4	0	0	4	4	0	0	4
Prohibited Medication	4	4	5	13	5	6	7	18
Study Diary Not Returned	1	0	0	1	1	0	0	1
Study Medication and Diary Not Returned	0	0	1	1	0	0	1	1
Unblinded Study Medication	4	1	9	14	4	1	9	14
Visit 2 Not Done	0	1	0	1	0	0	0	0
Diary and Study Medication Not Returned and Potentially Misdosed	1	0	0	1	1	0	0	1
Did Not Have 85%-120% Compliance Rate	6	6	4	16	6	6	4	16
Did Not Have At Least 14 Days Of Treatment	9	11	13	33	9	11	13	33
Out Of Window For Visit 3	13	13	19	45	13	13	18	44
Protocol Violation	1	1	2	4	1	1	1	3

2.4.3.2.5 Retention of Reserve Samples:

Each investigational site where study medication was dispensed to at least 1 subject randomly selected 1 block of consecutively numbered subject boxes of study medication to be maintained as retention samples. The investigator maintained these bioequivalence study medication samples for each shipment of study medication received as per 21CFR 320.38(e). The investigators are to store the retain sample study medication until such time as notification is received from the sponsor that the samples are no longer required.

Reviewer's Comments:

During the OSI inspections, reserve samples were collected at three sites and no issues were reported.

2.4.3.2.6 Baseline Characteristics

Demographic

Table 1.5 list the demographics for the ITT population. According to the sponsor's analysis, the treatment groups in the ITT population were comparable for all demographic characteristics (all $p > 0.05$). Similar results were seen in the mITT and PP populations.

Table 1.5: Demographic Characteristics for Intent-to-Treat Population: ALT 0416-01-01/Tacrolimus 0.1% (per sponsor)*

Demographic	Test (N=269)	Reference (N=260)	Placebo (N=264)	Total (N=793)	p value
Gender (n,%)					0.245[2]
Male	121 (45.0%)	102 (39.2%)	103 (39.0%)	326 (41.1%)	
Female	148 (55.0%)	158 (60.8%)	161 (61.0%)	467 (58.9%)	
Ethnicity (n,%)					0.452[2]
Hispanic or Latino	31 (11.5%)	34 (13.1%)	31 (11.7%)	96 (12.1%)	
Not Hispanic or Latino	238 (88.5%)	226 (86.9%)	233 (88.3%)	697 (87.9%)	
Race[1] (n,%)					NA
American Indian / Alaskan Native	4 (1.5%)	2 (0.8%)	2 (0.8%)	8 (1.0%)	
Asian	9 (3.3%)	19 (7.3%)	12 (4.5%)	40 (5.0%)	
Black/African American	103 (38.3%)	85 (32.7%)	90 (34.1%)	278 (35.1%)	
Native Hawaiian / Pacific Islander	4 (1.5%)	1 (0.4%)	0 (0.0%)	5 (0.6%)	
White	147 (54.6%)	151 (58.1%)	158 (59.8%)	456 (57.5%)	
Other	6 (2.2%)	8 (3.1%)	6 (2.3%)	20 (2.5%)	
Age (years)					0.703[3]
Mean ± SD	43.0 ± 16.29	43.7 ± 16.74	43.3 ± 17.14	43.3 ± 16.70	
Median	43.0	44.0	43.5	43.0	
Min, Max	18.0, 90.0	18.0, 86.0	18.0, 88.0	18.0, 90.0	
Weight (lbs)					0.055[3]
Mean ± SD	184.5 ± 46.80	182.5 ± 47.26	175.6 ± 46.10	180.9 ± 46.82	
Median	180.0	172.0	170.0	174.0	
Min, Max	94.0, 365.0	95.0, 348.7	90.0, 415.0	90.0, 415.0	
Height (inches)					0.451[3]
Mean ± SD	66.8 ± 3.90	66.2 ± 4.75	66.0 ± 4.90	66.3 ± 4.54	
Median	67.0	66.0	66.0	66.0	
Min, Max	56.0, 80.0	28.7, 78.3	26.0, 76.0	26.0, 80.0	

* From Sponsor's April 8, 2010 submission, Final Report Version 1.0 ALT 0416-01-01 Table 11.3.
[1] Patients could have self-reported more than one race.
[2] p values for treatment group comparisons from Cochran-Mantel-Haenszel test, adjusted for pooled study site.
[3] p values for treatment group comparisons from Friedman's test using treatment group and pooled study site as factors.

No patient had a positive urine pregnancy test at Baseline and no patient became pregnant during the study.

Baseline Dermatological Examination:

According to the sponsor's analysis (shown in Table 1.6), ITT patients were comparable at Baseline with regard to the severity of atopic dermatitis as evaluated by the IGE ($p = 0.544$) and % BSA ($p = 0.872$). All patients who were randomized had an IGE score of moderate or severe at Baseline. All patients who were randomized had $\geq$ 10% BSA affected at Baseline. Similar results were seen in both the mITT and PP populations.

Table 1.6: Baseline Dermatological Characteristics for Intent-to-Treat Population: ALT 0416-01-01/Tacrolimus 0.1% (per sponsor)*

Demographic	Test (N=269)	Reference (N=260)	Placebo (N=264)	Total (N=793)	p value
IGE (n,%)					0.544[1]
Moderate	237 (88.1%)	225 (86.5%)	236 (98.4%)	698 (88.0%)	
Severe	32 (11.9%)	35 (13.5%)	28 (10.6%)	95 (12.0%)	
% Body Surface Area					0.872[2]
Mean ± SD	22.8 ± 17.49	22.3 ± 17.76	22.5 ± 17.33	22.5 ± 17.50	
Median	15.0	15.5	15.0	15.0	
Min, Max	10.0, 99.0	10.0, 97.0	10.0, 99.0	10.0, 99.0	

* From Sponsor's April 8, 2010 submission, Final Report Version 1.0 ALT 0416-01-01 Table 11.4.
[1] p values for treatment group comparisons from Cochran-Mantel-Haenszel test, adjusted for pooled study site.
[2] p values for treatment group comparisons from Friedman's test using treatment group and pooled study site as factors.

2.4.3.3 Results

2.4.3.3.1 Primary Endpoint

The primary efficacy endpoint was the proportion of patients in each treatment group who had an IGE rating of "Clear" or "Almost Clear" (hereafter referred to as "**success**") for atopic dermatitis at Visit 3 (End of Study).

According to the sponsor's and FDA's analysis, in the PP population, the two active treatments were comparable with regard to the proportion of patients with success at Visit 3 (Table 1.7). The 90% confidence interval on the difference between active treatments was within the limit of [-0.20, 0.20] for both analyses.

According to the sponsor's and FDA's analysis, in the mITT population, the two active treatments were comparable with regard to the proportion of patients with success at Visit 3. Both the Test product and the Reference product showed superiority over Placebo in the mITT population with regard to the proportion of patients with success on the IGE at Visit 3 (all $p < 0.05$).

Table 1.7: Primary Endpoint Analysis: Proportion of Patients with Clinical Success on the Investigator's Global Evaluation: ALT 0416-01-01/Tacrolimus 0.1% (per sponsor and FDA Statistician)*

	Sponsor			FDA		
	Test	**Reference**	**Placebo**	**Test**	**Reference**	**Placebo**
PP Population						
N	210[1]	211[1]	195	181	190	
Success[2]	104 (49.5%)	121 (57.3%)	67 (34.4%)	93 (51.38%)	109 (57.37%)	
90% CI for Test and Reference	(-0.163, 0.006[3])			(-0.150, 0.030)		
mITT Population						
N	257	252	249	228	232	211
Success[2]	124 (48.2%)	138 (54.8%)	83 (33.3%)	113 (49.56%)	125 (53.88%)	70 (33.18%)
(Test or Reference) vs. Placebo	p=0.001	p<0.001		p<0.001	p<0.001	

* From Sponsor's April 8, 2010 submission, Final Report Version 1.0 ALT 0416-01-01 Table 11.5.
mITT = modified intent-to-treat; N = number of patients; PP = per-protocol; vs = versus
[1]The last-observation-carried-forward approach was used to impute missing efficacy results for the mITT and PP patients who discontinued due to treatment failure. If Visit 2 was missing, the Early Termination Visit efficacy results were used to replace the missing Visit 2 efficacy results if Visit 3/Early Termination occurred on Day 10 or earlier.
[2] Success was defined as an Investigator's Global Evaluation rating of 0 (Clear) or 1 (Almost Clear) for atopic dermatitis.
[3] The sponsor's Confidence intervals for the proportional difference were calculated using Wald's method with Yates' continuity correction.
[4] The sponsor's values for comparing proportions used a Z-test with Yates' continuity correction.

2.4.4 Detailed Review of Bioequivalence Study with Clinical Endpoints for Tracolimus Ointment 0.03% Strength (Study ALT 0417-01-01)

2.4.4.1 Protocol Review

Sponsor's protocol #:	ALT 0417-01-01
Title	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.03% to PROTOPIC® (Tacrolimus) Ointment 0.03% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis
Objectives	The objectives of this study were to compare the safety and efficacy profiles of Nycomed US Inc.'s tacrolimus ointment 0.03% (Test product) to those of Astellas Pharma US, Inc.'s PROTOPIC® (tacrolimus) Ointment 0.03% and to demonstrate superior efficacy of the two active ointments over that of the Nycomed US Inc. Vehicle (Placebo) in the treatment of atopic dermatitis.

2.4.4.1.1 Study Design

Overall Study Design and Plan

Same as Study ALT 0416-01-01 ("Study 0416") except for modification of the enrollment age to at least 8 years of age, modification to the number of medication application days to 28 days and the addition of Visit 4 (at Day 28 ± 3 days) as the End of Study Visit/Early Termination.

Additionally, due to the potential packaging error, patients who received or potentially received incorrect study medication were requested to enroll in a separate protocol (0417-01-02) and to return to the site for two additional follow-up visits. The first visit occurred as soon as possible after the patient was notified and the second visit occurred one year later.

The study schedule for ALT 0417-01-01 is depicted in Table 2.1.

Procedures and Observations:

A summary of the study procedures performed at each visit is given in Table 2.1.

Table 2.1: Study Schedule: ALT 0417-01-01/Tacrolimus 0.03% (per sponsor)*

Visit Number	Visit 1 Baseline	Visit 2	Visit 3	Visit 4 End of Study/ Early Termination	Unscheduled Visit
Visit Day	**Day 1**	**Day 4 (-0, +2 Days)**	**Day 14 (±3 Days)**	**Day 28 (±3 Days)**	
Screening/Consent	X				
Demographics	X				
Medical History	X				
Physical Examination[1]	X				
Urine Pregnancy Test[2]	X				
Inclusion/Exclusion Criteria Review	X				
Assessment of Diagnosis of Atopic Dermatitis	X				
Assessment of Signs and Symptoms of Target Lesions	X	X	X	X	X
Pruritus Assessment	X	X	X	X	X
Blood Draw		X			
Investigator's Global Evaluation	X	X	X	X	X
Adverse Event Reporting		X	X	X	X
Concomitant Medication Review	X	X	X	X	X
Drug Dispensing, if applicable	X	X			If applicable
Patient Instruction/Compliance Review	X	X	X	X	X
Drug Return, Accountability		X	X	X	If applicable

* From Sponsor's November 18, 2010 submission, Final Report Version 1.0 ALT 0417-01-01 Table 9.1.
[1] Physical examinations included vital signs (height, weight, body temperature, pulse, respiration rate, and blood pressure).
[2] Performed on females of childbearing potential only and completed at the site prior to enrollment into the study.

Reviewer Comments:

The Draft Guidance on Tacrolimus Ointment/Topical, 0.03% (March 2012) recommends that the End of Study visit be on Study Day 29. The sponsor used Study Day 28 as the End of Study visit. Since the same difference in date is applied to all study arms, this discrepancy should not have any clinical significance.

Study Population

Inclusion & Exclusion Criteria:

Same as Study 0416 except for modification of Inclusion Criterion #5 from "at least 18 years of age" to "at least 8 years of age."

Reviewer Comments:

- *Based on the sponsor's baseline dermatological characteristics analysis of the ITT population (see **Error! Reference source not found.**), the median baseline % BSA is 15.0% in all treatment groups. The FDA statistician confirmed that the baseline % BSA in the FDA's mITT and PP populations are similar among the treatment arms (p = 0.9766) and the median baseline % BSA in the FDA's mITT population is 15% for all treatment groups (see **Error! Reference source not found.**). Given that the mean baseline % BSA is >20% in all treatment groups and the baseline % BSA is similar among the treatment groups, it is acceptable that the median baseline % BSA is <20% in all treatment groups.*

Table 2.2: *Summary of % Total Body Surface Area Affected at Baseline for the FMITT Population: ALT 0417-01-01/Tacrolimus 0.03% (per FDA Statistician)*

% Body Surface Area	Total N=716	Tacrolimus 0.03% N=240	Protopic ®0.03% N=240	Placebo N=236	p-value[a]
Mean (STD)	21.36 (16.53)	22.04 (18.57)	20.81 (15.12)	21.24 (15.73)	0.7094
Median	15	15	15	15	
Range	10-90	10-90	10-80	10-90	

[a] p-values were obtained from using a general linear model with treatment as factor

- *The number of enrolled patients with diabetes was evenly distributed amongst the treatment arms (Test 12; Reference 9; Placebo 11). Therefore, it is acceptable that patients with stable diabetes were enrolled into this study.*
- *Same as Study 0416, any patients who used 1) systemic antibiotics, 2) calcipotriene or other vitamin D preparations, or 3) retinoids (all items within 14 days of baseline) should be excluded from the FDA mITT and PP populations.*
- *Same as Study 0416, any patient who used an antihistamine within 7 days prior to the baseline visit should be excluded from the FDA mITT and PP populations.*

Criteria for removal from the study:

Same as Study 0416.

Prior and Concomitant Therapy and Precautions/Restrictions:

Same as Study 0416.

Treatments:

Same as Study 0416 except for modifications to the treatment arms as follows:

Test (A)	Tacrolimus ointment 0.03% Manufactured by Nycomed US Inc., Lot #s Z431 and 710C
Reference (B)	PROTOPIC® (tacrolimus) Ointment 0.03% Manufactured by Astellas Pharma US, Inc Lot #s 26471 and 30221
Placebo (C)	Vehicle of Test product Manufactured by Nycomed US Inc., Lot #s Z034 and 711C

Compliance:

Same as Study 0416 except for modification to apply the medication twice daily for 28 days.

Randomization & Blinding:

Same as Study 0416 except for modification of each patient's treatment unit. Each unit consisted of one kit box of study medication as follows:

Kit Boxes 0001 to 1095 contained eight 100-gram tubes of study medication
Kit Boxes 2000 to 2965 and 3000 to 3701 contained four 100-gram tubes of study medication

In addition, at the time study enrollment was suspended on 10/28/08, due to the discovery of a packaging error, 483 patients (out of 900 total) were enrolled. Same as Study 0416, a new randomization code was generated and new clinical kits were created after the outside third party packaging vendor (b) (4) evaluated the unused kits. (b) (4) also unblinded the unused and used study kits from the first randomization. (b) (4) provided the results of the used study supplies evaluation to the sponsor's Clinical Operations ("Clin Ops") Department in the form of a "blinded" memos on 7/14/09. The memos confirmed that 5 patient was confirmed to be mis-dosed and 19 patients were considered potentially mis-dosed due to at least 1 tube of study drug not returned. On 7/17/09, (b) (4) provided a final "unblinded" results in the form of a memo to a single unblinded statistician at (b) (4). The memo included the patients numbers of those patients who were mis-dosed and those who were potentially mis-dosed.

Deficiency (8/8/13 ECD Item B.2):

When were the used study medication kits sent to (b) (4) for unblinding?

Response

The used study medication kits (defined as kits that were assigned to enrolled study subjects) from kit series 0001-1095 were sent to (b) (4) on 3/30/09. (b) (4) began unblinding these used kits on 4/7/09.

Reviewer assessment

Acceptable. See the sponsor's response to deficiency item B.3 below.

Deficiency (8/8/13 ECD Item B.3):

Were the used study medication kits sent to (b) (4) *for unblinding after the study participants completed the study?*

Response

Yes. Study participants in the 0001-1095 series completed the study in 2008. After these subjects completed the study, kits were sent to (b) (4) on 3/30/09. Unblinding at (b) (4) began on 4/7/09. Study integrity was maintained by utilizing a third party outside vendor to conduct all unblinding procedures.

Reviewer assessment

Acceptable

Deficiency (8/8/13 ECD Item B.5):

Clarify who generated the first and second sets of randomization schedule. Provide their contact information.

Response

The randomization schedule for kits 0001 through 1095 (Packaging 1) was generated by (b) (4) (b) (4)

(b) (4)

The randomization schedules for kits 2000 through 2965 (Packaging 2) and kits 3000 through 3701 (Packaging 3) were generated by (b) (4)

(b) (4)

Reviewer assessment

Acceptable.

Deficiency (8/8/13 ECD Item B.6):

At what point in the study timeline did the Project Management (PM) Department of Nycomed receive a copy of the randomization code? Who had access to the randomization code maintained in the PM Department?

Response

The Project Management (PM) representative received the randomization code prior to the start of enrollment for subjects in that series and maintained such until database lock.

This responsibility was transferred to other Project Management representatives over the course of the study due to changes in staffing. However access continued to remain controlled and limited to PM only. Project Management made no decisions regarding conduct of these clinical studies.

Reviewer assessment

Acceptable. When a sponsor does not package the test materials, the sponsor can generate the randomization code and thus would have a copy of the randomization code. Therefore, it is acceptable that the sponsor's Project Management representative, who is not part of the Clinical Operations, has a copy of the randomization code.

Deficiency (8/8/13 ECD Item B.7):

Who packaged the study medications for this study? Provide their contact information.

Response

The packaging of kits 0001 through 1095 (Packaging 1) was conducted at the Fougera Pharmaceuticals Inc. Hicksville facility by the production staff.

Fougera Pharmaceuticals Inc.
55 Cantiague Rock Road
Hicksville, NY 11801
631-454-7677
Gary Price- Associate Director, Quality Systems

The packaging of kits 2000 through 2965 (Packaging 2) and kits 3000 through 3701 (Packaging 3) were conducted at were conducted at (b) (4).

(b) (4)

Reviewer assessment

Acceptable.

Deficiency (8/8/13 ECD Item B.8):

Clarify if new study medication kits were assembled for the second set of randomization or if the unblinded, unused study kids were re-blinded for the second set of randomization.

Response

The unused, sealed kits from Packaging 1 (kits 0001 through 1095) were returned to the Fougera Distribution Center in Arizona using insulated shipper boxes, with temptales (temperature monitoring devices) included in each. Once returned, all unused kits were shipped in bulk to (b) (4). The kits were sorted into Test, Reference and Placebo groups and then systematically unblinded to determine if there were any packaging errors in the unused kits. Once sorted by treatment arm, a second randomization code generated by (b) (4) was applied to these tubes creating kits 2000 through 2965.

Reviewer assessment

Acceptable

Deficiency (8/8/13 ECD Item B.9):

Clarify how many of the used study kits from the first randomization code was unblinded by (b) (4). Provide a list of all the used study kits that were unblinded by (b) (4).

Response

A 'used kit' is defined as a kit of study medication assigned to an enrolled study subject. A total of 483 used kits from the first randomization code were unblinded by (b) (4) Please refer to ALT 0417-01-01 Used Unblinded Kits for a detailed list of these kits.

Reviewer assessment

A total of 900 patients were enrolled and randomized to receive study medication kits, which means that (b) (4) unblinded 53.67% (483 out of 900) of the medication kits from this study.

Deficiency (8/8/13 ECD Item B.10):

Provide a copy of the "blinded" memo that was sent from (b) (4) to "Clin Ops" on 7/14/09.

Response

Please refer to ALT 0417-01-01 Blinded (b) (4) Memo to Clin Ops 7-15-09. Please note that the memo was originally provided on 7/14/09 but it was not signed. Fougera requested that the memo be signed, therefore a revised blinded final version with signature was provided 7/15/09.

Reviewer assessment

A copy of the memo is provided in the response. In the memo, the patient numbers are blackened out such that the patient identity can't be determined. No other patient identifiers are included in the memo. Acceptable.

Deficiency (8/8/13 ECD Item B.11):

Provide a copy of the "unblinded" memo that was sent from (b) (4) *on 7/17/09.*

Response

Please refer to ALT 0417-01-01 Unblinded (b) (4) (b) (4) 7-17-09

Reviewer assessment

A copy of the memo is provided in the response. This "unblinded" memo is the same as the "blinded" memo from (b) (4) *to "Clin Ops" except the patient numbers are not blackened out. Acceptable.*

Deficiency (8/8/13 ECD Item B.12):

Did "Clin Ops" receive a "unblinded" memo after hard database lock? If so, provide of copy of this memo.

Response

Hard database lock took place on 10/29/09. On 12/3/09, Fougera requested that (b) (4) provide a copy of the 7/15/09 memo with the blinding boxes removed for review. A separate official 'unblinded memo' was not issued. Please refer to ALT 0417-01-01 Unblinded Version of (b) (4) Memo to Clin Ops provided 12-3-09.

Reviewer assessment

The "unblinded" version is the same memo as the "blinded" memo from (b) (4) *to "Clin Ops" except the patient numbers are not blackened out. Acceptable.*

Reviewer Comments:

- *During the OSI inspections of the clinical sites, no issues were noted regarding the appropriate maintenance of a sealed/blinded randomization code.*
- *The sponsor's blinding appears appropriate. The sponsor submitted enough evidence to assure that the integrity of the study data was not impacted by the packaging error and the unblinding of the used study medication kits.*

2.4.4.1.2 Endpoints/Variables

Efficacy & Safety Measures

Same as Study 0416.

Primary Endpoint

Same as Study 0416 except for modifications to reflect the addition of Visit 4 as the End of Study Visit.

2.4.4.1.3 Statistical analysis plan

Patient Populations & General Considerations:

Same as Study 0416 except for modification to the PP population to reflect the change in number of medication application days to 28 days and the addition of Visit 4 as the End of Study Visit.

Deficiency (8/8/13 ECD Item B.4):

Of the mis-packaged tubes discovered in the definitely mis-dosed patients' returned medication kits, clarify how many of the mis-packaged tubes that those patients (Patients (b) (6) (b) (6)) actually used and if the definitely mis-dosed patients used any non-mis-packaged tubes from the medication kits.

Response

Accountability of the number of tubes dispensed to and returned by subjects was recorded in Case Report Forms during the study. Once the packaging error was discovered and the tubes were unblinded at (b) (4), a count was conducted on the number of tubes per kit box, the number of those tubes that were of the incorrect lot, and whether or not the foil seal on both the incorrect and correct tubes was broken (indicating that it was used). Of the five definitely mis-dosed subjects, one subject used both incorrect and correct tubes, and four subjects used only the incorrect tubes.

Subject Number	Total # of Tubes Dispensed	Total # of Tubes Returned	Total # of Incorrect Tubes Used (Broken Foil Seal)	Total # of Correct Tubes Used	Dosed with Both Correct and Incorrect Tubes?
(b) (6)	2	2	2	0	No
	8	8	2	6	Yes
	3	3	3	0	No
	2	2	1	0	No
	1	1	1	0	No

Reviewer assessment

Given that the definitely mis-dosed patients are excluded from the PP population, the use of both the mis-packaged and correctly packaged tubes or only the mis-packaged tubes should not impact the results. The use of both tubes would affect the safety data. However, the sponsor separated out this patient (with the other potentially mis-dosed patients) into a separate group of their own for the safety analysis.

Reviewer's Comments:

This reviewer agrees that the definitely mis-dosed patients (Patient (b) (6) (b) (6)) and the potentially mis-dosed patients (Patients (b) (6) (b) (6) (b) (6)) should be excluded from the PP population but included in the mITT population as "analyzed as randomized" unless there is

a reason for exclusion from the mITT population. For each patient that was definitely mis-dosed, the sponsor provided the number of tubes that was found to be mis-packaged in the returned medication kit. However, it is unclear if those patients only used the mis-packaged tubes or also used a correctly packaged tube.

Missing values or Dropouts:

For the analyses of efficacy, a last-observation-carried-forward (LOCF) approach was used for missing efficacy results in the mITT population. In the PP population, the LOCF approach was used only for patients who had at least 14 days of treatment and met PP criteria up to the time of early study discontinuation due to worsening disease or lack of improvement, had a study drug compliance rate of at least 80%, and had at least one post-baseline value for the IGE. Data from the Early Termination Visit were to be slotted back to the appropriate Interim Visit under the following conditions:

- If both Visit 2 and Visit 3 were missing and Visit 4/Early Termination was on Day 9 or earlier, Visit 4/Early Termination was slotted to Visit 2
- If both Visit 2 and Visit 3 were missing and Visit 4/Early Termination was later than Day 9 and earlier than Day 21, Visit 4/Early Termination was slotted to Visit 3
- If only Visit 3 was missing and Visit 4/Early Termination was earlier than Day 21, Visit 4/Early Termination was slotted to Visit 3
- No slotting was performed under other conditions

Reviewer's Comments:

The sponsor's statistical plan for missing values and dropouts is acceptable.

Site Pooling

Same as Study 0416 except for the sites numbers for the geographical regions:

Region	Site
Latin America	33, 34, 35, 36
Midwest	15, 20, 21, 22, 25, 29*, 31, 39*, 40, 50, 53, 54
Northeast	7, 8, 19, 23, 32, 47
Southeast	1, 5, 6, 9, 11, 17, 27, 28, 30, 37, 42, 43*, 45
Southwest	3, 4, 14, 16, 38, 52
West	2, 10, 12, 13, 18, 26, 46, 48, 49, 51, 55, 56, 57, 58*

* These sites did not enroll any patients during the course of the study; therefore, they are not presented in any of the listings

Reviewer's Comments:

The FDA statistician did not utilize site pooling in their analysis. The FDA statistician states that "[w]hen we explored pooling the sites according to the sponsor's algorithm, the results were not substantially different."

Baseline Comparability

Same as Study 0416.

Primary & Secondary Endpoints Analyses

Same as Study 0416 except for modifications to reflect the addition of Visit 4 as the End of Study Visit.

Changes to the Planned Analyses

There were two amendments to the original planned analyses, dated 6/20/08: Amendment 1 is dated 10/07/09 and Amendment 2 is dated 10/28/09.

Prior to database lock on 10/29/09, it was noted that there was a potential packaging error associated with some of the study medication kits and that 24 subjects were either incorrectly dosed or potentially incorrectly dosed with tacrolimus ointment 0.1%. Subjects who were randomized to one treatment group but potentially erroneously received a different treatment assignment due to the error in packaging had to be replaced; therefore, additional subjects were enrolled to meet the new sample size (ie, 24 subjects in each group were enrolled to account for the 24 subjects who were potentially affected by the packaging error). The protocol and SAP were updated to reflect the changes to the analyses due to this error, as well as address any statistical concerns that could have resulted from the new sample size.

Updates to the original SAP with Amendment 1were the same as for Study 0416.

Deficiency (8/8/13 ECD Item B.4):

Describe in detail the SAP changes made with Amendment 2.

Response

There were two amendments to the original planned analysis, dated 6/20/08: Amendment 1 is dated 10/7/09 and Amendment 2 is dated 10/28/09. The final amended SAP is provided in Appendix 16.1.9 of the Clinical Study Report.

- Original SAP (version 1.0) dated 6/20/08 was based on Clinical Study Protocol ALT 0417-01-01 (Sections 8.2 to 8.7 in the study protocol dated 20 February 2008)
- SAP Amendment 1 (version 2.0) dated 10/7/09 was based on Clinical Study Protocol ALT 0417-01-01 Rev 0.3 (Section 8.2 to Section 8.7 in the study protocol dated 04 August 2009)
- SAP Amendment 2 (version 3.0) dated 10/28/09 was based on Clinical Study Protocol ALT 0417-01-01 Rev 0.3 (Section 8.2 to Section 8.7 in the study protocol dated 04 August 2009)

The following updates were implemented with Amendment 2:

Page	Section	Paragraph	Line	Original Text	Revised Text	Justification
1	2.2	2	1	"it was determined that 24 subjects were either incorrectly…"	Changed to "approximately 24 subjects…"	Since some subjects had missing tubes, the exact number of mis-dosed subjects was not known
1	2.2	2	2.3	"instead of Tacrolimus Ointment 0.3% or Vehicle, as randomized"	Changed to "instead of Tacrolimus Ointment 0.03%, Protopic Ointment 0.03% or Vehicle, as randomized."	Strength incorrectly listed as 0.3%- updated to 0.03%; Listed out all three treatment arms for clarity
1	2.2	2	4	"A total of 867 subjects will "	"A minimum of 867 subjects will ensure…"	To align with protocol
3	4.1	4	1	"Since there is apotential for a packaging error…"	Change to "Since there was a potential of a packaging…"	Grammatical
3	4.2	1	4	"In the PP population, the LOCF approach will only be used for subjects who discontinued due to treatment failure or lack of improvement for their subsequent visits after discontinuation"	"In the PP population, the LOCF approach will only be used for subjects who had at least 14 days of treatment and met per-protocol criteria up to the time of early study discontinuation due to worsening disease or lack of improvement, took applications with a compliance rate of at least 80%, and had at least one treatment value for the IGE."	Added further clarification to population
29	Listing 16.2.2			'Race' and 'Ethnicity' columns	Switched order of columns to 'Ethnicity' then 'Race'	Formatting

Reviewer assessment

Changes made to the SAP in Amendments 1 and 2 are acceptable.

2.4.4.2 Study Conduct

2.4.4.2.1 Changes to the Conduct of the Study

Same as Study 0416 (including the dates of the amendments which are as follows: Amendment 1 is dated 2/20/08, Amendment 2 is dated 6/24/08, and Amendment 3 is dated 8/04/09) except for the addition of the following:

- Under Amendment 1, the following additional change was added: Text was removed from the Precautions section indicating subjects should not apply study medication to their face; this was included in the original protocol in error.

- Under Amendment 2, the following additional changes were added
    - Additionally, the drop-out rate was planned to be assessed in order to ensure a sufficient number of subjects was achieved for the final analyses.
    - An error in the sample size was corrected from 185 subjects in each treatment arm to 265 subjects in each treatment arm.
- Under Amendment 3, the following additional change was added: Safety follow-up trial 0417-01-02 was added in order to collect additional safety data for mis-dosed and potentially mis-dosed subjects. These subjects were requested to participate in two visits conducted one year apart.

Reviewer's Comments:

The first patient was enrolled on 1/10/08. All of the sponsor's protocol amendments were implemented after the first patient was enrolled.

2.4.4.2.2 Statistical and Analytical Issues

During the course of the study and prior to database lock on 10/29/09, it was noted by the sponsor that there was a potential packaging error associated with some of the study medication kits (eg, patients may have received treatment not according to the randomization code for Protocol ALT 0417-01-01); therefore, the efficacy analyses performed on the PP and mITT populations excluded potentially incorrectly dosed patients from the PP population but included potentially incorrectly dosed patients in the mITT population so that they were "analyzed as randomized," while the safety analysis performed on the ITT population included potentially incorrectly dosed patients so that they were "analyzed as dosed." Additionally, it was noted that there were a small number of mITT patients enrolled at some study sites; therefore, general considerations were updated to include an algorithm for site pooling for those sites with fewer than 3 patients per treatment group in the mITT population.

Reviewer's Comments:

See "Reviewer's Comments" under "General Considerations" in Section 2.4.4.1.3 Statistical analysis plan.

2.4.4.2.3 Patient Disposition:

As shown in Table 2.3: Patient Enrollment and Final Study Disposition: ALT 0417-01-01/Tacrolimus 0.03% (per sponsor)*, a total of 900 patients were enrolled into the study and randomized to one of the three treatment groups: 303 patients in the Test group, 297 patients in the Reference group, and 300 patients in the Placebo group. One patient was excluded from the sponsor's ITT population: Patient (b) (6) (Test group) did not apply study medication and was therefore excluded from all analyses. Overall, 874 patients (97.1%) were included in the sponsor's mITT population: and 692 patients (76.9%) were included in the sponsor's PP population.

Of the 900 patients who were randomized to study treatment, 809 patients (89.9%) completed the study and 91 patients (10.1%) discontinued prematurely. The most common reasons for

discontinuation, regardless of treatment group, were patient withdrew consent (30 patients, 3.3%) and patient lost to follow-up (28 patients, 3.1%).

Overall, a total of 12 patients (1.3%) were discontinued from the study because their condition worsened to the degree that it was unsafe to continue in the study: 3 patients (1.0%) in the Test group, 1 patient (0.3%) in the Reference group, and 8 patients (2.7%) in the Placebo group. Overall, a total of 7 patients (0.8%) were discontinued from the study due to an AE: 2 patients (0.7%) each in the Test and Reference groups and 3 patients (1.0%) in the Placebo group. The AEs leading to discontinuation from the study were recorded as follows: application site irritation, application site pruritus, application site reaction, blister, and contact dermatitis.

Table 2.3: Patient Enrollment and Final Study Disposition: ALT 0417-01-01/Tacrolimus 0.03% (per sponsor)*[*]

	Test	Reference	Placebo	Total	p-value[3]
Patients enrolled	303	297	300	900	
Patients randomized[1]	303 (100%)	297 (100%)	300 (100%)	900 (100%)	
Patients completed study[2]	275 (90.8%)	272 (91.6%)	262 (87.3%)	809 (89.9%)	
Patients discontinued from study[2]	28 (9.2%)	25 (8.4%)	38 (12.7%)	91 (10.1%)	
Reason discontinued:					
Patient withdrew consent	7 (2.3%)	10 (3.4%)	13 (4.3%)	30 (3.3%)	0.435
Patient's condition worsened to the degree that it was unsafe to continue in the study	3 (1.0%)	1 (0.3%)	8 (2.7%)	12 (1.3%)	0.624
Patient's drug code was unblinded	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)	0.495
Significant protocol violation	6 (2.0%)	4 (1.3%)	1 (0.3%)	11 (1.2%)	0.752
Prohibited concomitant therapy	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.1%)	NA
Lost to follow-up	10 (3.3%)	7 (2.4%)	11 (3.7%)	28 (3.1%)	0.486
Administrative reasons	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.1%)	NA
Adverse event	2 (0.7%)	2 (0.7%)	3 (1.0%)	7 (0.8%)	1.000
Patients included in ITT population[1]	302 (99.7%)	297 (100%)	300 (100%)	899 (99.9%)	
Patients included in mITT population[2]	294 (97.0%)	287 (96.6%)	293 (97.7%)	874 (97.1%)	
Patients included in PP population	226 (74.6%)	238 (80.1%)	228 (76.0%)	692 (76.9%)	

* From Sponsor's November 18, 2010 submission, Final Report Version 1.0 ALT 0417-01-01 Tables 10.1 and 11.1.
[1] The denominator was the number of patients enrolled.
[2] The denominator was the number of patients randomized.
[3] p-value were from Pearson's chi-square test or Fisher's exact test, comparing the Test and Reference groups.

Reviewer's Comments:

All the patients who were discontinued from the study due to worsening condition were both appropriately included/excluded from the sponsor's mITT and PP populations.

2.4.4.2.4 Protocol Violations:

Patients with protocol violations were excluded from the sponsor's PP population. As seen in **Error! Reference source not found.**, a total of 11 patients (1.2%) were discontinued from the study due to a significant protocol violation: 6 patients (2.0%) in the Test group, 4 patients (1.3%) in the Reference group, and 1 patient (0.3%) in the Placebo group. An additional 2 patients (1 patient each in the Test and Reference groups) were excluded from the sponsor's PP population due to a significant protocol violation.

Deficiency (8/8/13 ECD Item B.14):

Clearly specify the protocol violations for the 11 patients who were discontinued from the study due to a significant protocol violation and for the additional 2 patients who were excluded from the PP population for significant protocol violations.

Response:

Subject Number	Protocol Violation
(b) (6)	***Prohibited medication***; Did not have at least 14 days of treatment; Out of window for Visit 4; Did not have 85%-120% compliance rate Additional information: Prohibited concomitant medication Triamcinolone Cream started during the study for Adverse Event 'Skin Burning, Erythema and Itching after study drug application'; Early Termination
	Did not meet inclusion/exclusion criteria; Did not have at least 14 days of treatment; Out of window for Visit 4; Did not have 85%-120% compliance rate Additional information: Subject had Multiple Sclerosis and was treating with Betaseron- Medical Monitor told the site to disenroll; Subject was dropped the same day they were enrolled; Returned to clinic (b) (6) to return study medication
	Did not meet inclusion/exclusion criteria; Prohibited medication Additional information: Monitored discovered that subject did not have protocol specified washout from topical steroids for Desonide 0.05%; Monitor notified site on (b) (6) to discontinue subject
	Prohibited medications used Additional information: Claritin D (as needed) used for seasonal allergies; Intralesional Celestone Soluspan and topical Fluocinonide used for atopic dermatitis; Prednisone used for burning at application site and atopic dermatitis
	Medical Monitor deemed protocol violation; Did not have at least 14 days of treatment; Out of window for Visit 4 Additional information: Subject [age 14] has a history of Down's Syndrome and should not have been enrolled in trial- Vulnerable subject
	Subject did not complete 14 day washout of Triamcinolone Cream Additional information: Subject enrolled 13 days after using Triamcinolone Cream for the treatment of atopic dermatitis
	Did not have 85%-120% compliance rate; Did not have at least 14 days of treatment; Out of window for Visit 4 Additional information: Subject was discontinued due to non-compliance with medication applications
	Did not have 85%-120% compliance rate; Did not have at least 14 days of treatment; Out of window for Visit 4 Additional information: Subject discontinued due to protocol violation: Non-compliance with drug applications

Subject Number	Protocol Violation
(b) (6)	***Non-compliance with appointments***; Did not have at least 14 days of treatment; Out of window for Visit 4 Additional information: Subject was terminated from study due to non-compliance keeping her appointments
	Non-compliance with appointments; Did not have at least 14 days of treatment; Out of window for Visit 4 Additional information: Subject was terminated early due to non-compliance with keeping her visits on time and schedule
	Unblinded Study Medication; Did not have at least 14 days of treatment; Out of window for Visit 4 Additional information: Subject's mom used a plastic tube dispenser that shredded the label off the tube of study medication- Mom claimed the tube dispenser to be returned, therefore tube was cut in order to release it and return the dispenser; Study medication returned to third party dispenser, maintaining the blind for the investigator
	Non-compliance with appointments; Did not have at least 14 days of treatment; Out of window for Visit 4; Did not have 85%-120% compliance rate; Did not have any post baseline IGE; Did not have data on IGE at Visit 4 Additional information: Subject was terminated from the study as he was out of window and could not comply with study requirements; Subject spoke with PI and said he would send back study medication and study diary, but patient never returned, therefore total number of applications is unknown
	Prohibited medication; Did not have at least 14 days of treatment; Out of window for Visit 4; Did not have 85%-120% compliance rate Additional information: Subject was terminated from the study due to current use of oral prednisone for atopic dermatitis

Reviewer's assessment

Based on the protocol violations for the above patients, the sponsor appropriately excluded them from the PP population. These patients should remain excluded from the FDA PP population.

Patients with minor protocol deviations were not excluded from the sponsor's PP population if they met all other criteria for that population.

Patients who did not meet all inclusion criteria and none of the exclusion criteria were excluded from the sponsor's mITT and PP populations. Overall, 4 patients fell into this category for exclusion from the mITT and PP populations: Patient (b) (6) in the Test group and Patients 5-(b) (6) in the Reference group. Additionally, the sponsor and/or medical monitor disagreed with the investigator's assessment of inclusion/exclusion criteria for Patient (b) (6) (Test group) and Patient (b) (6) (Placebo group). These patients were excluded from the sponsor's PP population but included in the sponsor's mITT population.

As seen in **Error! Reference source not found.**, 1 patient (0.3%) in the Reference group was discontinued from the study due to unblinding study medication. An additional 10 patients were

found to have unblinded study medication but were not discontinued due to this reason: 8 patients in the Test group and 1 patient each in the Reference and Placebo groups. All patients who were potentially aware of their drug code were considered unblinded and excluded from the sponsor's PP population.

Due to the packaging error, 5 patients (Patients (b) (6) who were randomized to placebo treatment received at least one tube of tacrolimus 0.1% ointment. Nineteen (19) patients (Patients (b) (6) (b) (6) (b) (6) who were randomized to the placebo group are considered potentially misdosed because they did not return one or more tubes of study medication. These 24 patients were summarized in the safety analyses as "analyzed as dosed." For demographic, baseline, and efficacy summaries and analyses, these patients were analyzed according to the randomization schedule, ie, "analyzed as randomized." These patients were excluded from the sponsor's PP population and included in the sponsor's mITT population if they met all other criteria for inclusion in this population.

Reviewer's Comments:

The following changes are recommended:

Exclude from FDA mITT and PP populations	
Used exclusionary medication prior to and during study	
Patient Number	**Violation**
(b) (6)	acyclovir
	Advair
	bactrim
	benzoyl peroxide
	brompheniramine
	cephalexin
	certirizine
	certirizine and and pseudoephedrine
	chlorpheniramine
	desloratadine
	diphenhydramine

(b) (6)	fexofenadine
	hydroxyzine
	levocetirizine
	loratadine
	loratadine and pseudoephedrine
	periactin
	Tamiflu
	terbinafine oral
	Tylenol Allergy
Inappropriate washout period	
(b) (6)	amoxicillin
	cetirizine
	clindamycin and benzoyl peroxide
	diphenhydramine
	ketoconazole
	loratadine
	tacrolimus
Exclusionary medical condition	
(b) (6)	benign skin lesion
	common variable immune deficiency
	contact dermatitis
	dyschromia
	folliculitis
	ichythyosis vulgaris
	lichen nitidus
	lichen simplex chronicus
	recurrent hives
	tinea corporis
	xerosis
Exclude from FDA PP population	
Used exclusionary medication during study	
(b) (6)	acyclovir
	amoxicillin
	amoxicillin and clavulanate
	azelastine
	azithromycin
	bactrim
	cefdinir

[redacted]	Dimetapp Cold & Cough
	diphenhydramine
	doxycycline
	erythromycin
	fluconazole
	griseofulvin
	levocetirizine
	loratadine
	loratadine and pseudoephedrine
	mupirocin and zinc oxide
	Nyquil
	penicillin
	Symbicort
	Tamiflu
	Theraflu
Exclude from FDA mITT population	
disagreed with the investigator's assessment of inclusion/exclusion criteria	
[redacted]	

This review notes the following: twelve patients ([redacted]) were noted to have discontinued the study early for worsening condition. All of these patients were appropriately included in/excluded from the sponsor's mITT and PP populations. Patient [redacted] did not have any post-baseline data and is appropriately excluded from the sponsor's mITT and PP populations. Patients [redacted] are excluded from the sponsor's PP population for not having at least 14 days of treatment. These patients should remain excluded from the FDA's PP population. Patients [redacted] are included in the sponsor's mITT and PP population. These patients should remain included in the FDA's mITT and PP populations. Although Patient [redacted] discontinued the study early for worsening AD after 14 days of study medication use, this patient was using an exclusionary medication (cetirizine) prior to study enrollment and continued to use the medication throughout the study. Therefore, Patient [redacted] should continue to be excluded from the FDA PP population and also excluded from the FDA mITT population, as stated above.

Table 2.4 provide the FDA's summary of patient disposition.

Table 2.4: Number of Subjects in the Sponsor's and FDA's ITT, MITT and PP Populations: ALT 0417-01-01/Tacrolimus 0.03% (per FDA Statistician)

	Sponsor				FDA			
	Test	**Reference**	**Placebo**	**Total**	**Test**	**Reference**	**Placebo**	**Total**
Enrolled and Randomized	**303**	**297**	**300**	**900**	**303**	**297**	**300**	**900**
Total ITT population	**302**	**297**	**300**	**899**	**302**	**297**	**300**	**899**
Total exclusion from ITT population	1	0	0	1	1	0	0	1
Total MITT population	**294**	**287**	**293**	**874**	**240**	**240**	**236**	**716**
Total exclusion from MITT population	9	10	7	26	63	57	64	184
Reason for exclusion from MITT								
Did Not Have Any Post baseline IGE	7	7	7	21	7	7	7	21
Did Not Meet Inclusion/Exclusion Criteria	1	3	0	4	55	50	57	162
Not in ITT; Did Not Have Any Post baseline IGE	1	0	0	1	1	0	0	1
Total PP population	**226**	**238**	**228**	**692**	**182**	**198**	**176**	**556**
Total Exclusion from PP population	77	59	72	208	121	99	124	344
Reason for exclusion from PP								
Excluded from MITT	9	10	7	26	63	57	64	184
Diary Not Returned	1	1	0	2	1	1	0	2
Infected AD	0	0	1	1	0	0	1	1
Sponsor and Medical Monitor disagrees with Inclusion/Exclusion Criteria	0	0	1	1	--	--	--	--
Misdosed	0	0	4	4	0	0	4	4
Unblinded Study Medication	7	1	1	9	5	1	1	7
Potentially Misdosed	0	0	6	6	0	0	5	5
Prohibited Medication	4	3	4	11	8	5	12	25
Did Not Have 85%-120% Compliance Rate	7	7	1	15	6	5	1	12
Did Not Have At Least 14 Days Of Treatment	16	13	27	56	13	10	19	42
Out Of Window For Visit 4	27	21	19	67	21	18	16	55
Protocol Violation	6	3	1	10	4	2	1	7

2.4.4.2.5 Retention of Reserve Samples:

Each investigational site where study medication was dispensed to at least 1 subject randomly selected 1 block of consecutively numbered subject boxes of study medication to be maintained as retention samples. The investigator maintained these bioequivalence study medication samples for each shipment of study medication received as per 21CFR 320.38(e). The investigators are to store the retain sample study medication until such time as notification is received from the sponsor that the samples are no longer required.

Reviewer's Comments:

During the OSI inspections, reserve samples were collected at three sites and no issues were reported.

2.4.4.2.6 Baseline Characteristics

Demographic

Table 2.5 list the demographics for the ITT population. According to the sponsor's analysis, the treatment groups in the ITT population were comparable for most demographic characteristic (P > 0.05) except ethnicity (p=0.013). Generally, similar results were seen in the mITT and PP populations.

Table 2.5: Demographic Characteristics for Intent-to-Treat Population: ALT 0417-01-01/Tacrolimus 0.03% (per sponsor)*

Demographic	Test (N=302)	Reference (N=297)	Placebo (N=300)	Total (N=899)	p value
Gender (n,%)					0.557[2]
Male	116 (38.4%)	103 (34.7%)	114 (38.0%)	333 (37.0%)	
Female	186 (61.6%)	194 (65.3%)	186 (62.0%)	566 (63.0%)	
Ethnicity (n,%)					0.013[2]
Hispanic or Latino	42 (13.9%)	61 (20.5%)	47 (15.7%)	150 (16.7%)	
Not Hispanic or Latino	260 (86.1%)	236 (79.5%)	253 (84.3%)	749 (83.3%)	
Race[1] (n,%)					NA
American Indian / Alaskan Native	1 (0.3%)	4 (1.3%)	3 (1.0%)	8 (0.9%)	
Asian	15 (5.0%)	12 (4.0%)	17 (5.7%)	44 (4.9%)	
Black/African American	144 (47.7%)	125 (42.1%)	125 (41.7%)	394 (43.8%)	
Native Hawaiian / Pacific Islander	3 (1.0%)	2 (0.7%)	0 (0.0%)	5 (0.6%)	
White	139 (46.0%)	159 (53.5%)	157 (52.3%)	455 (50.6%)	
Other	4 (1.3%)	2 (0.7%)	2 (0.7%)	8 (0.9%)	
Age (years)					0.902[3]
N	302	297	300	899	
Mean ± SD	27.74 ± 18.11	28.8 ± 18.99	27.6 ± 17.34	28.0 ± 18.14	
Median	21.5	23.0	22.5	22.0	
Min, Max	8.0, 84.0	8.0, 82.0	8.0, 80.0	8.0, 84.0	

Weight (lbs)					0.716[3]
N	302	297	299	898	
Mean ± SD	149.5 ± 54.89	152.6 ± 56.12	153.1 ± 56.23	151.7 ± 55.71	
Median	150.0	150.0	152.2	150.0	
Min, Max	43.0, 295.0	48.2, 315.0	45.0, 315.0	43.0, 315.0	
Height (inches)					0.999[3]
N	302	297	299	898	
Mean ± SD	62.9 ± 6.64	63.2 ± 5.92	63.3 ± 6.34	63.1 ± 6.30	
Median	64.0	64.0	64.0	64.0	
Min, Max	29.9, 75.0	44.0, 78.0	47.0, 77.0	29.9, 78.0	

* From Sponsor's November 18, 2010 submission, Final Report Version 1.0 ALT 0417-01-01 Table 11.3.
[1] Patients could have self-reported more than one race.
[2] p values for treatment group comparisons from Cochran-Mantel-Haenszel test, adjusted for pooled study site.
[3] p values for treatment group comparisons from Friedman's test using treatment group and pooled study site as factors.

No patient became pregnant during the study.

Reviewer's Comments:

Although there was a difference for ethnicity in the ITT population (p=0.013) and mITT population (p=0.028), there was no difference for ethnicity in the PP population (p=0.122). In addition, the treatment groups were comparable for race in all three (ITT, mITT and PP) populations. Thus, the difference noted for ethnicity should not impact the results.

Baseline Dermatological Examination

According to the sponsor's analysis (shown in Table 2.6), ITT patients were comparable at Baseline with regard to the severity of atopic dermatitis as evaluated by the IGE (p = 0.426) and % BSA (p = 0.935). All patients who were randomized and had an IGE score of moderate or severe at Baseline. All patients who were randomized had ≥ 10% BSA affected at Baseline. Similar results were seen in both the mITT and PP populations.

Table 2.6: Baseline Dermatological Characteristics for Intent-to-Treat Population: ALT 0417-01-01/Tacrolimus 0.03% (per sponsor)*

Demographic	Test (N=302)	Reference (N=297)	Placebo (N=300)	Total (N=899)	p value
IGE (n,%)					0.426[1]
Moderate	260 (86.1%)	264 (88.9%)	267 (89.0%)	791 (88.0%)	
Severe	42 (13.9%)	33 (11.1%)	33 (11.0%)	108 (12.0%)	
% Body Surface Area					0.872[2]
Mean ± SD	23.1 ± 18.65	21.4 ± 16.17	21.5 ± 15.68	22.0 ± 16.89	
Median	15.0	15.0	15.0	15.0	
Min, Max	10.0, 90.0	10.0, 92.0	10.0, 90.0	10.0, 92.0	

* From Sponsor's November 18, 2010 submission, Final Report Version 1.0 ALT 0417-01-01 Table 11.4.
[1] p values for treatment group comparisons from Cochran-Mantel-Haenszel test, adjusted for pooled study site.
[2] p values for treatment group comparisons from Friedman's test using treatment group and pooled study site as factors.

2.4.4.3 Results

2.4.4.3.1 Primary Endpoint

The primary efficacy endpoint was the proportion of patients in each treatment group who had an IGE rating of "Clear" or "Almost Clear" (hereafter referred to as "success") for atopic dermatitis at Visit 4 (End of Study).

According to the sponsor's and FDA's analysis, in the PP population, the two active treatments were comparable with regard to the proportion of patients with success at Visit 4 (Table 2.7). The 90% confidence interval on the difference between active treatments was within the limit of [-0.20, 0.20] for both analyses.

According to the sponsor's and FDA's analysis, in the mITT population, the two active treatments were comparable with regard to the proportion of patients with success at Visit 4 Both the Test product and the Reference product showed superiority over Placebo in the mITT population with regard to the proportion of patients with success on the IGE at Visit 4 (all $p < 0.05$).

Table 2.7: Primary Endpoint Analysis: Proportion of Patients with Clinical Success on the Investigator's Global Evaluation: ALT 0417-01-01/Tacrolimus 0.03% (per sponsor and FDA Statistician)[*]

	Sponsor			FDA		
	Test	**Reference**	**Placebo**	**Test**	**Reference**	**Placebo**
PP Population						
N	226[1]	238[1]	228[1]	182	198	
Success[2]	123 (54.4%)	130 (54.6%)	86 (37.7%)	99 (54.40%)	105 (53.03%)	
90% CI for Test and Reference	(-0.082, 0.078[3])			(-0.07584, 0.10314)		
mITT Population						
N	294[1]	287[1]	293[1]	240	240	236
Success[2]	150 (51.0%)	152 (53.0%)	95 (32.4%)	122 (50.83%)	126 (52.50%)	76 (32.20%)
(Test or Reference) vs. Placebo	p=0.001	p<0.001		p<0.001	p<0.001	

***** From Sponsor's November 18, 2010 submission, Final Report Version 1.0 ALT 0417-01-01 Table 11.5.
mITT = modified intent-to-treat; N = number of patients; PP = per-protocol; vs = versus
[1]The last-observation-carried-forward approach was used to impute missing efficacy results for the mITT and PP patients who discontinued due to treatment failure.
[2] Success was defined as an Investigator's Global Evaluation rating of 0 (Clear) or 1 (Almost Clear) for atopic dermatitis.
[3] The sponsor's confidence intervals for the proportional difference were calculated using Wald's method with Yates' continuity correction.
[4] The sponsor's p values for comparing proportions used a Z-test with Yates' continuity correction.

2.4.5 Bioequivalence Conclusion

The FDA's statistical analysis shows the 90% CI of the test - reference difference between products for the primary endpoint in the proportion of patients in the per-protocol population in each group with treatment success were (-15.023%, 3.048%) for Study 0416 (0.1% strength) and (-7.584%, 10.314%) for Study 0417 (0.03% strength), which are within the established bioequivalence limits of [-0.20, 0.20]. The proportion of patients with treatment success for the Test and Reference products were demonstrated by the FDA's analysis to be superior to placebo in both studies.

2.5 Comparative Review of Safety

2.5.1 Brief Statement of Conclusions

These studies showed similar adverse events (AEs) with use of the test and reference products in both studies. A brief summary is provided below.

Study #	Total (N)	Test (n)	RLD (n)	Placebo (n)	Comment
Study 0416 (0.1% strength)	793	269	260	264	Tacrolimus concentration levels within levels observed during RLD PK studies.
Patients with at least one AEs	65 (8.2%)	17 (6.3%)	25 (9.6%)	23 (8.7%)	• p=0.202 (test vs. RLD) • No SAEs or deaths were reported in any group
Discontinued study drug due to above AE	14 (1.8%)	1 (0.4%)	9 (3.5%)	4 (1.5%)	p=0.02 (test vs. RLD)
Study 0417 (0.03% strength)	899	302	297	300	Tacrolimus concentration levels within levels observed during RLD PK studies.
Patients with at least one AEs	163 (18.1%)	52 (17.2%)	53 (17.8%)	55 (19.9%)	• p=0.840 (test vs. RLD) • No deaths were reported in any group
SAE	2	1	0	1	p=1.000 (test vs. RLD)
Discontinued study drug due to above AE	19 (1.9%)	5 (1.7%)	3 (1.0%)	11 (4.0%)	p=0.725 (test vs. RLD)

Study 0417-01-02 (0.03% strength follow-up)	5	NA	NA	NA	One year follow-up study.
Patients with at least one AEs	4 (80.0%)	NA	NA	NA	

2.5.2 Description of Adverse Events

2.5.2.1 Bioequivalence Study with Clinical Endpoints for Tacrolimus Ointment 0.1% Strength (Study ALT 0416-01-01)

Of the 793 ITT patients, 65 patients (8.2%) experienced one or more treatment-emergent AEs (TEAEs) during the study, regardless of relationship to study medication during the study: 6.6% (17/259) for the Test group, 9.6% (25/260) for the Reference group, and 8.7% (23/263) for the Vehicle group (Table 3.1). According to the sponsor's analysis, the two active treatment groups were comparable and there was no significant statistical difference between the two active treatment groups with regard to the occurrence of AEs (P = 0.202). Skin-related TEAEs accounted for the majority of all TEAEs and were reported by a higher percentage of patients, regardless of treatment group.

There were 10 patients[1] in the Test group who were affected by the potential packaging error associated with study medication. An additional treatment group, the Potential Incorrect Dose group, was included in all safety summaries in order for these 10 patients to be "analyzed as dosed." No patients in the Potential Incorrect Dose group experienced a TEAE during the study.

Most TEAEs were mild or moderate in severity. The Reference and Placebo groups had a higher proportion of patients who experienced severe TEAEs than did in the Test group (2.7%, 3.0%, and 0.8%, respectively). The difference between the Test and Reference groups was not statistically significant (p=0.397). No patients experienced a serious AE. No deaths were reported.

Fourteen patients discontinued the study medication due to a TEAE; of these, 12 patients discontinued from the study due to a TEAE and 2 patients discontinued from the study due to worsening of their condition. This includes 1 patient (Patient (b) (6) in the Reference group) who was erroneously noted as having discontinued due to an AE; this patient completed the study on (b) (6). The TEAEs leading to discontinuation of study medication and/or from the study included application site rash, application site irritation, pruritus, atopic dermatitis, skin burning sensation, headache, drug hypersensitivity, and influenza.

Reviewer's Comments:

- *Those patients who discontinued the study due to worsening of their condition were appropriately included in/excluded from the sponsor's PP population. These patients should continue to remain included/excluded in the FDA's PP population.*

(b) (6)

- *According to the CRF, Patient* [redacted] *did discontinue the study medication* [redacted]*) due to an AE of "skin burning". The patient's study diary confirms that the first dose was applied on* [redacted] *and the last dose of study medication was applied on* [redacted] *which is less than the required 7 days of treatment needed for inclusion in the PP population. Even though the patient did return for all 3 visits and was evaluated, this patient should remain excluded from the FDA's PP population. This error should have no impact on the results.*

Additionally, due to an error in the original memo documenting this mis-dosing issue, Patient [redacted] (Placebo group) was erroneously included in the Potential Incorrect Dose group; this patient should have been included in the Vehicle group for the safety summaries; however, since this patient had no TEAEs during the study this error did not affect the safety analyses.

As seen in Table 3.1, more TEAEs were considered to be related (possibly, probably, or definitely) to study medication than not related to the study medication, regardless of treatment group. The difference between the Test and Reference groups was not statistically significant (p=0.213 for related TEAEs and p=0.970 for not related TEAEs). The majority of related (possibly, probably, or definitely) TEAEs for the Test and Reference groups occurred in the System Organ Class of "General Disorders and Administration Site Conditions" and included application site erythema, application site exfoliation, application site irritation, application site pruritus, application site rash, and application site reaction.

As seen in Table 3.1, more TEAEs were considered to be skin-related.

Table 3.1: Overall Summary of Adverse Events for Intent-to-Treat Population (per sponsor)*

	Test (N=259)	Reference (N=260)	Placebo (N=263)	Potential Incorrect Dose[2] (N=11)	p-value[3]
Number of patients with at least one treatment-emergent AE	17 (6.6%)	25 (9.6%)	23 (8.7%)	0 (0.0%)	0.202
Number of patients with at least one serious treatment-emergent AE	0	0	0	0	NA
Number of patients with at least one related treatment-emergent AE[1]	9 (3.5%)	15 (5.8%)	14 (5.3%)	0	0.213
Number of patients with at least one not related treatment-emergent AE	8 (3.1%)	10 (3.8%)	9 (3.4%)	0	0.970
Number of patients with at least one skin-related AE	10 (3.9%)	16 (6.2%)	13 (4.9%)	0	
Number of patients with at least one not skin-related AE	7 (2.7%)	9 (3.5%)	10 (3.8%)	0	
Number of patients discontinuing the study drug due to a treatment-emergent AE	1 (0.4%)	9 (3.5%)	4 (1.5%)	0	0.020
Number of deaths	0	0	0	0	NA
Number of patients with at least one:					
Mild treatment-emergent AE	10 (3.9%)	14 (5.4%)	9 (3.4%)	0	0.397
Moderate treatment-emergent AE	5 (1.9%)	4 (1.5%)	6 (2.3%)	0	
Severe treatment-emergent AE	2 (0.8%)	7 (2.7%)	8 (3.0%)	0	
Not related treatment-emergent AE	8 (3.1%)	10 (3.8%)	9 (3.4%)	0	0.970
Possibly related treatment-emergent AE	4 (1.5%)	5 (1.9%)	6 (2.3%)	0	
Probably related treatment-emergent AE	2 (0.8%)	4 (1.5%)	6 (2.3%)	0	
Definitely related treatment-emergent AE	3 (1.2%)	6 (2.3%)	2 (0.8%)	0	

* From Sponsor's April 8, 2010 submission, Final Report Version 1.0 ALT 0416-01-01 Tables 12.1 and 12.5.
AE = adverse event; NA = not applicable
Patients who reported more than one treatment-emergent adverse event were only counted once under the strongest relationship and/or severity.
Note: Due to an error in the original memo documenting which patients were potentially misdosed, Patient (b) (6) (Placebo group) was erroneously included in the Potential Incorrect Dose group. This patient should have been included in the Placebo group for the safety summaries; however, since this patient had no TEAEs during the study this error did not affect the safety analyses.
[1] The "Related" category includes possibly, probably, and definitely related treatment-emergent adverse events.
[2] This group included patients who either applied or potentially applied incorrect study medication.
[3] The P value for comparing the Test and Reference treatments used a chi-square test or Fisher's exact test if more appropriate.

No TEAE occurred in more than 5% of patients in any treatment group; however, the most common TEAE that occurred in ≥ 1.5% of patients in any treatment group were application site irritation, application site pruritus, and atopic dermatitis (Table 3.2).

Table 3.2: Most Common (≥ 1.5%) Treatment-Emergent Adverse Events for Intent-to-Treat Population (per sponsor)*

System Organ Class/ Preferred Term	Test (N=259)	Reference (N=260)	Placebo (N=263)	Potential Incorrect Dose[1] (N=11)
General disorders and administration site conditions	7 (2.7%)	13 (5.0%)	6 (2.3%)	0
Application site irritation	3 (1.2%)	6 (2.3%)	0	0
Application site pruritus	2 (0.8%)	8 (3.1%)	4 (1.5%)	0
Skin and subcutaneous tissue disorders	3 (1.2%)	2 (0.8%)	8 (3.0%)	0
Dermatitis atopic	1 (0.4%)	1 (0.4%)	4 (1.5%)	0

* From Sponsor's April 8, 2010 submission, Final Report Version 1.0 ALT 0416-01-01 Table 12.2.
At each level of summarization (system organ class/preferred term), patients who reported more than one treatment-emergent adverse event were only counted once.
Note: Due to an error in the original memo documenting which patients were potentially misdosed, Patient (b) (6) (Placebo group) was erroneously included in the Potential Incorrect Dose group. This patient should have been included in the Placebo group for the safety summaries; however, since this patient had no TEAEs during the study this error did not affect the safety analyses.
[1]This group included patients who either applied or potentially applied incorrect study medication.

As seen in Table 3.3, severe TEAEs were as follows: application site irritation, application site pruritus, drug hypersensitivity, sinusitis, arthralgia, myalgia, .headache, allergic dermatitis, atopic dermatitis, and rash.

Table 3.3: Treatment-Emergent Severe Adverse Events for Intent-to-Treat Population (per sponsor)*

Preferred Term	Test (N=259)	Reference (N=260)	Placebo (N=263)	Potential Incorrect Dose[1] (N=11)
Number of patients with at least one treatment-emergent severe adverse event	2 (0.8%)	7 (2.7%)	8 (3.0%)	0
Application site irritation	1 (0.4%)	3 (1.2%)	0	0
Application site pruritus	0	4 (1.5%)	1 (0.4%)	0
Drug hypersensitivity	0	1 (0.4%)	0	0
Sinusitis	0	0	1 (0.4%)	0
Arthralgia	0	1 (0.4%)	0	0
Myalgia	0	0	1 (0.4%)	0
Headache	0	0	1 (0.4%)	0
Dermatitis allergic	0	0	1 (0.4%)	0
Dermatitis atopic	1 (0.4%)	1 (0.4%)	3 (1.1%)	0
Rash	0	0	1 (0.4%)	0

* From Sponsor's April 8, 2010 submission, Final Report Version 1.0 ALT 0416-01-01 Table 12.3.
Patients who reported more than one treatment-emergent adverse event were only counted once.
Note: Due to an error in the original memo documenting which patients were potentially misdosed, Patient (b) (6) (Placebo group) was erroneously included in the Potential Incorrect Dose group. This patient should have been included in the Placebo group for the safety summaries; however, since this patient had no TEAEs during the study this error did not affect the safety analyses.
[1]This group included patients who either applied or potentially applied incorrect study medication.

Tacrolimus Concentration

At Visit 2, a blood sample was drawn for the assay of tacrolimus concentration. Results are listed by patient in Listing 16.2.10 of the sponsor's study report. Generally, most concentration results were considered to be low (< 3.0 ng/mL; reference range = 5 to 20 ng/mL). Only one of the patients had a high value or approached the upper limit (20 ng/mL); the highest value in the Test and Reference groups was 20.0 ng/mL (Patient (b) (6) Test group). Patients in the Vehicle group were not required to have their assays tested since they were not randomized to one of the active treatment groups.

Deficiency (8/8/13 ECD Item A.16):

Regarding the assay of tacrolimus concentration, the study report states that "Subjects in the Vehicle group were not required to have their assays tested since they were not randomized to one of the active treatment groups." Given that this was a double blinded study, how did the investigative sites know which patients were in the placebo group?

Response

As this was a double blind study, investigative sites did not know the treatment arm allocation for their subjects. Blood samples were obtained from all enrolled subjects and shipped to the central laboratory for analysis. The Project Management representative at Fougera supplied the randomization code directly to a single unblinded representative at (b) (4). Clinical Operations was not copied on this correspondence. Prior to conducting analysis of the blood sample, the laboratory compared the subject number to the randomization code. If the subject was allocated to the Vehicle group, the laboratory did not conduct the tacrolimus assay testing.

Reviewer assessment:

Acceptable. However, it would have been preferred for all the blood samples to be assayed without a copy of the randomization code being shared with the laboratory prior to database lock. Alternatively, the chance for bias would be decreased if the sponsor did not maintain a copy of the randomization code at all and the third party who generated the randomization code supplied the randomization code to (b) (4).

Deficiency (8/8/13 ECD Item A.17):

Explain why the assay was cancelled for the following patients: (b) (6) (b) (6). *Provide a copy of these patients' CRFs.*

Response

Prior to conducting analysis of an assay sample, the laboratory compared the subject number to the randomization code. If the subject was allocated to the Vehicle group, the laboratory did not conduct the tacrolimus assay testing.

Subject Number	Details per (b) (4) Memo
(b) (6)	Cancelled in error
	Test originally ordered but cancelled (in error)
	Cancelled due to sample integrity
	Cancelled due to sample integrity
	Cancelled in error
	Cancelled due to specimen clotting
	Cancelled in error
	Cancelled because subject ID was originally submitted to (b) (4) as (b) (6) which was on the placebo listing
	Cancelled in error
	Cancelled in error

In six cases, an error was made during this verification step and the lab inadvertently cancelled the testing in error. In addition, several samples were cancelled due to sample integrity or clotting. Upon review of data listings, Fougera inquired about these cancelled tests; (b) (4) provided a memo with an explanation for each subject. Please refer to ALT 0416-01-01 (b) (4) (b) (4) Memo issued 3/2/10.

Reviewer assessment:

Acceptable

Reviewer's Comments:

The tacrolimus concentration levels observed during this study are within the levels observed during the RLD pharmacokinetic studies. The peak tacrolimus blood concentrations ranged from undetectable to 20 ng/mL after single or multiple doses of 0.03% and 0.1% Protopic Ointment, with 85% (75/88) of the patients having peak blood concentrations less than 2 ng/mL. The concentration levels are similar between the test and reference groups during this ANDA study.

Table 3.4: Trough Level Concentrations (including potentially misdosed patients; per reviewer)

Trough Level Result	Test (N=250)	Reference (N=241)
<3.0	238	234
3.3	0	1
3.5	1	0
3.6	2	0
4.0	2	0
4.1	2	0
6.8	0	1
7.2	0	1
9.2	2	0
20.0	1	0
TNP*	6	4

* TNP = Test not performed

Table 3.5: Trough Level Concentrations (excluding potentially misdosed patients; per reviewer)

Trough Level Result	Test (N=241)	Reference (N=241)
<3.0	230	234
3.3	0	1
3.5	1	0
3.6	1	0
4.0	1	0
4.1	1	0
6.8	0	1
7.2	0	1
9.2	0	0
20.0	1	0
TNP*	6	4

* TNP = Test not performed

2.5.2.2 Bioequivalence Study with Clinical Endpoints for Tacrolimus Ointment 0.03% Strength (Study ALT 0417-01-01)

Of the 899 ITT patients, 163 patients (18.1%) experienced one or more treatment-emergent AEs (TEAEs) during the study, regardless of relationship to study medication during the study: 17.2% (52/302) for the Test group, 17.8% (53/297) for the Reference group, and 19.9% (55/276) for the Placebo group (Table 4.1). According to the sponsor's analysis, the two active treatment groups were comparable and there was no significant statistical difference between the two active treatment groups with regard to the occurrence of TEAEs (p=0.840). Skin-related TEAEs accounted for the majority of all TEAEs and were reported by a higher percentage of patients than were non-skin-related TEAEs.

In the Placebo group, there were 19 patients[2] who were potentially misdosed and 5 patients[3] who were definitely mis-dosed with study medication not per the randomization code. An additional treatment group, the Potential Incorrect Dose group, was included in all safety summaries in order for these 24 patients to be "analyzed as dosed." Three of these patients (12.5%) experienced a TEAE during the study.

Most TEAEs were mild or moderate in severity. Severe TEAEs occurred in the Test and Placebo groups only (1.3% and 2.2%, respectively). The difference in the severity of TEAEs between the Test and Reference groups was not statistically significant (p=0.164). Two patients experienced a serious AE: 1 patient each in the Test (influenza and ovarian cyst) and Placebo

(b) (6)

groups (angina pectoris). Neither SAE was considered to be related to the study medication and no deaths were reported.

Nineteen patients discontinued the study medication due to a TEAE; of these, 7 patients discontinued from the study due to a TEAE and 12 patients discontinued from the study due to worsening of their condition. The TEAEs leading to discontinuation of study medication and/or from the study included application site irritation, application site pruritus, application site reaction, atopic dermatitis, infected dermatitis, contact dermatitis, blister, and eye swelling.

Reviewer's Comments:

Those patients who discontinued the study due to worsening of their condition were appropriately included in/excluded from the sponsor's PP population. These patients should continue to remain included/excluded in the FDA's PP population.

As seen in Table 3.1, more TEAEs were considered to be not related to study medication than were considered to be related (possibly, probably, or definitely) to study medication: 8.6% of patients in the Test group, 10.4% of patients in the Reference group, 10.5% of patients in the Placebo group, and 8.3% of patients in the Potential Incorrect Dose group. The difference between the Test and Reference groups was not statistically significant (p=0.588 for related TEAEs and p=0.436 for not related TEAEs). The majority of related (possibly, probably, or definitely) TEAEs for the Test and Placebo groups occurred in the System Organ Class of "General Disorders and Administration Site Conditions" and included application site dermatitis, application site erythema, application site hypersensitivity, application site irritation, application site photosensitivity reaction, application site pruritus, application site reaction, and application site warmth.

Table 4.1: Overall Summary of Adverse Events for Intent-to-Treat Population (per sponsor)*

	Test (N=302)	Reference (N=297)	Placebo (N=276)	Potential Incorrect Dose[2] (N=24)	p-value[3]
Number of patients with at least one treatment-emergent AE	52 (17.2%)	53 (17.8%)	55 (19.9%)	3 (12.5%)	0.840
Number of patients with at least one serious treatment-emergent AE	1 (0.3%)	0	1 (0.4%)	0	1.000
Number of patients with at least one related treatment-emergent AE[1]	26 (8.6%)	22 (7.4%)	26 (9.4%)	1 (4.2%)	0.588
Number of patients with at least one skin-related AE	32 (10.6%)	25 (8.4%)	35 (12.7%)	1 (4.2%)	
Number of patients with at least one not skin-related AE	20 (6.6%)	28 (9.4%)	20 (7.2%)	2 (8.3)	
Number of patients discontinuing the study drug due to a treatment-emergent AE	5 (1.7%)	3 (1.0%)	11 (4.0%)	0	0.725
Number of deaths	0	0	0	0	NA
Number of patients with at least one:					
Mild treatment-emergent AE	30 (9.9%)	33 (11.1%)	26 (9.4%)	2 (8.3)	0.164
Moderate treatment-emergent AE	18 (6.0%)	20 (6.7%)	23 (8.3%)	1 (4.2%)	
Severe treatment-emergent AE	4 (1.3%)	0	6 (2.2%)	0	
Not related treatment-emergent AE	26 (8.6%)	31 (10.4%)	29 (10.5%)	2 (8.3)	0.436
Possibly related treatment-emergent AE	16 (5.3%)	9 (3.0%)	14 (5.1%)	0	
Probably related treatment-emergent AE	7 (2.3%)	9 (3.0%)	7 (2.5%)	1 (4.2%)	
Definitely related treatment-emergent AE	3 (1.0%)	4 (1.3%)	5 (1.8%)	0	

* From Sponsor's November 18, 2010 submission, Final Report Version 1.0 ALT 0417-01-01 Tables 12.1 and 12.5.
AE = adverse event; NA = not applicable
Patients who reported more than one treatment-emergent adverse event were only counted once under the strongest relationship and/or severity.
[1] The "Related" category includes possibly, probably, and definitely related treatment-emergent adverse events.
[2] This group included patients who either applied or potentially applied incorrect study medication.
[3] The P value for comparing the Test and Reference treatments used a chi-square test or Fisher's exact test if more appropriate.

The most common TEAE, which were events that were reported by at least 5% of the patients in any treatment group, was headache (Table 4.2).

Table 4.2: Most Common (≥ 1.5%) Treatment-Emergent Adverse Events for Intent-to-Treat Population (per sponsor)*

System Organ Class/ Preferred Term	Test (N=302)	Reference (N=297)	Placebo (N=276)	Potential Incorrect Dose[2] (N=24)
Number of Patients with System Organ Class >5% in any Treatment Group	3 (1.0%)	7 (2.4%)	3 (1.1%)	2 (8.3%)
Nervous System Disorders	3 (1.0%)	7 (2.4%)	3 (1.1%)	2 (8.3%)
Headache	3 (1.0%)	7 (2.4%)	3 (1.1%)	2 (8.3%)

* From Sponsor's November 18, 2010 submission, Final Report Version 1.0 ALT 0417-01-01 Table 12.2.
At each level of summarization (system organ class/preferred term), patients who reported more than one treatment-emergent adverse event were only counted once.
[1]This group included patients who either applied or potentially applied incorrect study medication.

As seen in Table 3.3, severe TEAEs were as follows: angina pectoris (0.4% of patients in the Placebo group), application site hypersensitivity (0.3% of patients in the Test group), headache (0.4% of patients in the Placebo group), and atopic dermatitis (1.0% of patients in the Test group and 1.4% of patients in the Placebo group).

Table 4.3: Treatment-Emergent Severe Adverse Events for Intent-to-Treat Population (per sponsor)*

Preferred Term	Test (N=302)	Reference (N=297)	Placebo (N=276)	Potential Incorrect Dose[2] (N=24)
Number of patients with at least one treatment-emergent severe adverse event	4 (1.3%)	0	6 (2.2%)	0
Angina pectoris	0	0	1 (0.4%)	0
Application site hypersensitivity	1 (0.3%)	0	0	0
Headache	0	0	1 (0.4%)	0
Dermatitis atopic	3 (1.0%)	0	4 (1.4%)	0

* From Sponsor's November 18, 2010 submission, Final Report Version 1.0 ALT 0417-01-01 Table 12.3.
Patients who reported more than one treatment-emergent adverse event were only counted once.
[1]This group included patients who either applied or potentially applied incorrect study medication.

Tacrolimus Concentration

At Visit 2, a blood sample was drawn for the assay of tacrolimus concentration. Results are listed by patient in Listing 16.2.10. Generally, most concentration results were considered to be at the low end of the reference range (< 3.0 ng/mL; reference range = 5 to 20 ng/mL). None of the patients had a high value or approached the upper limit (20 ng/mL); the highest value in either the Test or Reference group was 12.5 ng/mL (Patient (b) (6) Reference group). Patients in the Placebo group were not required to have assays performed since they were not randomized to one of the active treatment groups.

Deficiency (8/8/13 ECD Item B.15):

Regarding the assay of tacrolimus concentration, the study report states that "Subjects in the Vehicle group were not required to have their assays tested since they were not randomized to one of the active treatment groups." Given that this was a double blinded study, how did the investigative sites know which patients were in the placebo group?

Response

As this was a double blind study, investigative sites did not know the treatment arm allocation for their subjects. Blood samples were obtained from all enrolled subjects and shipped to the central laboratory for analysis. The Project Management representative at Fougera supplied the randomization code directly to a single unblinded representative at (b) (4) Clinical Operations was not copied on this correspondence. Prior to conducting analysis of the blood sample, the laboratory compared the subject number to the randomization code. If the subject was allocated to the Vehicle group, the laboratory did not conduct the tacrolimus assay testing.

Reviewer assessment:

Acceptable. However, it would have been preferred for all the blood samples to be assayed without a copy of the randomization code being shared with the laboratory prior to database lock. Alternatively, the chance for bias would be decreased if the sponsor did not maintain a copy of the randomization code at all and the third party who generated the randomization code supplied the randomization code to (b) (4)

Reviewer's Comments:

- *All the mis-dosed or potentially mis-dosed patients were in the Placebo group. Therefore, no change in the results if these patients are included or excluded.*
- *The tacrolimus concentration levels observed during this study are within the levels observed during the RLD pharmacokinetic studies. In the RLD pharmacokinetic studies, the peak tacrolimus blood concentrations ranged from undetectable to 20 ng/mL after single or multiple doses of 0.03% and 0.1% Protopic Ointment, with 85% (75/88) of the patients having peak blood concentrations less than 2 ng/mL. The concentration levels are similar between the test and reference groups during this ANDA study.*

Table 4.4: Trough Level Concentrations (per reviewer)

Trough Level Result	Test (N=276)	Reference (N=274)
<3.0	273	270
3.0	2	0
5.2	1	0
7.0	0	1
12.5	0	1
TNP*	0	2

* TNP = Test not performed. According to Listing 16.2.10, the blood samples for Patients (b) (6) were not analyzed "due to specimen received clotted."

2.5.2.3 Safety Monitoring Study (Study ALT 0417-01-02)

Twenty-four subjects who participated in study ALT 0417-01-01 were identified as having been incorrectly dosed (5 subjects) or potentially incorrectly dosed (19 subjects) due to a packaging error. A safety study to monitor these subjects was conducted. This study consisted of 2 visits 1 year apart.. At Visit 1 (Day 1), the subject's medical history was recorded along with concomitant medications. They were compared to the medical history and concomitant medications present at the completion of ALT 0417-01-01 and anything new was noted. The target lesions identified during participation in ALT 0417-01-01 were used in 0417-01-02. A physical examination including a complete body exam of the skin, with a focus on the areas treated with study medication during participation in ALT 0417-01-01, was performed. Subjects returned to the office for Visit 2 (Day 365 ±14) End of Study/Early Termination. Changes in the subject's health, since Visit 1, were recorded as medical events. Changes in the subject's concomitant medications were also recorded. A physical examination including a complete body exam of the skin, with a focus on the areas treated with study medication during participation in ALT 0417-01-01, was performed. When possible, the same investigator conducted the physical

examination at all visits. Subjects were able to schedule a visit at any time during the study at the investigator's discretion and Unscheduled Visit procedures were followed.

Of these 24 subjects, only 5 subjects were enrolled into the study, 2 of which were mis-dosed and 3 subjects were potentially mis-dosed.

Incidence of all new medical history events since completion of ALT 0417-01-01 and medical events reported during the study are summarized in Table 12.1

Table 5.1: Incidence of Medical History/Events by MedDRA System Organ Class and Preferred Term (per sponsor)

	Preferred Term	Study Participants (N=5)
Subjects with at Least One Medical History/Event		5 (100%)
GASTROINTESTINAL DISORDERS	Total	1 (20.0%)
	CROHN'S DISEASE	1 (20.0%)
IMMUNE SYSTEM DISORDERS	Total	3 (60.0%)
	DRUG HYPERSENSITIVITY	1 (20.0%)
	SEASONAL ALLERGY	2 (40.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Total	1 (20.0%)
	HAEMANGIOMA	1 (20.0%)
	MELANOCYTIC NAEVUS	1 (20.0%)
NERVOUS SYSTEM DISORDERS	Total	2 (40.0%)
	HEADACHE	1 (20.0%)
	MIGRAINE	1 (20.0%)
	NEUROPATHY PERIPHERAL	1 (20.0%)
PSYCHIATRIC DISORDERS	Total	1 (20.0%)
	ANXIETY	1 (20.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Total	2 (40.0%)
	ASTHMA	2 (40.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Total	5 (100%)
	DERMATITIS ATOPIC	5 (100%)
	DERMATITIS CONTACT	1 (20.0%)
	HYPERHIDROSIS	1 (20.0%)
	LENTIGO	1 (20.0%)
VASCULAR DISORDERS	Total	1 (20.0%)
	HYPERTENSION	1 (20.0%)

Counts reflect numbers of subjects reporting one or more history/event that map to the MedDRA Version 14.0 system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one history/event are counted only once.

Of the five subjects enrolled, 5 (100%) subjects reported new medical history/events. The most frequently occurred events were atopic dermatitis (100%) and seasonal allergies (40%). All new medical history/events were determined by the study investigator to be not related to the study medication.

Reviewer's Comments:

- *Four of the 5 subjects were adults. Given that the 0.1% dose is approved for use in adults and both the 0.03% and 0.1% dose is labeled for twice daily use, the dose of tacrolimus administered during the original study was within the labeled recommendations.*
- *Of the 5 subjects in this safety study, only 1, who was potentially mis-dosed, was pediatric (15 years old at enrollment into the original study). There were 4 other pediatric subjects (potentially mis-dosed with the 0.1% dose) who were not enrolled into this safety study.*
- *Although the sponsor's study report narrates that all 5 subjects reported new medical history/events, only 4 subjects are noted to have new medical history/events based on the complete listing by subject as provided in Appendix 16.2.5 of the study report. The pediatric subject did not report any new event. This subject reported that atopic dermatitis was ongoing since the age of 1. No other medical history/events was reported.*
- *There isn't enough information from this study to make any conclusions about the increased risk, if any, related to the exposure of these subjects to the 0.1% ointment rather than the 0.03% placebo.*

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Review of the OSI Report

An OSI inspection was requested on 12/9/11. On 5/23/12, upon awareness of the packaging/dosing error by this reviewer, the OSI inspection request was converted to a "For-Cause ANDA Pre-Approval Data Validation Inspection." The following sites were inspected:

1. Commonwealth Clinical Research Specialists, Inc., Richmond, VA; Principal Investigator Robert Call, M.D. (Study ALT 0416-01-01 Site 5 & Study ALT 0417-01-01 Site 5) inspected from 7/9/12 to 7/20/12 and Form FDA-483 issued. Final classification: VAI
2. Miami Dermatology Research Institute, LLC, North Miami Beach, FL; Principal Investigator Tory Sullivan, M.D. (Study ALT 0417-01-01 Site 37) inspected from 6/13/12 to 7/3/12 and Form FDA-483 issued. Final classification: VAI
3. Radiant Research, Columbus, OH; Principal Investigator Michelle Chambers, M.D. (Study ALT 0416-01-01 Site 6 & Study ALT 0417-01-01 Site 40) insptected from 11/1/12 to 11/13/12 and no Form FDA-483 issued. Final classification: NAI

According to the EIR review (dated December 14, 2012 and finalized on 1/9/13), the following are the objectionable findings at the 2 sites:

1. For Commonwealth Clinical Research Specialists, Inc., Richmond, VA (PI: Robert Call, M.D.): **An investigation was not conducted in accordance with the investigational**

plan. Specifically:

a. Not all subjects enrolled in the study met the protocol inclusion/exclusion criteria. For Study ALT 0416, Patient (b) (6) reported an allergy to erythromycin; however, the subject was enrolled in the study. For Study ALT 0417, Patient (b) (6) reported an allergy to erythromycin; however, the subject was enrolled in the study.
b. Not all patients enrolled in the study were assigned to treatment according to the procedures specified in the study protocol. Two subjects were assigned treatment kit boxes out of sequence.
c. Not all concomitant medications required to be recorded by the study protocol including prescription, OTC medications and dietary supplements were captured and reported to the sponsor. For Study ALT 0416, Patient (b) (6) reported taking the dietary supplement Xaio Feng San for 4 years; however, this dietary supplement was not reported to the sponsor in the CRF. Patient (b) (6) (also for Study ALT 0416) reported taking Black Cohash, Vitamin D, and Calcium; however these dietary supplements were not reported to the sponsor in the CRF.

2. For Miami Dermatology Research Institute, LLC, North Miami Beach, FL (PI: Tory Sullivan, M.D.): **Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specifically:**

a. Six of 20 patients enrolled in Study ALT 0417 had discrepancies in their data between the 3 different types of study forms which documented the investigational study drug dispensation and recovery. Data variation among the source documents, CRFs, and Drug Dispensing/Accountability Logs resulted in 13 discrepancies.

Reviewer's Comment:

- *For comment #1.a: The sponsor has already excluded both patients from the mITT and PP populations for not meeting inclusion/exclusion criteria. These patients will remain excluded from the FDA's mITT and PP populations.*
- *For comment #1.b: In the PI's written response, the PI acknowledged this error and generated an SOP to prevent future occurrences. This finding would not have a significant impact on the overall study outcome. Therefore, no change to the study data analysis is needed.*
- *For comment #1.c: The sponsor has already excluded Patient (b) (6) from the PP population and Patient (b) (6) from the mITT and PP populations for other reasons unrelated to this finding. These patients will remain excluded from the FDA's respective populations.*
- *For comment #2.a: In the PI's written response, the PI acknowledged this observation and indicated that these discrepancies occurred due to transcription errors. The EIR reviewer notes that the number of used, unused and missed tubes shipped back to the sponsor after the completion of the study matched with the total number of tubes originally received from the sponsor. It was also noted that the missed tubes were usually due to patients being lost to follow-up. Since the number of drug applications were captured in the patient's Study Drug Diary Card, this finding would not have a*

significant impact on the overall study outcome. Therefore, no change to the study data analysis is needed.

- *It should be noted that the OSI inspections were at the clinical site levels. The clinical sites were not aware of the packaging error and thus that aspect of the study was not evaluated by the OSI. After discussions with members of the OSI, it was decided that information needed to determine data integrity from the unblinding of the medications by the third party* (b) (4) *could be obtained through communications with the sponsor by this reviewer.*

2.6.2 Review of the FDA Statistical Report

The FDA statistical analyses support the bioequivalence of the Test and the Reference products. The FDA's statistical analysis shows the 90% CI of the test - reference difference between products for the primary endpoint in the proportion of patients in the per-protocol population in each group with treatment success were (-15.023%, 3.048%) for Study 0416 (0.1% strength) and (-7.584%, 10.314%) for Study 0417 (0.03% strength), which are within the established bioequivalence limits of [-0.20, 0.20]. The proportion of patients with treatment success for the Test and Reference products were demonstrated by the FDA's analysis to be superior to placebo in both studies. For details of the FDA statistical analyses, please see Sections 2.4.3.3 and 2.4.4.3 ("Results") of this review.

2.7 Formulation

Table 6.1: Tacrolimus Ointment 0.03%

Ingredient	**Function**	**Test (%w/w)**	**RLD[1] (% w/w)**
Tacrolimus	Active	0.03	0.03[2]
White Petrolatum, USP	(b) (4)		
Mineral Oil, USP			
Propylene Carbonate, NF			
White Wax, NF			
Paraffin, NF			

(b) (4)

Table 6.2: Tacrolimus Ointment 0.1%

Ingredient	Function	Test (%w/w)	RLD[1] (% w/w)
Tacrolimus	Active	0.1	0.1[2]
White Petrolatum, USP	(b) (4)		
Mineral Oil, USP			
Propylene Carbonate, NF			
White Wax, NF			
Paraffin, NF			

(b) (4)

Reviewer's Comment:

The test and reference products are qualitatively the same. However, they are quantitatively different. The quantitative differences are acceptable at the levels listed from a regulatory perspective, as determined by the filing review from the Regulatory Support Branch. (b) (4)

(b) (4)

2.8 Conclusion and Recommendation

2.8.1 Conclusion

The FDA's statistical analysis shows the 90% CI of the test - reference difference between products for the primary endpoint in the proportion of patients in the per-protocol population in each group with treatment success were (-15.023%, 3.048%) for Study 0416 (0.1% strength) and (-7.584%, 10.314%) for Study 0417 (0.03% strength), which are within the established bioequivalence limits of [-0.20, 0.20]. The proportion of patients with treatment success for the

Test and Reference products were demonstrated by the FDA's analysis to be superior to placebo in both studies.

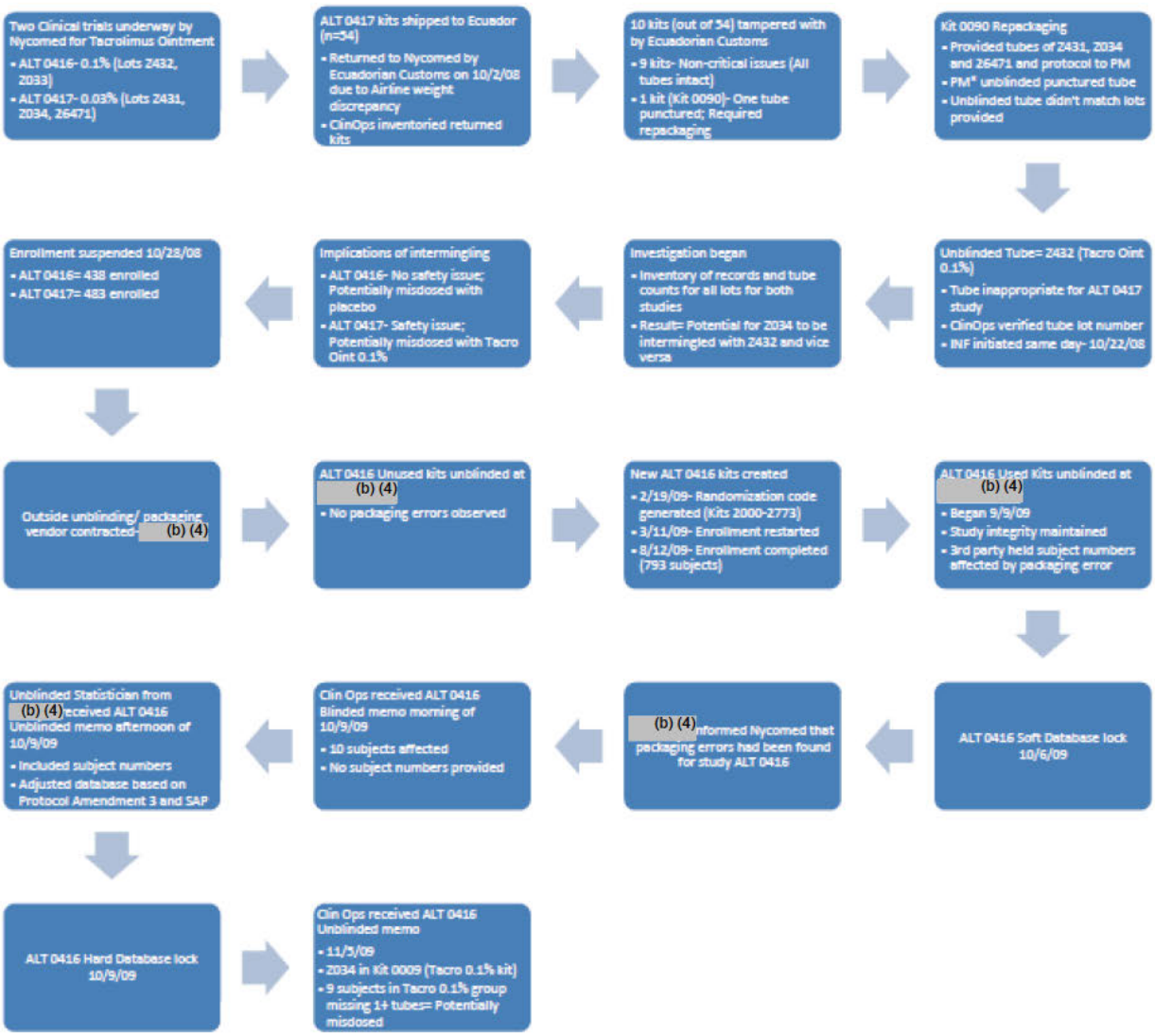
2.8.2 Recommendations

This application is recommended for approval from a clinical bioequivalence standpoint.

3 Appendix

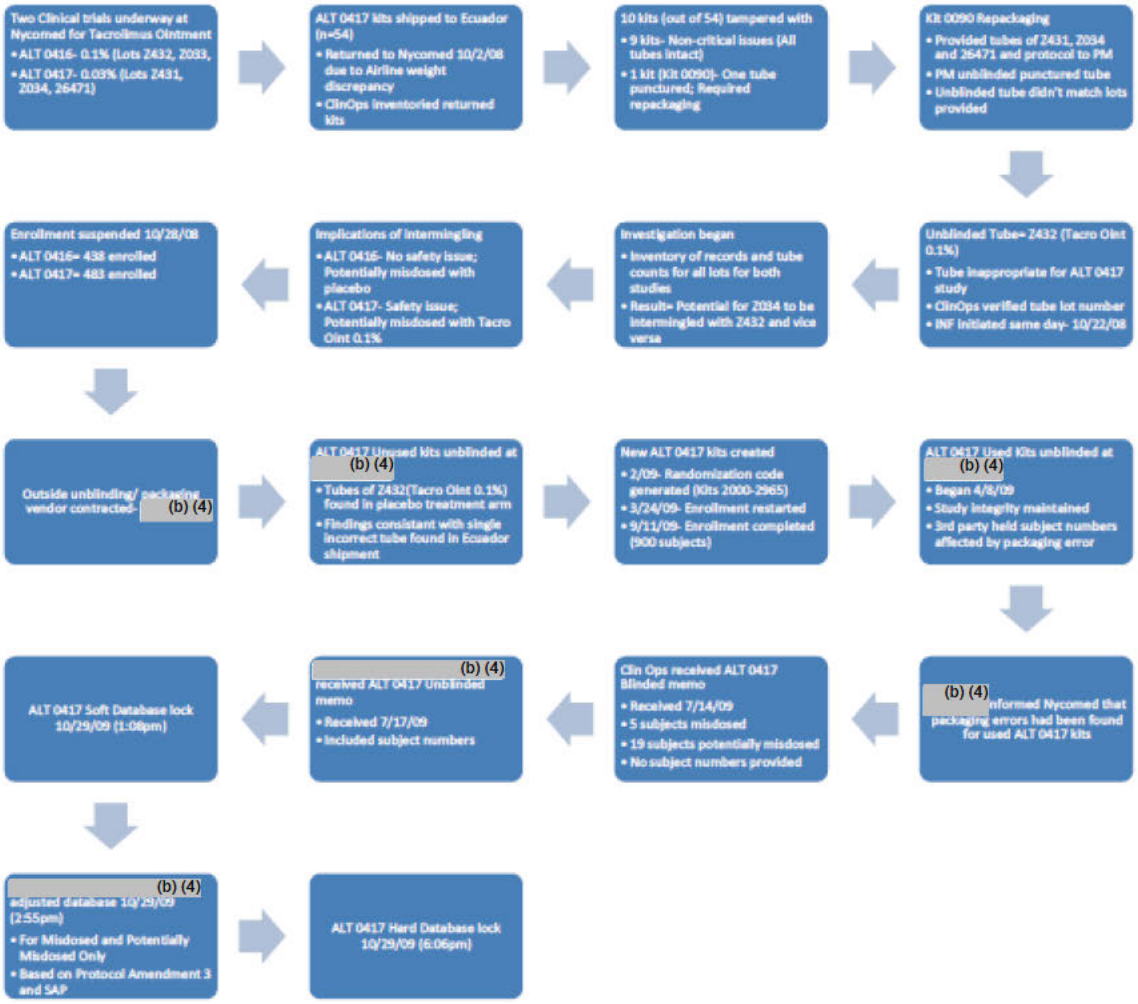
3.1 Packaging/Dosing Error Discovery and Actions Taken

3.1.1 Study ALT 0416-01-01 (Tacrolimus Ointment, 0.1%)



* Project Management is a separate department from Clinical Operations. Project Management securely maintains the randomization code and makes no decisions regarding clinical study conduct.

3.1.2 Study ALT 0417-01-01 (Tacrolimus Ointment, 0.03%)



CLINICAL BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200744 APPLICANT: Fougera Pharmaceuticals Inc

DRUG PRODUCT: Tacrolimus Ointment, 0.1% and 0.03%

The Division of Clinical Review has completed its review and has no further questions at this time.

The data submitted to ANDA 200744, using the primary endpoint of the proportion of patients in the per-protocol population in each group with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, based on a 4-point scale, within all treatment areas) based on the Investigator's Global Assessment at the end of treatment (i.e., week 2 visit for Study 0416 and week 4 visit for Study 0417), are adequate to demonstrate bioequivalence of Fougera Pharmaceuticals Inc's Tacrolimus Ointment, 0.03% and 0.1% with the reference listed drug Protopic® (Tacrolimus Ointment), 0.03% and 0.1%, respectively.

Please note that the clinical bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH H Seung
10/07/2013

JOHN R PETERS
10/07/2013

DALE P CONNER
10/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200744Orig1s000

OTHER REVIEWS

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 14, 2012

TO: John R. Peters
Acting Director, Division of Clinical Review
Office of Generic Drugs

FROM: Young Moon Choi, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations; and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering ANDA 200-744, Tacrolimus ointment 0.1% and 0.03%, sponsored by Nycomed US, Inc.

At the request of the Division of Clinical Review, Office of Generic Drugs, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections for the following two bioequivalence studies:

Study Number: ALT 0416-01-01
Study Title: "A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.1% to PROTOPIC® (Tacrolimus) Ointment 0.1% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis"

Study Number: ALT 0417-01-01
Study Title: "A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed

US Inc.'s Tacrolimus Ointment 0.03% to PROTOPIC® (Tacrolimus) Ointment 0.03% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis"

Following three sites were inspected:

- Clinical Site-1: Commonwealth Clinical Research Specialists, Inc., Richmond, VA
- Clinical Site-2: Radiant Research, Columbus, OH
- Clinical Site-3: Miami Dermatology Research Institute, LLC North Miami Beach, FL

The inspections were initiated as "For-Cause" inspections because of a potential packaging error discovered by the sponsor's project management team. The inspections at all sites included thorough examination of study records, facilities, and equipment, and interviews and discussions with the firm's management and staff. For all audits, **no evidence was found to suggest that any of the subjects enrolled in these studies received a study article that had been mislabeled and repackaged into a kit containing the wrong strength of Tacrolimus ointment**.

The following is a brief summary of inspections at the three sites, followed by the list of observations at each site, sites' responses to Form FDA-483s, and OSI/DBGLPC evaluations.

At Clinical Site-1, Commonwealth Clinical Research Specialists, Inc., Mr. Hugh McClure, an ORA investigator, and Dr. Seunguen Cho, a pharmacologist of DBGLPC, audited the two studies from 7/9/12 to 7/20/12. During the inspection, reserve samples were collected. At the conclusion of the inspection, Form FDA-483 was issued (Attachment 1). The site's response to the inspectional observations dated 8/3/12 was received by DBGLPC on 12/5/12 (Attachment 2).

At Clinical Site-2, Radiant Research, two ORA investigators from the Cincinnati District Office, Mr. Thomas W. Nojek and Mr. Richard W. Berning, audited the two studies from 6/13/12 to 7/3/12. During the inspection, reserve samples were collected. At the conclusion of the inspection, a Form FDA-483 was issued citing the observation of a 'failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation'. The observation was relevant to Study ALT 0417-01-01 (Attachment 3). The site's response to the

inspectional observations dated 7/16/12 was received by DBGLPC on 12/10/12 (Attachment 4).

At Clinical Site-3, Miami Dermatology Research Institute, LLC, Mr. Craig A. Garmendia, an ORA investigator from the Florida District Office, audited the Study ALT 0417-01-01 from 11/01/2012 to 11/13/2012. During the inspection, reserve samples were collected. No Form FDA-483 was issued at the close of this inspection.

OBSERVATION at Clinical Site 1

An investigation was not conducted in accordance with the investigational plan. Specifically:

Protocol No. ALT 0416-01-01:
Not all subjects enrolled in the study met the protocol inclusion/exclusion criteria. For example:
The study protocol excluded prospective subjects who have a known hypersensitivity to any of the following (in any dosage form): tacrolimus, macrolides (i.e. erythromycin), or any excipient of the ointment (Exclusion Criteria # 13). According to the source documentation (participant Information Sheet and General Database form) for the Visit l-Day 1 (Baseline) visit, Subject (b) (6) reported an allergy to erythromycin; however, the subject was enrolled in the study.

Protocol No. ALT 0417-01-01:
The study protocol excluded prospective subjects who have a known hypersensitivity to any of the following (in any dosage form): tacrolimus, macrolides (i.e. erythromycin), or any excipient of the ointment (Exclusion Criteria # 13). According to the source documentation (General Database Form and Medical History) for the Visit 1-Day 1 (Baseline) visit, Subject (b) (6) reported an allergy to erythromycin; however, the subject was enrolled in the study.

In the written response to this observation (Attachment 2), Dr. Call, the principal investigator (PI), acknowledged that the subject should not have been randomized based upon the protocol exclusion criteria, and stated that as corrective action, he and his staff generated SOP CL 023, "Principal Investigator Confirmation of Eligibility Criteria" in order to prevent future occurrences. This deviation was reported to both the sponsor and CRRI.

This reviewer recommends the reviewing officer note that Subject (b) (6) of Study ALT 0416-01-01 and Subject (b) (6) of Study 0417-01-01 were hypersensitive to erythromycin; these records have not been submitted to the ANDA.

Protocol No. ALT 0416-01-01:

Not all subjects enrolled in the study were assigned to treatment according to the procedures specified in the study protocol. According to the Treatment Assignment procedures, subject numbers and corresponding treatment kit boxes were to be assigned sequentially in the order in which subjects were enrolled at each center. Subjects (b) (6) were enrolled in the study on (b) (6), respectively. According to the treat assignment procedures, the subject enrolled on (b) (6) should have been assigned (b) (6) and the subject enrolled on (b) (6) should have been assigned (b) (6)

In the written response to this observation (Attachment 2), Dr. Call acknowledged that the treatment kits were incorrectly assigned and as a corrective action, Dr. Call and his staff also generated SOP CL 024 "Principal Investigator Confirmation of Randomization Order" to prevent future occurrences.

In this reviewer's opinion, the issue of an initial incorrect assignment has no impact on data integrity because the design of the study was double-blind and the above randomization error was unlikely to have introduced a bias in subject selection.

Protocol No. ALT 0416-01-01:
Not all concomitant medications required to be recorded by the study protocol including prescription, over-the-counter (OTC) medications and dietary supplements were captured and reported to the sponsor for all subjects enrolled in the study. For example:
-Subject (b) (6) reported in the CCRS History and Database form dated (b) (6) under Current Medications, the dietary supplement Xaio Feng San taken for a period of 4 years. However, this dietary supplement was not captured and reported to the sponsor in the Prior/Concomitant Medications CRF.

-Subject (b) (6) the source documents including the General Database Form and Previous or Concomitant Medication Page record Black Cohash, Vitamin D, and Calcium; however, these dietary supplements were not captured and reported to the sponsor in the Prior/Concomitant Medications CRF.

In the written response to this observation (Attachment 2), Dr. Call acknowledged the issue, and indicated that in the future, the PI will confirm that concomitant medications are transferred from the source to the CRF. He also indicated that (b) (4) (b) (4) will be conducting monthly routine internal audits and will document all findings in accordance with QA SOP, QAUOOI "Quality Assurance (Single-Site or Single-Office)"

In this reviewer's opinion, the reviewing officer should note the concomitant medications of subjects (b) (6) because these records have not been submitted to the ANDA.

OBSERVATION at Clinical Site 2

Protocol No. ALT 0417-01-01:
Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specfically: Six of twenty subjects enrolled in study protocol ALT 0417-01-01 had discrepancies in their data between the three different types of study forms which documented the investigational study drug dispensation and recovery. Data variation among the source documents, Case Report Forms, and Drug Dispensing/Accountability Logs resulted in 13 discrepancies.

The specific data discrepancies found in each subject's records are described below:

Subject (b) (6) (2 discrepancies): Visit 2 (b) (6) source documents and case report forms state that two tubes of the investigational study drug were dispensed; the Drug Dispensing/Accountability Log states that only one tube was dispensed. Visit 3 (b) (6) source documents state two tubes were dispensed at this visit; the Case Report Forms state one tube was dispensed and the Drug Dispensing/Accountability Log states zero tubes were dispensed.

Subject (b) (6) (1 discrepancy): Visit 2 (b) (6) source documents and Case Report Forms state that two tubes of investigational study drug were dispensed; the Drug Dispensing/ Accountability Log states that one tube was dispensed.

Subject (b) (6) (2 discrepancies): Visit 2 (b) (6) source documents and Case Report Forms state that two tubes of investigational study drug were dispensed; the Drug Dispensing/Accountability Log states that one tube was dispensed. Additionally, the source documents and Case Report Forms state

that zero tubes were collected at Visit 2; the Drug Dispensing/Accountability Log states that one tube was collected.

Subject (b) (6) (3 discrepancies): Visit 2 (b) (6) source documents state that zero tube of investigational study drug was collected; however, the Case Report Forms and Drug Dispensing/ Accountability Log state that one tube was collected at this visit. Visit 3 (b) (6) source documents and Case Report Forms state that one tube of investigational study drug was dispensed; however, the Drug Dispensing/Accountability Log states that two tubes were dispensed. Additionally, Visit 3 source documents and Case Report Forms state that zero tubes were collected at the visit, but the Drug Dispensing/Accountability Log states that two tubes were collected at this time.

Subject (b) (6) (3 discrepancies): Visit 2 (b) (6) source documents and Case Report Forms state that zero tubes of investigational study drug were collected at this visit; however, the Drug Dispensing/Accountability Log states that one tube was collected. Visit 3 (b) (6) source documents and Case Report Forms state that one tube of study drug was dispensed at this visit; however, the Drug Dispensing/Accountability Log states that zero tubes were dispensed. Additionally, Visit 3 source documents and Case Report Forms state that one tube of study drug was collected during this visit, but the Drug Dispensing/Accountability Log states that zero tubes were collected.

Subject (b) (6) (2 discrepancies): Visit 1 (b) (6) source documents state that two tubes of investigational study drug were dispensed during this visit; however; the Case Report Forms and Drug Dispensing/Accountability Log state that one tube was dispensed. Visit 2 (b) (6) source documents and Drug Dispensing/Accountability Log state that one tube of study drug was dispensed; the Case Report Forms from this visit state that two tubes were dispensed.

In addition to the six subjects with data discrepancies, the Drug Dispensing/Accountability Log for Subject (b) (6) on Visit 2 (b) (6) does not have data for the number of tubes of investigational study drug dispensed on that day. Two values were previously entered, then later crossed out and dated.

Despite these record discrepancies, the "itemized inventory of clinical supplies" shipped back to the sponsor after the completion of the study described the numbers of used, unused and

missed tubes for each identified kit, and it matched with the total numbers of tubes received originally from the sponsor. It was noted that the missed tubes were usually due to the loss of subject to follow-up. Furthermore, CRF and source documents recorded at each visit captured the number of drug applications that patients reported. Based on the evaluation of CRF and source documentation, no evidence was found to suggest that any subject received incorrect study articles. Therefore, it is the opinion of this reviewer that the issue of the discrepancy of tube numbers in Drug Dispensing/Accountability Log vs. CRF and source data will have little or no impact on data integrity or accuracy.

In the written response to this observation (Attachment 4), Dr. Chambers, the principal investigator, acknowledged the observation, and indicated that these discrepancies occurred due to transcription errors. The PI will prevent these errors in the future by validating drug accountability.

CONCLUSION:
For the above inspections, this DBGLPC reviewer recommends the following:

- Accept the data from the audited studies ALT 0416-0101 and ALT 0417-0101 for your review.

- Note that Subject (b) (6) (Study ALT-0416-01-01) and (b) (6) (Study ALT 0417-01-01) were hypersensitive to erythromycin.

- Note that Subject (b) (6) had taken Xaio Feng San, a dietary supplement for four years at the time of Study ALT 0416, and Subject (b) (6) had taken dietary supplements, such as Black Cohash, Vitamin D, and Calcium at the time of Study ALT 0416-01-01.

Final Classification:
VAI - Commonwealth Clinical Research Specialists, Inc., Richmond, VA (FEI 3003822002)
VAI - Radiant Research, Columbus, OH (FEI 3009607386)
NAI - Miami Dermatology Research Institute, LLC North Miami Beach, FL (FEI3009572447)

Attachment 1. Form FDA-483 issued at Commonwealth Clinical Research Specialists, Inc., Richmond, VA

Attachment 2. The response from Commonwealth Clinical Research Specialists, Inc. to Form FDA-483

Attachment 3. Form FDA-483 issued at Radiant Research, Columbus, OH

Attachment 4. The response from Radiant Research to Form FDA-483

CC:
DBGLPC: Taylor/Haidar/Skelly/Cho/Choi/Dejernett/CF
DCR/OGD/Peters/Patel
BLT-DO/ORA BLT Acting DIB/Harris
FLA-DO/Sinninger/Torres/Garmendia
CIN-DO/Harriger/Allen/Nojek/Berning
ORA/HQ: McClure
Draft: YMC 12/14/2012
Edit: JC 12/17/2012, 12/18/2012, SHH 12/18/2012
OSI: File # 6289; O:\BIOEQUIV\EIRCOVER\200744 Nyc Tac.doc
FACTS: 1411580

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6000 Metro Drive, Suite 101 Baltimore, MD 21215 (410) 779-5455 Fax:(410) 779-5707 Industry Information: www.fda.gov/oc/industry	07/09/2012 - 07/20/2012
	FEI NUMBER 3003822002

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Annette Bennett, Chief Executive Officer & Research Director

FIRM NAME	STREET ADDRESS
Robert S. Call , M.D.	9920 Independence Park Drive, Suite 101 Clinical Research Partners
CITY, STATE, ZIP CODE, COUNTRY Richmond, VA 23233	TYPE ESTABLISHMENT INSPECTED Clinical Investigator

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

An investigation was not conducted in accordance with the investigational plan.

Specifically,

Protocol No. ALT 0416-01-01:

A. Not all subjects enrolled in the study met the protocol inclusion/exclusion criteria. For example:

The study protocol excluded prospective subjects who have a known hypersensitivity to any of the following (in any dosage form): tacrolimus, macrolides (i.e. erythromycin), or any excipient of the ointment (Exclusion Criteria # 13). According to the source documentation (Participant Information Sheet and General Database form) for the Visit 1-Day 1 (Baseline) visit, Subject (b) (6) reported an allergy to erythromycin; however, the subject was enrolled in the study.

Protocol No. ALT 0417-01-01:

The study protocol excluded prospective subjects who have a known hypersensitivity to any of the following (in any dosage form): tacrolimus, macrolides (i.e. erythromycin), or any excipient of the ointment (Exclusion Criteria # 13). According to the source documentation (General Database Form and Medical History) for the Visit 1-Day 1 (Baseline) visit, Subject (b) (6) reported an allergy to erythromycin; however, the subject was enrolled in the study.

Protocol No. ALT 0416-01-01:

B. Not all subjects enrolled in the study were assigned to treatment according to the procedures specified in the study protocol. According to the Treatment Assignment procedures, subject numbers and

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Hugh M. McClure III, Investigator Hugh M. McClure III	07/20/2012

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6000 Metro Drive, Suite 101 Baltimore, MD 21215 (410) 779-5455 Fax:(410) 779-5707 Industry Information: www.fda.gov/oc/industry	07/09/2012 - 07/20/2012
	FEI NUMBER 3003822002

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Annette Bennett, Chief Executive Officer & Research Director

FIRM NAME	STREET ADDRESS
Robert S. Call , M.D.	9920 Independence Park Drive, Suite 101 Clinical Research Partners
CITY, STATE, ZIP CODE, COUNTRY Richmond, VA 23233	TYPE ESTABLISHMENT INSPECTED Clinical Investigator

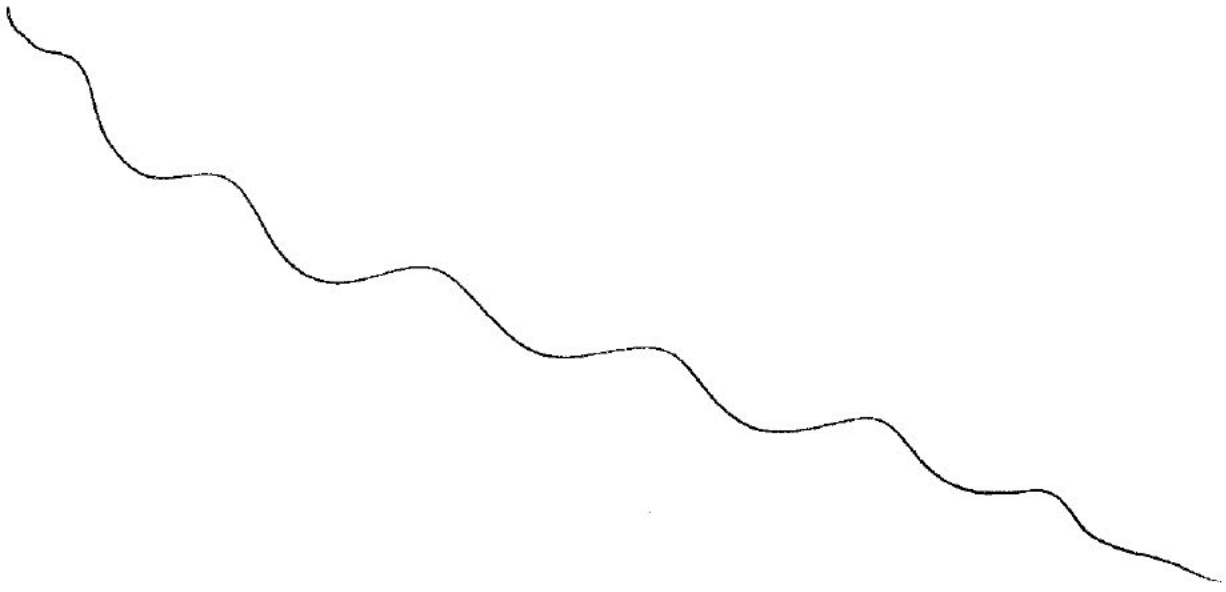
corresponding treatment kit boxes were to be assigned sequentially in the order in which subjects were enrolled at each center. Subject (b) (6) were enrolled in the study on (b) (6) respectively. According to the treat assignment procedures, the subject enrolled on (b) (6) should have been assigned (b) (6) and the subject enrolled on (b) (6) should have been assigned (b) (6).

Protocol No. ALT 0416-01-01:

C. Not all concomitant medications required to be recorded by the study protocol including prescription, over-the-counter (OTC) medications and dietary supplements were captured and reported to the sponsor for all subjects enrolled in the study. For example:

-Subject (b) (6) reported in the CCRS History and Database form dated (b) (6) under Current Medications, the dietary supplement Xaio Feng San taken for a period of 4 years. However, this dietary supplement was not captured and reported to the sponsor in the Prior/Concomitant Medications CRF.

-Subject (b) (6) the source documents including the General Database Form and Previous or Concomitant Medication Page record Black Cohash, Vitamin D, and Calcium; however, these dietary supplements were not captured and reported to the sponsor in the Prior/Concomitant Medications CRF.



SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Hugh M. McClure III, Investigator Hugh M. McClure III	DATE ISSUED 07/20/2012

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YOUNG M CHOI
01/08/2013

SAM H HAIDAR
01/09/2013

WILLIAM H TAYLOR
01/09/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200744Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: I	Team: 13	PM: Mandy Kwong	Electronic ANDA: Yes ☒ No ☐

ANDA #:200744
Firm Name:Fougera Pharmaceuticals Inc.
ANDA Name:Tacrolimus Ointment 0.1% and 0.03%
RLD Name:Protopic (tacrolimus) Ointment, 0.03% and 0.1% of Astellas Pharma US, Inc.

Electronic AP Routing Summary Located:
V:\Chemistry Division I\Team 13\Electronic AP Summary\200744.ARS.doc

AP/TA Letter Located:
V:\Chemistry Division I\Team 13\Approval Letters\200744.AP.doc

Project Manager Evaluation: **Date: 8-26-14 Initials:** MK

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 4-8-2010	Date of Application 4-8-2010	Date Acceptable for Filing 9-9-2010
Patent Certification (type) PIV to PIII	Date Patent/Excl. expires '727 exp 9-9-14	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☒ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☐ Pending ☐☐ ☒ Acceptable ☐ OAI *EES Date Acceptable: 2-27-14* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☒ No ☐ Comment: New strenght added
Date of Acceptable Quality (Chemistry) 9-8-14 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio Clinical 10-18-13 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 12-18-13 Attached labeling to Letter: Yes ☐ No ☒ Comment:
Date of Acceptable Sterility Assurance (Micro) N/A

Methods Val. Samples Pending: Yes ☐ No ☒**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 9-8-14 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☒

☒ Regulatory Support

☐ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☐ Division

☒ Bob West / Johnny Young

☐ Kathleen Uhl

☒Filed AP Routing Summary in DARRTs	☒Notified Firm and Faxed Copy of Approval Letter	☒ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 9/8/2014**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Protopic Ointment NDA# 50-777 Date Checked 9/8/14 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day Is a forfeiture memo needed: Yes ☐ No ☒ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒☐	

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:

Comments:ANDA submitted on 4/9/2010, BOS=Protopic NDA 50-777, PIV to '907 and '727. RTR issued on 6/24/2010. ANDA subsequently ACK for filing for the 0.1% strength on 9/9/2010 (LO dated 9/15/2010). Patent Amendment rec'd on 9/23/2010-notice sent via (b) (4) to Leydig Voit and Mayer in Washington D.C. with notice delivered on 9/21/2010, notice sent via (b) (4) o Astellas Pharma US in Deerfield IL with notice delivered on 9/21/2010, notice sent to Astellas PHarma in Tokyo Japan with notice delivered on 9/22/2010. Patent Amendment rec'd on 11/2/2010-CA 10 CV 5599 filed in the D of NJ on 10/27/2010, copy of the CA not submitted in this amendment so no way of telling which patents are in suit, 30 month stay associated with the 0.1% is 3/22/2013. Patent Amendment rec'd on 11/3/2010-letter from innovator: CA 10 CV 5599 filed in the D of NJ for infringement of the '727 and '907 patents.

New Strength Amendment rec'd on 11/22/2010 for inclusion of the 0.03% strength, BOS=Protopic NDA 50-777, PIV cert to the '90 727 patents. Patent Amendment rec'd on 12/1/2010-second copy of documentation of receipt of notice sent via (b) (4) which in this case applies to the 0.03% strength, last notice received on 11/22/2010, 30 month stay associated with the 0.03% is 5/22/2013. Patent Amendment rec'd on 12/17/2010-notice of filing of amendment to CA 10 CV 5599 to include the 0.03%. Patent Amendment rec'd on 12/22/2010-Letter from Astellas indicating that CA 10 CV 6326 was filed in the D of NJ on 12/7/2010 for infringement of both the '727 and '907 patents. Patent Amendment rec'd on 9/5/2012-sponsor changed cert on the '907 patent to PII as it expired on 1/31/2012 and to PIII on the '727 patent which expires on 9/9/2014.

ANDA is eligible for TA only due to their change of certification from PIV to PIII on 9/9/2014. It is noted that both of the strengths under this ANDA were identified as being eligible for 180 day exclusivity. This ANDA was included on a list of ANDAs for which expedited review will be granted in an attempt to avoid a forfeiture of 180 day exclusivity. That said, once this ANDA changed their certification from PIV to PIII they effectively forfeited eligibility for 180 day exclusivity.

Last patent expires on September 9, 2014. On or after 9/9/2014 this ANDA is eligible for Full Approval as there will be no unexpired patents or exclusivities which preclude approval of this application. Application is no longer eligible for 180 day exclusivity.

2. ***Labeling Endorsement***

Reviewer, Beverly Wietzman: Labeling Team Leader, John Grace:

Date9-8-14 Date9-8-14/Lillie Golson, for

REMS required? REMS acceptable?

☒Yes ☒No ☐Yes ☐No ☒n/a

Comments:

From: Golson, Lillie D
Sent: Monday, September 08, 2014 12:07 PM
To: Kwong, Mandy; Golson, Lillie D
Cc: Weitzman, Beverly
Subject: FW: Request for Labeling Endorsement for ANDA #200744 Tacrolimus Ointment

Hello Mandy,

From a labeling standpoint, this application is acceptable for approval. Please endorse the AP routing form on behalf of Beverly and me (in John's absence).

Thanks

From: Weitzman, Beverly
Sent: Monday, September 08, 2014 11:23 AM
To: Golson, Lillie D
Cc: Grace, John F; Kwong, Mandy
Subject: FW: Request for Labeling Endorsement for ANDA #200744 Tacrolimus Ointment

The labeling review done by Beverly Weitzman and signed off by John Grace remains acceptable. There are no new changes to the RLD labeling at this time. No changes noted.

From: Kwong, Mandy
Sent: Monday, September 08, 2014 11:16 AM
To: Weitzman, Beverly; Grace, John F
Subject: Request for Labeling Endorsement for ANDA #200744 Tacrolimus Ointment

Good Morning Beverly and John,

Could you please provide the labeling endorsement for this ANDA? I have attached the latest labeling review and AP letter for your reference.

This is a 1st generic, and we are ready for full approval for tomorrow (9-9-14), when the PIII patent expires. I'm sorry for the short turn around time; there were some DMF issues that just got resolved as of Friday last week.

Thank you!

Mandy

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read **Date 9/8/14**
OGD Regulatory Counsel **Initials rlw/for**

Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments: N/A. There are currently no paragraph IV certifications associated with this ANDA.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 9/8/14**

Chemistry Div. **I (Raw)** **Initials rlw/for**

Comments: CMC Review #5 concluding that the CMC section of this ANDA is acceptable for approval was endorsed by Bing Cai, Ph.D., Deputy Director, Division of Chemistry I on 9/8/14.

OGD Office Management Evaluation

5. Peter Rickman **Date 9/8/14**
Director, DLPS **Initials rlw/for**

Para.IV Patent Cert: Yes☐ ☐ ☐ No☐
Pending Legal Action: Yes☐ ☐ No☐
Petition: Yes☐ No☐
Entered to APTrack database ☐
GDUFA User Fee Obligation Status Met☐ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Bioequivalence sturies with clinical endpoints found acceptable. Statistical review also found acceptable. Several of the study sites were inspected by OSI and found acceptable. Office-level bio endorsed 10/18/13.

Final-printed labeliong (FPL) found acceptable for approval 12/18/13, as endorsed 9/8/14. No REMS is required.

CMC found acceptable for approval (Chemistry Review #5) 9/8/14.

OR

6. Robert L. West **Date 9/8/14**
Deputy Director, OGD **Initials RLWest**

Para.IV Patent Cert: Yes☐ ☐ ☐ No☒
Pending Legal Action: Yes☐ ☐ No☒
Petition: Yes☐ No☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met☒ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: At present, Fougera has provided a paragraph III certification to the '727 patent which is due to expire on September 9, 2014. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

This first-generic ANDA is recommended for approval following expiratrion of the '727 patent on September 9, 2014.

7. ***OGD Director Evaluation***
Kathleen Uhl

Comments: RLWest for Jason Woo, M.D., M.P.H., Acting Director, Office of Regulatory Operations, 9/8/14.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

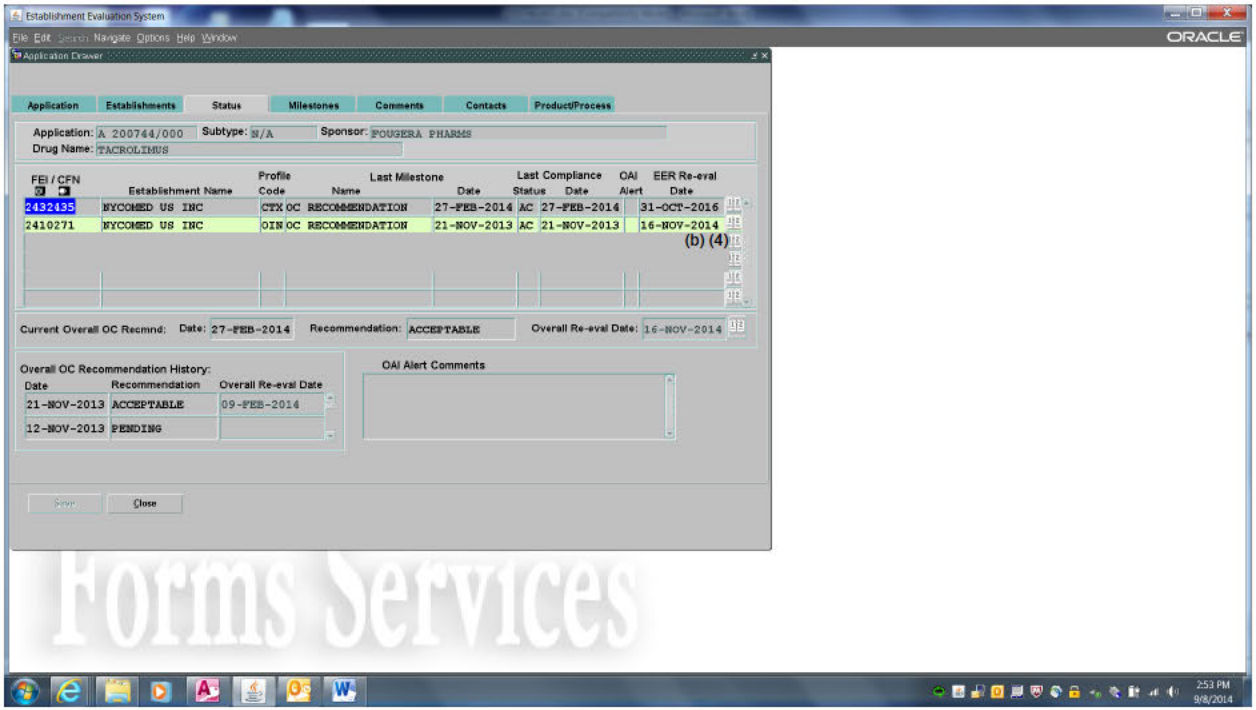
Comments:

8. Project Manager **Date 9-9-14**
Initials MK

Comments:

Check Communication and Routing Summary into DARRTS

EES DATA:


Establishment Evaluation System
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ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product/Process
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Subtype: N/A
Sponsor: FOUGERA PHARMS
Drug Name: TACROLIMUS
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Milestone Date
Last Compliance Status
Last Compliance Date
OAI Alert
EER Re-eval Date
2432435 NYCOMED US INC CTX OC RECOMMENDATION 27-FEB-2014 AC 27-FEB-2014 31-OCT-2016
2410271 NYCOMED US INC OIN OC RECOMMENDATION 21-NOV-2013 AC 21-NOV-2013 16-NOV-2014
(b) (4)
Current Overall OC Recmnd: Date: 27-FEB-2014 Recommendation: ACCEPTABLE Overall Re-eval Date: 16-NOV-2014
Overall OC Recommendation History:
Date
Recommendation
Overall Re-eval Date
21-NOV-2013 ACCEPTABLE 09-FEB-2014
12-NOV-2013 PENDING
OAI Alert Comments
Save
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2:53 PM
9/8/2014

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/s/

MANDY C KWONG
09/09/2014

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 200744

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Fougera Pharmaceuticals Inc. TEL: (631) 454-7677

ATTN: Amy M. Byrom FAX: (631) 756-5114

FROM: Tania Mazza FDA CONTACT PHONE: 240-276-9344

Dear Madam:

This communication is in reference to your abbreviated new drug application (ANDA) dated April 8, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Ointment 0.1% & 0.03%.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
CHEMISTRY

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Tania Mazza at 240-276-9344.

We have completed our review, and have the following comments:

PRODUCT QUALITY

1. (b) (4)

Sincerely yours,

{See appended electronic signature page}

Andre S. Raw, Ph.D.

Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JAMES M FAN
12/02/2013

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 200744

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Fougera Pharmaceuticals Inc. TEL: (631) 454-7677

ATTN: Amy M. Byrom FAX: (631) 756-5114

FROM: Tania Mazza FDA CONTACT PHONE: 240-276-9344

Dear Madam:

This communication is in reference to your abbreviated new drug application (ANDA) dated April 8, 2010 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Ointment, 0.1% and 0.03%. .

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
CHEMISTRY

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Tania Mazza at 240-276-9344 .

PRODUCT QUALITY

(b) (4)

Sincerely yours,

{See appended electronic signature page}

Andre S. Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

TANIA B MAZZA
11/06/2013

JAMES M FAN
11/06/2013

CLINICAL BIOEQUIVALENCE DEFICIENCY (EASILY CORRECTABLE)

ANDA 200744

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Fougera Pharmaceuticals Inc

TEL: (631) 719-2098

ATTN: Amy Byrom, Associate Director, Regulatory Affairs

FAX: (631) 756-5114

FROM: Nitin K. Patel

PROJECT MANAGER: (240) 402-3878
(301) 827-4141 (fax)

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 8, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Ointment, 0.1% and 0.03%. Reference is also made to your submissions dated September 8, 2010, November 18, 2010, and February 29, 2012.

The deficiencies presented below represent EASILY CORRECTABLE DEFICIENCIES identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies with an "EASILY CORRECTABLE DEFICIENCY AMENDMENT" within ten (10) business days. If you do not submit a complete response within ten (10) business days, this review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments. In addition, please notify the Project Manager identified above.

A partial response to this fax will not be processed as an amendment and will not start a review. Please submit official archival copies of your response to the ANDA. Please notify the above Project Manager when your amendment has been submitted.

Please direct any questions concerning this communication to the Project Manager identified above.

SPECIAL INSTRUCTIONS:
Your cover letter should clearly indicate that the response is a ***"Clinical Bioequivalence Amendment/Easily Correctable Deficiency".*** We also request that you include a copy of this communication with your response.

CLINICAL BIOEQUIVALENCE DEFICIENCY (EASILY CORRECTABLE) TO BE PROVIDED TO THE APPLICANT

ANDA: 200744

APPLICANT: Fougera Pharmaceuticals Inc

DRUG PRODUCT: Tacrolimus Ointment, 0.1% and 0.03%

A. In order to assist in the review of the clinical study ALT 0416-01-01 (for the 0.1% strength) for ANDA 200744 [A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.1% to PROTOPIC® (Tacrolimus) Ointment 0.1% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis], please provide the following information:

1. When the potential mispackaging was initially discovered, did the study participants stop study medication use?

2. When were the used study medication kits sent to (b) (4) for unblinding?

3. Were the used study medication kits sent to (b) (4) for unblinding after the study participants completed the study?

4. Clarify if the definitely misdosed patient (Patient (b) (6) used only the mispackaged tube or if that patient also used any correctly packaged tubes from the medication kits.

5. Provide contact information for (b) (4), who is listed as having generated the first set of randomization schedule.

6. Clarify if (b) (4) also generated the second set of randomization schedule. If not, who generated the second set of randomization schedule? Provide their contact information.

7. At what point in the study timeline did the Project Management (PM) Department of Nycomed receive a copy of the randomization code? Who had access to the randomization code maintained in the PM Department?

8. Who packaged the study medications for this study? Provide their contact information.

9. Clarify if new study medication kits were assembled for the second set of randomization or if the unblinded, unused study kids were reblinded for the second set of randomization.

10. Provide contact information for the outside unblinding/packaging vendor, (b) (4)

11. Clarify how many of the used study kits from the first randomization code was unblinded by (b) (4). Provide a list of all the used study kits that were unblinded by (b) (4)

(b) (4).

12. Provide a copy of the "blinded" memo that was sent from (b) (4) to "Clin Ops" the morning of 10/9/09.

13. Provide a copy of the "unblinded" memo that was sent from (b) (4) the afternoon of 10/9/09.

14. Provide a copy of the "unblinded" memo that was sent to "Clin Ops" on 11/5/09.

15. Clearly specify the protocol violations for the 3 patients who were discontinued from the study due to a significant protocol violation and for the additional 2 patients who were excluded from the PP population for significant protocol violations.

16. Regarding the assay of tacrolimus concentration, the study report states that "Subjects in the Vehicle group were not required to have their assays tested since they were not randomized to one of the active treatment groups.." Given that this was a double blinded study, how did the investigative sites know which patients were in the placebo group?

17. Explain why the assay was cancelled for the following patients: (b) (6) (b) (6). Provide a copy of these patients' CRFs.

B. In order to assist in the review of the clinical study ALT 0417-01-01 (for the 0.03% strength) for ANDA 200744 [A Safety Monitoring Extension to ALT 0417-01-01, a Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.03% to PROTOPIC® (Tacrolimus) Ointment 0.03% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis], please provide the following information:

1. When the potential mispackaging was initially discovered, did the study participants stop study medication use?

2. When were the used study medication kits sent to (b) (4) for unblinding?

3. Were the used study medication kits sent to (b) (4) for unblinding sent after the study participants completed the study?

4. Of the mispackaged tubes discovered in the definitely misdosed patients' returned medication kits, clarify how many of the mispackaged tubes that those patients (Patients (b) (6) (b) (6)) actually used and if the definitely misdosed patients used any non-mispackaged tubes from the medication kits.

5. Clarify who generated the first and second sets of randomization schedule. Provide their contact information.

6. At what point in the study timeline did the Project Management (PM) Department of Nycomed receive a copy of the randomization code, and who had access to the randomization code

maintained in the PM Department?

7. Who packaged the study medications for this study? Provide their contact information.

8. Clarify if new study medication kits were assembled for the second set of randomization or if the unblinded, unused study kids were reblinded for the second set of randomization.

9. Clarify how many of the used study kits from the first randomization code was unblinded by [redacted] (b) (4). Provide a list of all the used study kits that were unblinded by [redacted] (b) (4)

10. Provide a copy of the "blinded" memo that was sent from [redacted] (b) (4) to "Clin Ops" on 7/14/09.

11. Provide a copy of the "unblinded" memo that was sent from [redacted] (b) (4) on 7/17/09.

12. Did "Clin Ops" receive an "unblinded" memo after hard database lock? If so, provide a copy of this memo.

13. Describe in detail the SAP changes made with Amendment 2.

14. Clearly specify the protocol violations for the 11 patients who were discontinued from the study due to a significant protocol violation and for the additional 2 patients who were excluded from the PP population for significant protocol violations.

15. Regarding the assay of tacrolimus concentration, the study report states that "Subjects in the Vehicle group were not required to have their assays tested since they were not randomized to one of the active treatment groups." Given that this was a double blinded study, how did the investigative sites know which patients were in the placebo group?

16. The study report states that "Patients in the Placebo group were not required to have assays performed since they were not randomized to one of the active treatment groups." Given that this was a double blinded study, how did the investigative sites know which patients were in the placebo group?

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

NITIN K PATEL
08/07/2013

JOHN R PETERS
08/08/2013

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Team 3

FROM: Anurag Sharadendu

DATE: July 11, 2012

ANDA: 200744

NAME/TITLE OF INDIVIDUAL(S) from FDA: Anurag Sharadendu, chemist
FIRM: Fougera Pharmaceuticals Inc.
PRODUCT NAME: Tacrolimus Ointment, 0.1% and 0.03%
NAME/TITLE OF INDIVIDUAL(S) from Coastal: Amy Byrom
TEL #: 631-454-7677x2098

Notes of Conversation:

1. (b) (4)

SIGNATURE OF OGD REPRESENTATIVES:
Anurag Sharadendu, Ph.D., chemist

Location of Electronic Copy:

M:\T-CON\200744.T-CON.DOC

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/s/

ANURAG SHARADENDU
07/16/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 23, 2012

TO: Director, Investigations Branch
Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215

Director, Investigations Branch
Florida District Office
555 Winderly Place, Suite 200
Maitland, FL 32751

Director, Investigations Branch
Cincinnati District Office
6751 Steger Drive
Cincinnati, OH 45237

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: FY 2012, **FOR-CAUSE ANDA Pre-Approval Data Validation Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: ANDA 200-744
DRUG: Tacrolimus Ointment, 0.1% and 0.03%
SPONSOR: Nycomed US, Inc., USA

This memo requests inspections of the following two bioequivalence clinical endpoint studies:

Study Number: ALT 0417-01-01
Study Title: "A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.03% to PROTOPIC® (Tacrolimus) Ointment 0.03% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis"

This was a multicenter study conducted at 47 sites in the United States and 4 sites in Latin America

Clinical Site-1: Commonwealth Clinical Research Specialists, Inc.
9920 Independence Park Drive, Suite 101
Richmond, VA 23233
TEL: 804-288-7425

Clinical Investigator: Robert Call, MD

Clinical Site-2: Miami Dermatology Research Institute, LLC
16100 NE 16th Ave., Suite A
North Miami Beach, FL 33162
TEL: 305-652-8600

Clinical Investigator: Tory Sullivan, MD

Clinical Site-3: Radiant Research
1275 Olentangy River Road, Suite 202
Columbus, OH 43212
TEL: 614-294-3854

Clinical Investigator: Michelle Chambers, MD

Study Number: ALT 0416-01-01

Study Title: "A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.1% to PROTOPIC® (Tacrolimus) Ointment 0.1% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis"

This was a multicenter study conducted at 39 sites in the United States and 3 sites in Latin America

Clinical Site-1: Commonwealth Clinical Research Specialists, Inc.
9920 Independence Park Drive, Suite 101
Richmond, VA 23233
TEL: 804-288-7425

Clinical Investigator: Robert Call, MD

Clinical Site-2: Radiant Research
1275 Olentangy River Road, Suite 202
Columbus, OH 43212
TEL: 614-294-3854

Clinical Investigator: Michelle Chambers, MD

This inspection is considered FOR-CAUSE due to the following:

OGD has concerns regarding "potential" packaging error. This application was submitted for two strengths: 0.1% and 0.03%, with two separate submission dates.

Briefly, a discrepancy in package weights in shipping documentation for Ecuador for a similar study (Tacrolimus 0.03%) triggered an inspection of the shipment by Ecuadorian Customs. The shipment was returned to Nycomed and inspection of the returned shipment showed that Ecuadorian customs had inspected and tampered with ten (10) kits from the shipment.

During the packaging of replacement tubes for the ten altered kits from Ecuador, Project Management determined that an un-blinded tube did not match the replacements provided for repackaging.

Therefore, please investigate further this "potential" packaging error.

In addition, please confirm the sponsor's assertion that the investigators remained blinded throughout the study. The data in the ANDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, drug accountability, etc., the files of communication during the study conduct should be examined for their content. Please check the batch numbers of the test and reference formulations used in the study with the descriptions in documents submitted to the Agency. The site conducting the above bioequivalence study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. **Please confirm whether reserve samples were retained as required by 21 CFR 320.38 and 320.63.** Samples of the test and reference drug formulations should be collected and mailed to the Division of Drug Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg
1114 Market Street, Room 1002
St. Louis, MO 63101, USA

Please obtain a written assurance from the clinical investigator (CI) or the responsible person at the CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample.

Please have the records of all enrolled subjects audited at study sites #5, #6, #37 and #40. The subject records in the submission should be compared to the original documents at the firm. The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined. The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. **Since this is a blinded study, the inspected facility should have a sealed code available for FDA to break the blind. Please use the sealed code to verify that subjects were dosed according to the randomization code.** Please determine if the subjects met the protocol inclusion/exclusion criteria. Also, please verify that the subjects were compliant with the trial regimen.

Following the identification of the investigator, background materials will be forwarded directly.

Headquarters Contact Person: Sripal R. Mada, Ph.D.
(301)-796-4112

cc:
CDER OSI PM TRACK
OSI/DBGC/BB/Haidar/Skelly/Mada/Dejernett
OGD/DCR/Peters/Patel
HFR-CE250/Harris (BIMO), Smith/Bonnin (DIB)
HFR-SE250/Torres (BIMO), Sinninger/Singleton (DIB)
HFR-CE400/Teitell (DIB)
HFR-CE4525/Harriger (BIMO)
Draft: SRM 04/12/2012
Edit: MFS 04/12/2012, SHH 05/22/2012
DSI: 6289; O:\BE\assigns\bio200744.doc
FACTS: 1411580

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/s/

SRIPAL R MADA
05/23/2012

SAM H HAIDAR
05/29/2012

QUALITY DEFICIENCY - MINOR

ANDA 200744

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Fougera Pharmaceuticals Inc. TEL: (631) 454-7677

ATTN: Amy Byrom FAX: (631) 756-5114

FROM: Trang Q. Tran FDA CONTACT PHONE: (240) 276-8518

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 8, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Ointment, 0.03% and 0.1%.

Reference is also made to your amendments dated February 24 and March 15, 2012.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO APPLICANT.

ANDA: 200744 APPLICANT: Fougera Pharmaceuticals Inc.

DRUG PRODUCT: Tacrolimus Ointment, 0.03% and 0.1%

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term drug product stability data.

2. We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions. A risk-based, scientifically sound submission would be expected to include the following:

    - Quality target product profile (QTPP)
    - Critical quality attributes (CQAs) of the drug product
    - Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
    - Process design and understanding including identification of critical process parameters and in-process material attributes
    - Control strategy and justification

An example illustrating QbD concepts can be found online at FDA's Generic Drugs: Information for Industry webpage: *http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf*

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JAMES M FAN
04/20/2012
for Andre Raw

BIOEQUIVALENCY INFORMATION REQUEST

ANDA 200744

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Fougera Pharmaceuticals Inc.

TEL: (631) 454-7677

ATTN: Tanveer Ahmad, Ph.D.,
Vice President, Regulatory Affairs

FAX: (631) 756-5114

FROM: Nitin K. Patel

PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

Dear Sir:

This facsimile is a request for information from the Division of Clinical Review, regarding your ANDA 200744 for Tacrolimus Ointment, 0.1% and 0.03%, dated April 8, 2010 and November 19, 2010.

The information request is presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Your cover letter should clearly indicate that the response is a "Clinical Bioequivalency Amendment". We also request that you include a copy of this communication with your response.

Please direct any questions concerning this communication to the Project Manager identified above.

SPECIAL INSTRUCTIONS:

MEMORANDUM

ANDA 200744

To: **Fougera Pharmaceuticals Inc.**

Drug: **Tacrolimus Ointment, 0.1% and 0.03%**

From: **Sarah H. Seung, PharmD**
Clinical Reviewer, Division of Clinical Review
Office of Generic Drugs

John R. Peters, MD
Director, Division of Clinical Review
Office of Generic Drugs

Date: **March 6, 2012**

Re: **Request for Information**

In order to complete the review of the two bioequivalence studies with clinical endpoints for ANDA 200744 (**Study ALT 0416-01-01**, "A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.1% to Protopic® (Tacrolimus) Ointment 0.1% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis" and **Study ALT 0417-01-01**, " A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Nycomed US Inc.'s Tacrolimus Ointment 0.03% to Protopic® (Tacrolimus) Ointment 0.03% and Both Active Treatments to a Vehicle Control in the Treatment of Atopic Dermatitis"), please provide the following information:

1. Regarding the trough tacrolimus concentrations:

    a. Pre-study and during-study analytical method validation report for the analyte (tacrolimus).
    b. Raw analytical data and 20% of the chromatograms.
    c. SOP
    d. Bioanalytical assay validation results for the study.
    e. Provide justification for using the LOQ 3 ng/ml instead of a lower LOQ, as low as 0.2 ng/ml.

2. Regarding all submitted datasets:

    Provide a ".pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH H Seung
03/06/2012

JOHN R PETERS
03/06/2012

Telephone Fax

ANDA 200744

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8984

TO: Nycomed US Inc. TEL: 631 454-7677

ATTN: Amy Byrom FAX: 631 756-5114

FROM: Beverly Weitzman

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Ointment, 0.1% and 0.03%.
Pages (including cover): 3

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs
(OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200744

Date of Submission: April 08, 2010 and November 19, 2010

Applicant's Name: Nycomed US Inc.

Established Name: Tacrolimus Ointment 0.1% and 0.03%

Labeling Deficiencies:

1. **CONTAINER:** (0.1 % and 0.03%; 30 gram, 60 gram and 100 gram) - Please assure that you differentiate your product strengths, by using boxing, contrasting colors, or other means to differentiate the different strengths of your drug product as does the reference listed drug.
2. **CARTON:** (0.1 % and 0.03%; 30 gram, 60 gram and 100 gram) – See Container comment.
3. **INSERT:** Revise your package insert labeling to be in accord with the most recently approved labeling for the reference listed drug, Protopic Ointment, (NDA 050777/S-018: Approved October 4, 2011). We refer you to http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
4. **MEDICATION GUIDE:**
   a. See INSERT Comment.
   b. When submitting in final print, please ensure that the medication guide is provided as a separate or detachable labeling piece within the carton and your medication guide meets the minimum 10 point type font size requirement.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling and a side-by-side comparison of your proposed container and carton labeling with your last submission, with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JOHN F GRACE
11/21/2011
for Wm Peter Rickman

QUALITY DEFICIENCY - MINOR

ANDA 200744

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Nycomed US Inc. TEL: (631) 454-7677

ATTN: Amy Byrom FAX: (631) 756-5114

FROM: Trang Q. Tran FDA CONTACT PHONE: (240) 276-8518

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 8, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Ointment, 0.03% and 0.1%.

Reference is also made to your amendment dated September 16, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

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CHEMISTRY COMMENTS TO BE PROVIDED TO APPLICANT.

ANDA: 200744 APPLICANT: Nycomed US Inc.

DRUG PRODUCT: Tacrolimus Ointment, 0.03% and 0.1%

The deficiencies presented below represent MINOR deficiencies.

(b) (4)

(b) (4)

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JAMES M FAN
11/09/2011
for Andre Raw

QUALITY DEFICIENCY - MINOR

ANDA 200744

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Nycomed US Inc. TEL: (631) 454-7677

ATTN: Amy Byrom FAX: (631) 756-5114

FROM: Trang Q. Tran FDA CONTACT PHONE: (240) 276-8518

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 8, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Ointment, 0.03% and 0.1%.

Reference is also made to your amendment dated February 17 and March 4, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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Rockville, Maryland 20855

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4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAMES M FAN
05/25/2011
for Paul Schwartz

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 200744 **FIRM NAME**: NYCOMED US INC.

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): NA

First Generic Product Received? YES ON 0.03%

DRUG NAME: TACROLIMUS

DOSAGE FORM: OINTMENT, 0.1% AND 0.03% (NEW STRENGTH 0.03%)

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC1 TM 13 ☒***Activity***	***Bio Team 10: April Braddy*** ☒***Activity***
ANDA/Quality RPM: Trang Tran ☒ ***FYI***	Bio PM: Diana Solana ☐ ***FYI***
Quality Team Leader: Fan, James No assignment needed in DARRTS	***Clinical Endpoint Team Assignment:*** ☒***Activity***
Labeling Reviewer: Beverly Weitman ☒***Activity***	***Micro Review (No)*** ☐***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: NOVEMBER 19, 2010 **Received Date**: NOVEMBER 22, 2010

Comments: EC -1 + 1 YES **On Cards:** YES
Therapeutic Code: 4020700 NON-STEROIDAL ANTI-INFLAMMOTORY

Archival copy: ELECTRONIC (GATEWAY) **Sections** I
Review copy: NA E-Media Disposition: NA
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Johnny Young **Date 12/16/10**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☐ Yes ☒ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☐ Yes ☒ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. Requested EER
   ☐ Yes **(NA-NSA)**

ADDITIONAL COMMENTS REGARDING THE ANDA:

Amy Byrom 631.719.2098; (f) 631.756.5114

e-mailed 12/7/10

Has LONR
Has SPL

Z035 packaged in 30 g, 60 g and 100 g tubes
710C packaged in 100 g tubes
Z431 packaged in 100 g tubes

1. do not omit sections that have not changed ok
2. T/S missing for (b) (4), propylene carbonate, along w/COAs; Paraffin and Mineral Oil COAs missing from DP manufacturer ok
3. missing pp 4 and 5 (of 5) of COAs for all three tube sizes of Z035 batch ok
4. missing batch record page for 710C (filling) ok

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: NOVEMBER 18, 2010	☒
1.2.1	**Form FDA 3674 (C)**	☒
*	**Table of Contents (paper submission only)** NA	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒

1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) NO UPDATED SUBMITTED 2. List of Convictions statement (original signature) SAME	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) IV: '907 and '727 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☒ 3. Expiration of Patent(s): 9/9/2014 a. Pediatric exclusivity submitted? N b. Expiration of Pediatric Exclusivity?NA 4. Exclusivity Statement: YES no unexpired exclusivity	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient original Type II DMF No. original b. Type III DMF authorization letter(s) for container closure original 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) original	☒
1.12.11	**Basis for Submission** NDA# : 50-777 x Ref Listed Drug: PROTOPIC x Firm: ASTELLAS x ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use x 2. Active ingredients x 3. Inactive ingredients x 4. Route of administration x 5. Dosage Form x 6. Strength x	☒
1.12.14	**Environmental Impact Analysis Statement**	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒

1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) x **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained x **1.14.1.3** 1 package insert (content of labeling) submitted electronically x ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.) **30 g, 60 g, 100 g**	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained x **1.14.3.3** 1 RLD label and 1 RLD container label x	☒

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** x **Word Processed e.g., MS Word** x A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** x **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** x **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** x **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** x **Word Processed e.g., MS Word** x **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary x Table 4. Bioanalytical Method Validation x Table 6. Formulation Data x **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution x **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies x Table 3. Statistical Summary of the Comparative BA Data x **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study x **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies x	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information original** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer original** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) 2. Function or Responsibility 3. Type II DMF number for API 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization original**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) x **3.2.S.4.2 Analytical Procedures** **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples x 2. Samples-Statement of Availability and Identification of: a. Drug Substance covered by original statement as no batch no. is specified on it b. Same lot number(s) x **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) x 2. Applicant certificate of analysis x **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials** original	☒
3.2.S.6	**Container Closure Systems** original	☒
3.2.S.7	**Stability** original	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition x 2. Inactive ingredients and amounts are appropriate per IIG x	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report original	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) x 2. CGMP Certification: YES 3. Function or Responsibility x 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** x **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process x 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified x 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement x **3.2.P.3.4 Controls of Critical Steps and Intermediates** x **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation NA 2. Filter validation (if aseptic fill) NA **230 kg and 450 kg**	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified x **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) x 2. Suppliers' COA (specifications and test results) x **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA x	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** x **3.2.P.5.2 Analytical Procedures** x **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form x 2. Same lot numbers x **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form x **3.2.P.5.5 Characterization of Impurities** original **3.2.P.5.6 Justification of Specifications** x	☒
3.2.P.7	**Container Closure System*** 1. Summary of Container/Closure System (if new resin, provide data) orignal 2. Components Specification and Test Data original 3. Packaging Configuration and Sizes 30 g, 60 g and 100 g tubes 4. Container/Closure Testing original 5. Source of supply and suppliers address original	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted x 2. Expiration Dating Period (b) (4) **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments x **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data x 2. Batch numbers on stability records the same as the test batch x	☒

*** information on 2 new lots of 100 g tubes are included, with diagrams**

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1 Executed Batch Records** (b) (4) [redacted] **3.2.R.1.P.2 Information on Components** x **3.2.R.2.P Comparability Protocols** NA **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

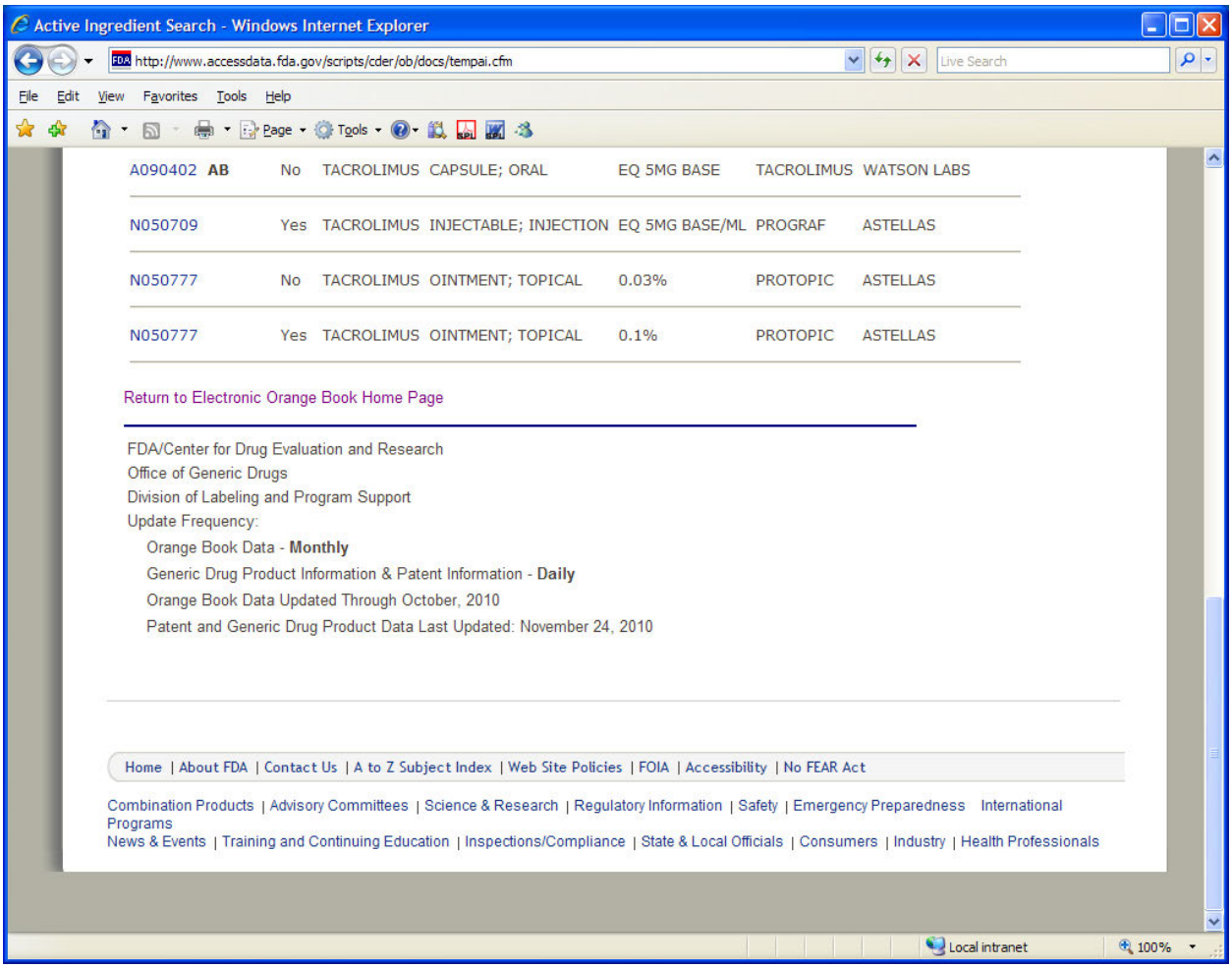
ACCEPTABLE

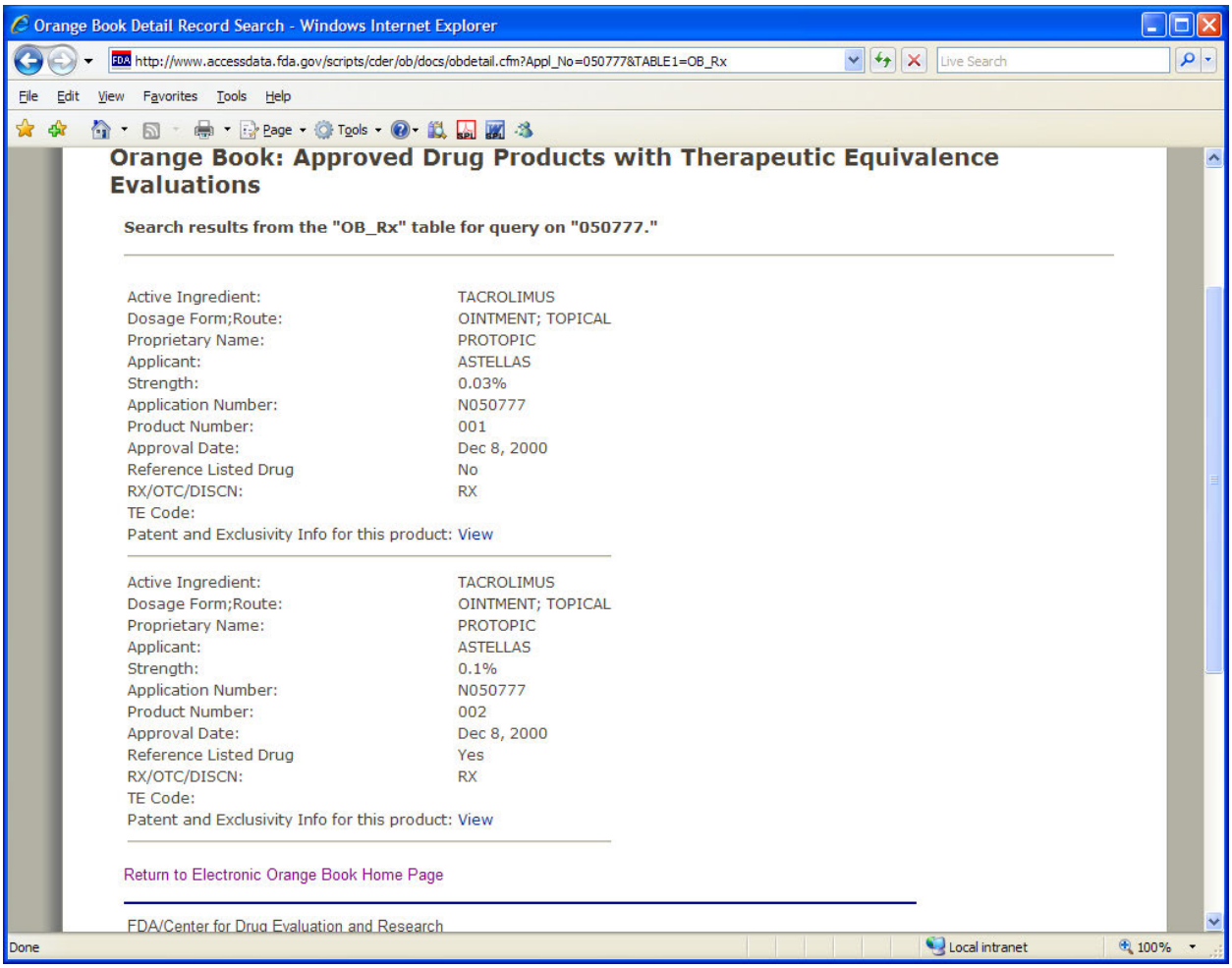
5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** Z431 and 710C **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☐

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 10. Study Information x Table 12. Dropout Information x Table 13. Protocol Deviations x **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information x Table 16. Composition of Meal Used in Fed Bioequivalence Study x **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples x Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses x Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples x **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: NA	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** YES STU/BIO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009


Active Ingredient Search - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
File Edit View Favorites Tools Help
A090402 AB No TACROLIMUS CAPSULE; ORAL EQ 5MG BASE TACROLIMUS WATSON LABS
N050709 Yes TACROLIMUS INJECTABLE; INJECTION EQ 5MG BASE/ML PROGRAF ASTELLAS
N050777 No TACROLIMUS OINTMENT; TOPICAL 0.03% PROTOPIC ASTELLAS
N050777 Yes TACROLIMUS OINTMENT; TOPICAL 0.1% PROTOPIC ASTELLAS
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through October, 2010
Patent and Generic Drug Product Data Last Updated: November 24, 2010
Home | About FDA | Contact Us | A to Z Subject Index | Web Site Policies | FOIA | Accessibility | No FEAR Act
Combination Products | Advisory Committees | Science & Research | Regulatory Information | Safety | Emergency Preparedness International Programs
News & Events | Training and Continuing Education | Inspections/Compliance | State & Local Officials | Consumers | Industry | Health Professionals
Local intranet
100%


Orange Book Detail Record Search - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=050777&TABLE1=OB_Rx
File Edit View Favorites Tools Help
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Search results from the "OB_Rx" table for query on "050777."
Active Ingredient: TACROLIMUS
Dosage Form;Route: OINTMENT; TOPICAL
Proprietary Name: PROTOPIC
Applicant: ASTELLAS
Strength: 0.03%
Application Number: N050777
Product Number: 001
Approval Date: Dec 8, 2000
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: TACROLIMUS
Dosage Form;Route: OINTMENT; TOPICAL
Proprietary Name: PROTOPIC
Applicant: ASTELLAS
Strength: 0.1%
Application Number: N050777
Product Number: 002
Approval Date: Dec 8, 2000
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
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Local intranet
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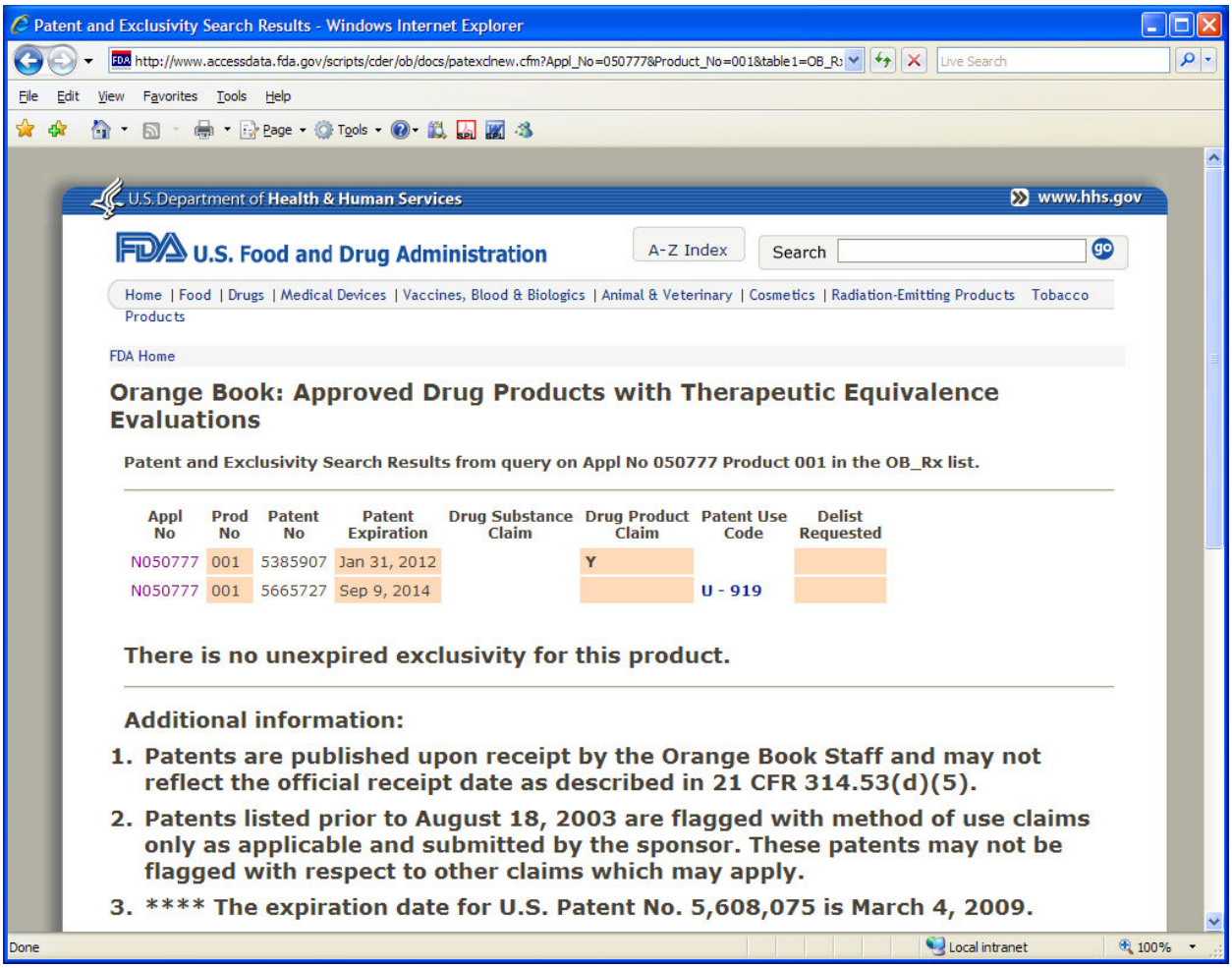
Patent and Exclusivity Search Results - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=050777&Product_No=001&table1=OB_Rx
File Edit View Favorites Tools Help
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
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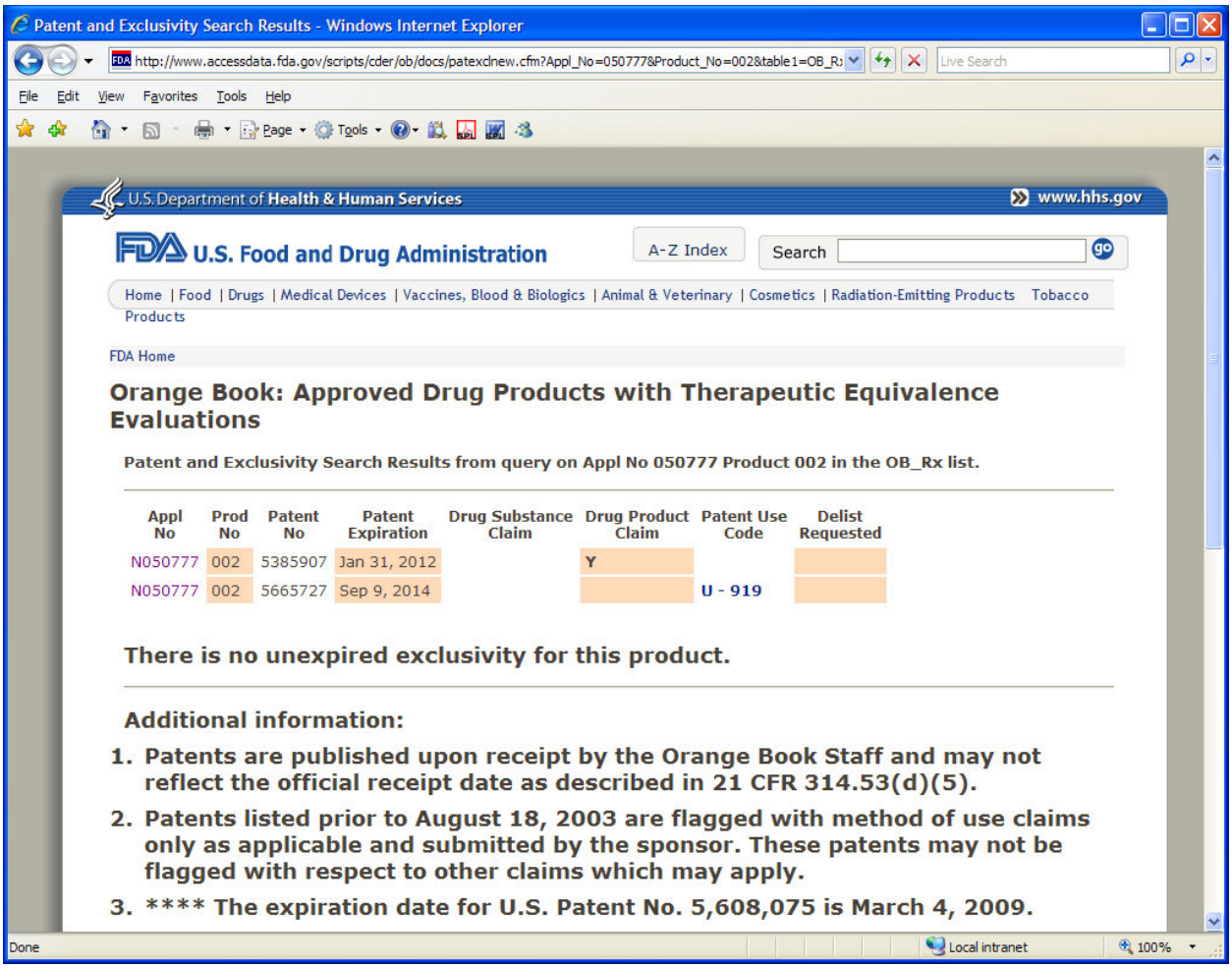
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Patent and Exclusivity Search Results from query on Appl No 050777 Product 001 in the OB_Rx list.
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N050777 | 001 | 5385907 | Jan 31, 2012 | | Y | |
N050777 | 001 | 5665727 | Sep 9, 2014 | | | U - 919 |
There is no unexpired exclusivity for this product.
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.
Done
Local intranet
100%



U - 919 FOR THE TREATMENT OF DERMATITIS

Table 2.3.P.1-1 Composition of Nycomed's proposed Tacrolimus Ointment 0.1% and 0.03%

Ingredient	Grade	Nycomed's proposed formulation w/w %		Batch Quantity per (b) (4)	Batch Quantity per (b) (4)	Function
Tacrolimus	N/A	0.1000 (0.1%)	0.0300 (0.03%)	(b) (4)		
Paraffin	NF	(b) (4)				
(b) (4) (White Wax) (1)	NF					
Mineral Oil	USP					
White Petrolatum	USP					
Propylene Carbonate	NF					

(b) (4)

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHNNY L YOUNG
01/24/2011

MARTIN H Shimer
01/31/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : November 27, 20101

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 200744 for Tacrolimus Ointment, 0.1% and 0.03% to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv). **The 0.03% is the new strength and new first generic product.**

Nycomed US Inc. has submitted ANDA 200744 for Tacrolimus Ointment, 0.1% and 0.03%. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Nycomed US Inc. on November 19, 2010 for its Tacrolimus product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDA E HOWARD

12/02/2010

New Strength and first generic on 0.03%
Eda

Response to Refusal

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 200744 **FIRM NAME**: NYCOMED US INC.

PIV: YES **Electronic or Paper Submission:** GATEWAY (ELECTRONIC DATA)

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: TACOLIMUS
DOSAGE FORM: OINTMENT, 0.1%

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC1 Team 3 ☒***Activity***	***Bio Team: 4 April Braddy*** ☒***Activity***
ANDA/Quality RPM: Trang Tran ☒ ***FYI***	Bio PM: Diana Solana ☐ ***FYI***
Quality Team Leader: Fan, James No assignment needed in DARRTS	***Clinical Endpoint Team Assignment: (No)*** ☒***Activity***
Labeling Reviewer: Beverly Weitman	***Micro Review (No)*** ☐***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: APRIL 8, 2010 **Received Date**: APRIL 9,2010

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 4020700 SKIN AGENTS

Archival copy: GATEWAY (ELECTRONIC DATA) **Sections** I
Review copy: NA E-Media Disposition: NA
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Johnny Young Date 9/9/10	Recommendation: ☒ FILE ☐ REFUSE to RECEIVE
Supervisory Concurrence/Date: _____	**Date:** _____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☒ Yes ☐ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☒ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☐ Yes ☒ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. Requested EER
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

Amy Byrom 631.454.7677 x2098; (f) 631.756.5114

Has SPL
2 exhibit batches were manufactured (b) (4)

1. Side-by-side should use highlighting to mark differences ok

RTR due to Clinical Study having been determined to be inadequate for filing acceptance.- see e-mail at end of checklist

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: APRIL 8, 2010	☒
1.2.1	**Form FDA 3674 (C)**	☒
*	**Table of Contents (paper submission only)** NA	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒

1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES SEE SECTION 1.3.3 2. List of Convictions statement (original signature) SAME	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) '907, '727 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☒ 3. Expiration of Patent(s): 9-09-2014 a. Pediatric exclusivity submitted? N b. Expiration of Pediatric Exclusivity?NA 4. Exclusivity Statement: YES no unexpired exclusivity U - 919 FOR THE TREATMENT OF DERMATITIS	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient x Type II DMF No. (b) (4) (6/23/05) b. Type III DMF authorization letter(s) for container closure x 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒
1.12.11	**Basis for Submission** NDA# : 50-777 x Ref Listed Drug: PROTOPIC x Firm: ASTELLAS x ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use x 2. Active ingredients x 3. Inactive ingredients x 4. Route of administration x 5. Dosage Form x 6. Strength x	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒

1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) x **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained x **1.14.1.3** 1 package insert (content of labeling) submitted electronically x ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained x **1.14.3.3** 1 RLD label and 1 RLD container label x	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** x **Word Processed e.g., MS Word** x A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** x **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** x **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** x **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** x **Word Processed e.g., MS Word** x **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary x Table 4. Bioanalytical Method Validation x Table 6. Formulation Data x **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution x **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies x Table 3. Statistical Summary of the Comparative BA Data x **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study x **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies x	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) x 2. Function or Responsibility x 3. Type II DMF number for API (b) (4) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) x **3.2.S.4.2 Analytical Procedures** x **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples x 2. Samples-Statement of Availability and Identification of: a. Drug Substance x b. Same lot number(s) **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) x 2. Applicant certificate of analysis x **3.2.S.4.5 Justification of Specification** x	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems DMF**	☒
3.2.S.7	**Stability DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition x 2. Inactive ingredients and amounts are appropriate per IIG x	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) x 2. CGMP Certification: YES SEE SECTION 3.2.P.3.1.2 3. Function or Responsibility x 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** x **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process x 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified x (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement x **3.2.P.3.4 Controls of Critical Steps and Intermediates** x **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation NA 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified x **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) x 2. Suppliers' COA (specifications and test results) x **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA x	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** x **3.2.P.5.2 Analytical Procedures** x **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form x 2. Same lot numbers **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form x **3.2.P.5.5 Characterization of Impurities** x **3.2.P.5.6 Justification of Specifications** x	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) x 2. Components Specification and Test Data x 3. Packaging Configuration and Sizes 30 g, 60 g and 100 g tubes w/caps 4. Container/Closure Testing x 5. Source of supply and suppliers address x	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted x 2. Expiration Dating Period (b) (4) **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments x **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data x 2. Batch numbers on stability records the same as the test batch x	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** (b) (4) [redacted] **3.2.R.1.P.2 Information on Components** x **3.2.R.2.P Comparability Protocols** NA **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

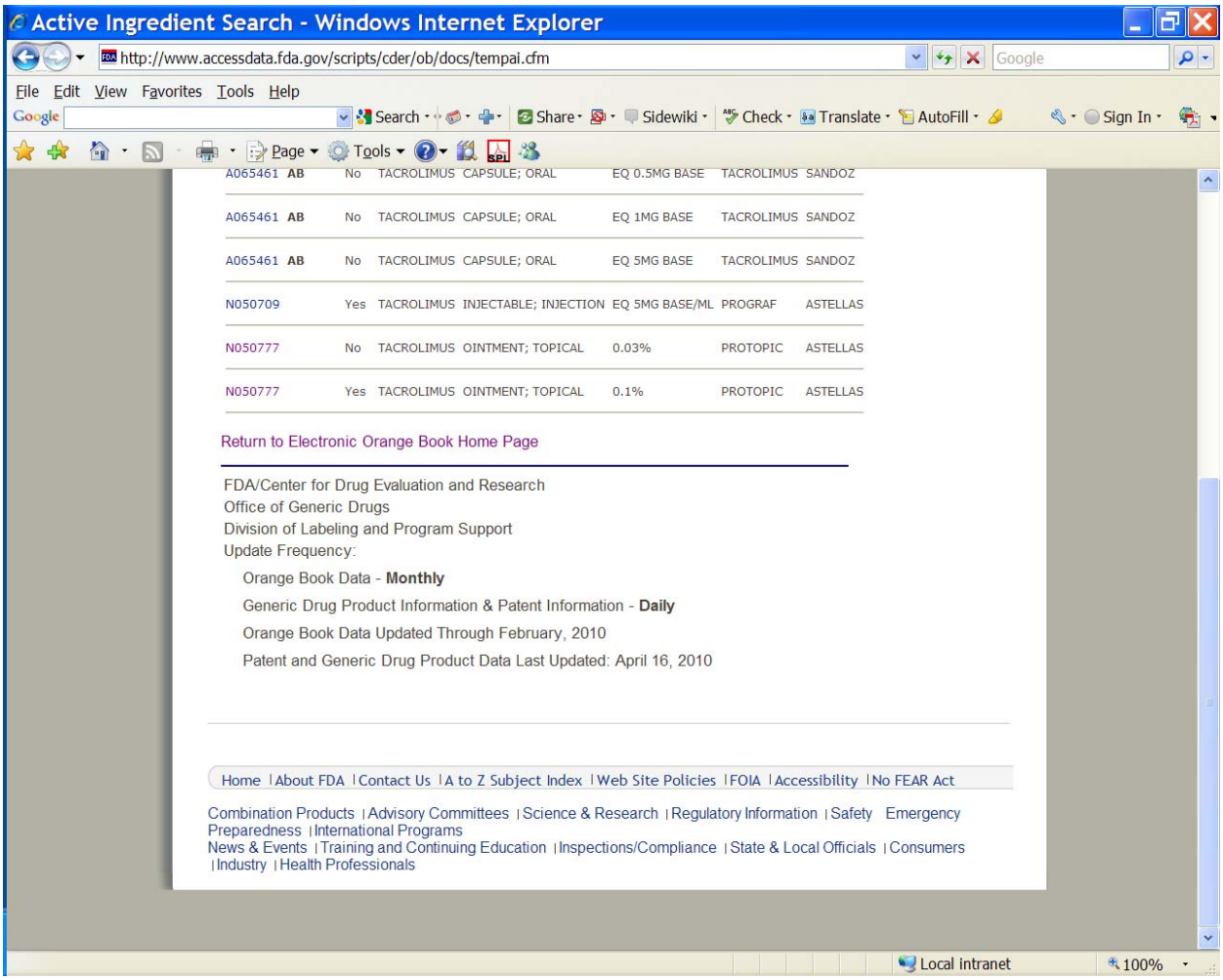
ACCEPTABLE

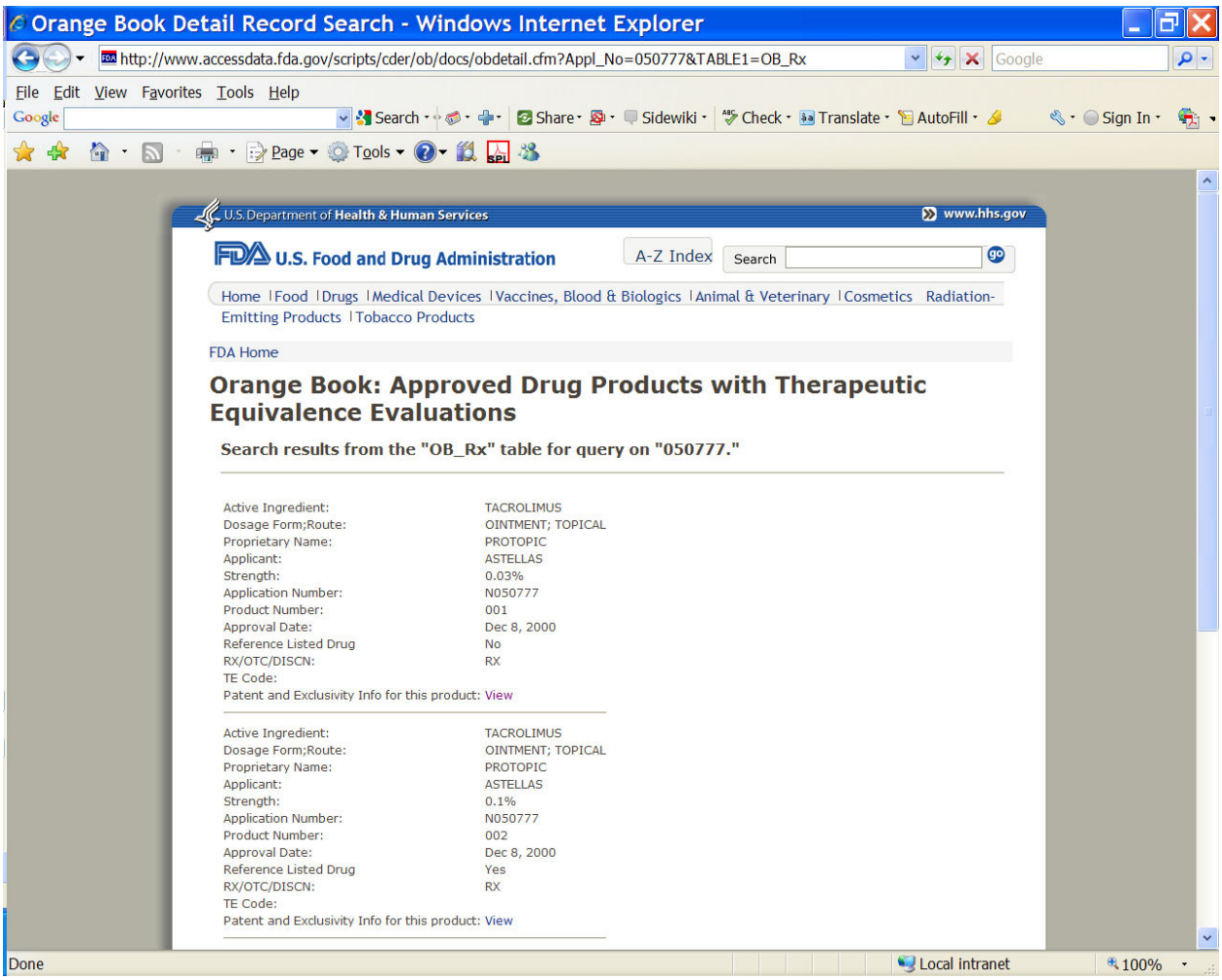
5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) NA b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) x **2. Lot Numbers of Products used in BE Study(ies):** Z432 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

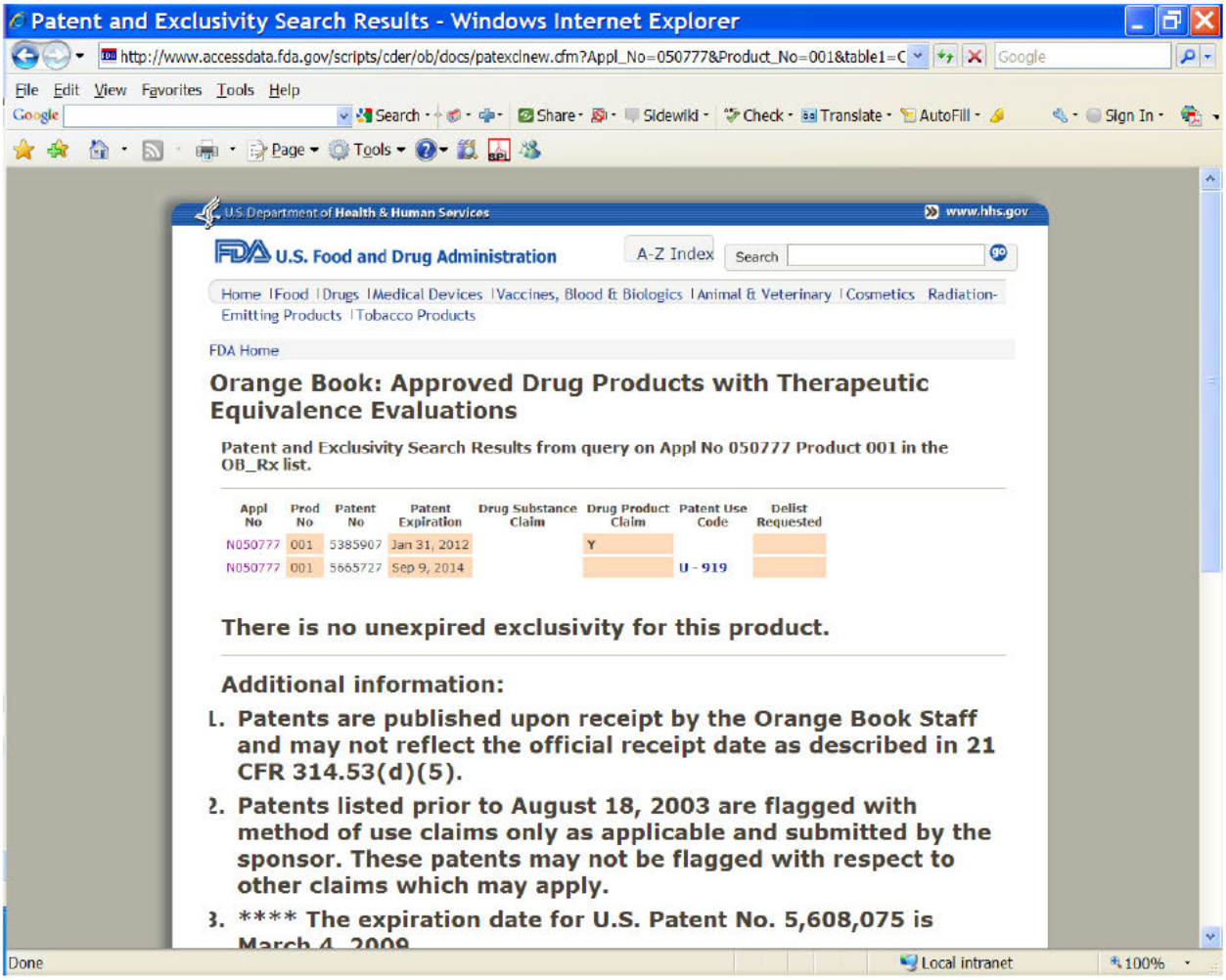
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 10. Study Information x Table 12. Dropout Information x Table 13. Protocol Deviations x **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information x Table 16. Composition of Meal Used in Fed Bioequivalence Study x **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses x Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples x **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: NA	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** YES /CLINICAL TEAM REVIEW NEEED 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted NA	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009


Active Ingredient Search - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
File Edit View Favorites Tools Help
A065461 AB No TACROLIMUS CAPSULE; ORAL EQ 0.5MG BASE TACROLIMUS SANDOZ
A065461 AB No TACROLIMUS CAPSULE; ORAL EQ 1MG BASE TACROLIMUS SANDOZ
A065461 AB No TACROLIMUS CAPSULE; ORAL EQ 5MG BASE TACROLIMUS SANDOZ
N050709 Yes TACROLIMUS INJECTABLE; INJECTION EQ 5MG BASE/ML PROGRAF ASTELLAS
N050777 No TACROLIMUS OINTMENT; TOPICAL 0.03% PROTOPIC ASTELLAS
N050777 Yes TACROLIMUS OINTMENT; TOPICAL 0.1% PROTOPIC ASTELLAS
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through February, 2010
Patent and Generic Drug Product Data Last Updated: April 16, 2010
Home | About FDA | Contact Us | A to Z Subject Index | Web Site Policies | FOIA | Accessibility | No FEAR Act
Combination Products | Advisory Committees | Science & Research | Regulatory Information | Safety Emergency Preparedness | International Programs
News & Events | Training and Continuing Education | Inspections/Compliance | State & Local Officials | Consumers | Industry | Health Professionals
Local intranet
100%


Orange Book Detail Record Search - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=050777&TABLE1=OB_Rx
File Edit View Favorites Tools Help
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Search results from the "OB_Rx" table for query on "050777."
Active Ingredient: TACROLIMUS
Dosage Form;Route: OINTMENT; TOPICAL
Proprietary Name: PROTOPIC
Applicant: ASTELLAS
Strength: 0.03%
Application Number: N050777
Product Number: 001
Approval Date: Dec 8, 2000
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: TACROLIMUS
Dosage Form;Route: OINTMENT; TOPICAL
Proprietary Name: PROTOPIC
Applicant: ASTELLAS
Strength: 0.1%
Application Number: N050777
Product Number: 002
Approval Date: Dec 8, 2000
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Done
Local intranet
100%



Ingredient	Grade	Nycomed's proposed formulation w/w %	Batch Quantity per	Batch Quantity per (b) (4)	Function (b) (4)
Tacrolimus	N/A	0.1000 (b) (4)			
Paraffin					
(b) (4) (b) (4) White Wax) (1)					
Mineral Oil					
White Petrolatum					
Propylene Carbonate					

(b) (4)

INGREDIENT	ROUTE:DOSAGE FORM	UNII	NDA COUNT	LAST NDA	APPROVAL DATE	DIV	MAXIMUM POTENCY/UNIT
PARAFFIN	(b) (4)						
WHITE WAX							
MINERAL OIL							
PETROLATUM, WHITE							
PROPYLENE CARBONATE							

Batch No.	Packaging	Target Weight (theoretical)	Bulk Yield	OOS Limit
(b) (4)				

Table 3 Primary Efficacy Analysis: Proportion of Subjects with Clinical Success on the Investigator's Global Evaluation

Population Statistics	Treatment Group			90% Confidence Interval for Bioequivalence	*P* value for Superiority	
	Test	Reference	Vehicle		Test versus Vehicle	Reference versus Vehicle
PP Subjects						
N	210	211	195			
Success	104 (49.5%)	121 (57.3%)	67 (34.4%)	-0.163, 0.006	0.003	< 0.001
Failure	106 (50.5%)	90 (42.7%)	128 (65.6%)			
mITT Subjects						
N	257	252	249			
Success	124 (48.2%)	138 (54.8%)	83 (33.3%)	-0.142, 0.012	0.001	< 0.001
Failure	133 (51.8%)	114 (45.2%)	166 (66.7%)			

From: Young, Johnny
Sent: Wednesday, July 28, 2010 4:20 PM
To: 'Amy Byrom'
Cc: Shimer, Martin; Patel, Nitin K. (CDER/OGD)
Subject: RE: Encrypted - ANDA 200744- Tacrolimus Ointment 0.1%

Hi Amy,

After checking with Clinical, your explanation below as to how the source document requirements will be fulfilled is acceptable from a filing standpoint. Should clinical require further information, this will be addressed as a review issue.

Thank you.

Johnny

From: Amy Byrom [mailto:Amy.Byrom@nycomedus.com]
Sent: Tuesday, July 27, 2010 12:03 PM
To: Young, Johnny
Cc: Theresa Leh
Subject: FW: Encrypted - ANDA 200744- Tacrolimus Ointment 0.1%

Hi Johnny,

I was wondering if you were able to get feedback from the clinical team regarding our clarification request on the Tacrolimus source documents. We are working on the submission and want to be sure that the response is complete and addresses all of concerns. Do you know when you might have feedback? Even an estimated date would be helping in planning our response.

I greatly appreciate your help.

Kind regards,
Amy

Amy M. Byrom
***Manager*, Regulatory Affairs**

Nycomed US Inc.
P.O. Box 2006
60 Baylis Road
Melville, NY 11747

Direct: (631) 719-2098
General: (631) 454-7677, x2098
Fax: (631) 756-5114
Email: amy.byrom@nycomedus.com

From: Hixon, Dena R
Sent: Monday, July 26, 2010 1:45 PM
To: Kim, Carol Y; Patel, Nitin K. (CDER/OGD)
Cc: Hixon, Dena R
Subject: RE: Encrypted - ANDA 200744- Tacrolimus Ointment 0.1%

Carol,
HIPAA regulations are all about protecting the privacy of the individual patient, so they may be obscuring names, initials, date of birth, or other personally-identifiable information. This should not be a problem for getting the information we are requesting.

From: Kim, Carol Y
Sent: Tuesday, July 20, 2010 1:53 PM
To: Patel, Nitin K. (CDER/OGD)
Cc: Hixon, Dena R
Subject: RE: Encrypted - ANDA 200744- Tacrolimus Ointment 0.1%

Nitin,

At this point, let's see what they can provide. If they submitted everything else and we need more information regarding the source document, then we can deal with it as a reviewer's issue.

I am not sure why they have to encrypt the source document or CRF so that we wouldn't be able to see.
I also don't know what "HIPAA-related regulations" refer to. Do you?
When we asked for the copy of the CRF or the source document, we didn't have this issue with other generic sponsors.
Can we perhaps ask them to include an explanation why certain information had to be concealed and what was concealed?
Thanks
carol

From: Patel, Nitin K. (CDER/OGD)
Sent: Tuesday, July 20, 2010 1:28 PM
To: Kim, Carol Y
Subject: FW: Encrypted - ANDA 200744- Tacrolimus Ointment 0.1%

Carol,

Need your help with the question below from Nycomed.
Thanks,

Nitin

From: Young, Johnny
Sent: Tuesday, July 20, 2010 12:48 PM
To: Patel, Nitin K. (CDER/OGD)
Subject: FW: Encrypted - ANDA 200744- Tacrolimus Ointment 0.1%

Hi Nitin,

Nycomed is preparing to assemble a response to RSB's RTR letter and has a question regarding a particular refusal point. Could you please forward this onto the clinical reviewer who was working on the prefiling review? I have attached the RTR letter for reference.

Thanks and let me know if there is anything else you need.

Johnny

From: Amy Byrom [mailto:Amy.Byrom@nycomedus.com]
Sent: Tuesday, July 20, 2010 12:28 PM
To: Young, Johnny
Cc: Rob Anderson; Theresa Leh
Subject: Encrypted - ANDA 200744- Tacrolimus Ointment 0.1%

Hi Johnny,

Thank you for getting back to me. I apologize if my voicemails were too confusing.

Here is the clarification we're looking for:

On Page 2 of the RTR letter, bullets 8, 9 and 10 request source documents in addition to the CRF. Our plan is to provide the copies of the source documents but with certain information obscured in order to comply with HIPAA regulations. The study sites will be obscuring the HIPAA-related information and Nycomed will have no input into which information will be concealed. Could you please confirm that this will be acceptable to fulfill the source document requirements?

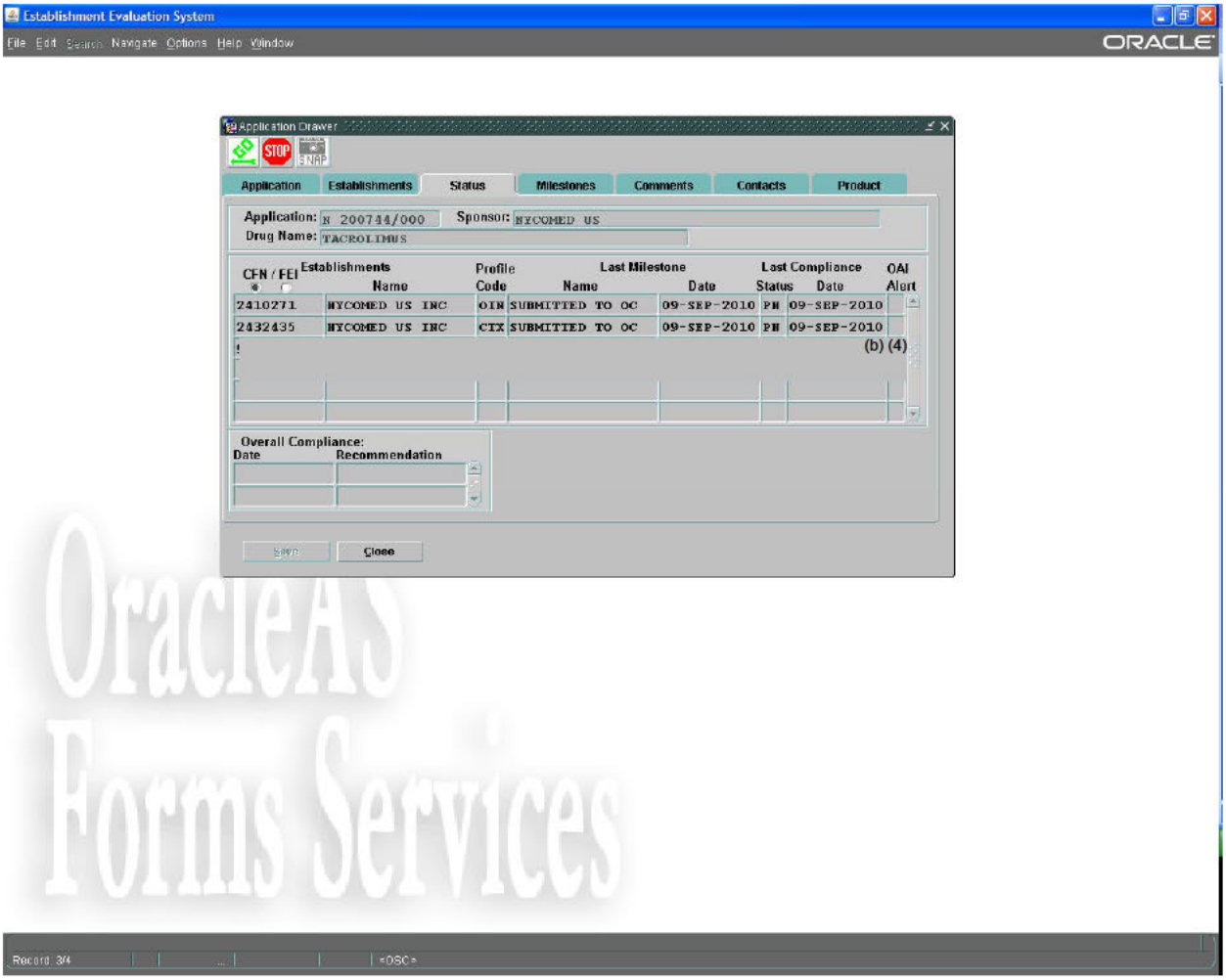
As always, I appreciate your help.

Kind regards,
Amy

Amy M. Byrom
***Manager*, Regulatory Affairs**

Nycomed US Inc.
P.O. Box 2006
60 Baylis Road
Melville, NY 11747

Direct: (631) 719-2098
General: (631) 454-7677, x2098
Fax: (631) 756-5114
Email: amy.byrom@nycomedus.com


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application Drawer
STOP
SNAP
Application
Establishments
Status
Milestones
Comments
Contacts
Product
Application: N 200744/000
Sponsor: NYCOMED US
Drug Name: TACROLIMUS
CFN / FEI
Establishments Name
Profile Code
Last Milestone Name
Last Milestone Date
Last Compliance Status
Last Compliance Date
OAI Alert
2410271 NYCOMED US INC OIN SUBMITTED TO OC 09-SEP-2010 PH 09-SEP-2010
2432435 NYCOMED US INC CIX SUBMITTED TO OC 09-SEP-2010 PH 09-SEP-2010
(b) (4)
Overall Compliance:
Date
Recommendation
Save
Close
OracleAS
Forms Services
Record: 3/4
<OSC>

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200744	ORIG-1	NYCOMED US INC	TACROLIMUS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHNNY L YOUNG
09/13/2010

MARTIN H Shimer
09/15/2010

From: Patel, Nitin K. (CDER/OGD)
Sent: Wednesday, June 23, 2010 2:38 PM
To: Young, Johnny
Cc: Patel, Nitin K. (CDER/OGD)
Subject: Additional information requested (ANDA 200744; Tacrolimus Ointment, 0.1%) prior to completing filing review

Johnny,

The Clinical Team needs to send out the attached comments to the firm, prior to completing our filing review.
Thanks.

Nitin

Nitin K. Patel, Pharm.D.
CDR, U.S. Public Health Service
Medical Affairs Coordinator, Clinical Team
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Phone: (240) 276-8887
Fax: (240) 276-8966

Please provide the following additional information for consideration of receiving your ANDA 200744:

1. When and how were the potential packaging/dosing errors discovered? Was it before or after the database lock?
2. For each patient who was reported to be mis-dosed during the study, please provide the patient number, randomized treatment assignment, study drug treatment received, drug treatment group for the ITT analysis, drug treatment group for the MITT analysis, date and time the dosing error was discovered.
3. Was an interim analysis performed or not? If not, when and why was the decision made to drop the interim analysis?
4. When were additional patients added to the study to meet the new sample size? Was it before or after breaking the blind? Please note that the list of randomization codes is dated 9/24/2007. Are the codes for the additional patients included in the submission? If not, please provide the codes for the additional patients.
5. Provide a list of patients who were later added to the study to meet the new sample size.
6. Did your MITT and PP population analysis include those patients who were later added to the study?
7. Did your MITT and PP population analysis include those patients who were incorrectly dosed?
8. Provide a copy of an original protocol dated 10/18/07 and the latest version of 11/5/07 prior to patient enrollment.

9. Provide a copy of an IRB approval letter for the protocol, each protocol amendment, and consent form.
10. Provide a definition for each variable and dataset provided under your "analysis" file.
11. Provide trough tacrolimus concentrations in SAS .xpt file for each patient as shown below. Date and time of blood drawn and the amount of dose taken for that level should be provided.
12. Provide a copy of CRF and source documents for all patients who were potentially mis-dosed (received wrong study drug treatments).
13. Provide a copy of CRF and source documents for all patients who were unblinded during the study.
14. Provide a copy of CRF and source documents for those patients who had statistical and analytical issues noted after the database lock on October 9, 2008 (page 57): (b) (6)
15. Provide a separate outcome analysis using the following conditions: the MITT population analysis comparing all treatment groups 1) including those who were mis-dosed using the "randomized study treatment", 2) including those who were mis-dosed using the "dosed study treatment", 3) excluding those who were mis-dosed.
16. Provide a summary dataset including the following separate line listing for each patient (if data exist) using the following headings, if applicable:

    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of Actual Treatment received (exposure): test product, RLD, placebo control
    i. Name of randomized treatment: test product, RLD, placebo control
    j. Name of actual treatment used for all patients in the ITT population
    k. Name of actual treatment used for all patients in the MITT population
    l. Name of treatment used for the PP population
    m. Duration of Treatment (total exposure in days)
    n. Previous use of atopic dermatitis treatment (yes/no)
    o. Reason for use of this product (e.g., intolerant of conventional therapies)
    p. Completed the study (yes/no)
    q. Reason for premature discontinuation of subject
    r. Subject required additional treatment for atopic dermatitis due to unsatisfactory treatment response (yes/no)
    s. Later added into the study to meet the new sample size (yes/no)
    t. Per Protocol (PP) population inclusion (yes/no)
    u. Reason for exclusion from PP population
    v. Intent to Treat (ITT) population inclusion (yes/no)

w. Reason for exclusion from ITT population
x. Modified to Treat (MITT) population inclusion (yes/no)
y. Reason for exclusion from MITT population
z. Safety population inclusion (yes/no)
aa. Reason for exclusion from Safety population
bb. Location of treatment area
cc. Size of treatment area at baseline (cm^2)
dd. Percent (%) Body Surface Area (BSA) involvement at baseline and at week 2
ee. IGE score at baseline and at week 2
ff. Individual signs and symptoms of severity of AD score of erythema, pruritus, induration/population/edema, lichenification, and excoriation at baseline and at week 2
gg. Tacrolimus trough blood concentration on day 4
hh. Weighed (dose) before and after the morning dose on day 4
ii. Time and date of tacrolimus trough blood sample
jj. Final designation as treatment success or failure based on IGE
kk. Treatment compliance: number of missed doses per subject
ll. Concomitant medication (yes/no)
mm. Adverse event(s) reported (yes/no)

17. Study data should be submitted to the OGD in electronic format.
    a. A list of file names included in the CD or diskette(s), with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
    b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
    c. SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
    d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
    e. Please provide a separate dataset for variables such as demographics, disease severity (IGE, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.
    f. The methods used to derive the variables should be included and explained.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200744	ORIG-1	NYCOMED US INC	TACROLIMUS

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/s/

NITIN K PATEL
06/23/2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : April 19, 2010

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 200744 for Tacrolimus Ointment, 0.1% to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Nycomed US Inc. has submitted ANDA 200744 for Tacrolimus Ointment, 0.1%. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Nycomed US Inc. on April 8, 2010 for its Tacrolimus product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200744	ORIG-1	NYCOMED US INC	TACROLIMUS

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/s/

EDA E HOWARD
04/20/2010