Amsterdam 29 May 2019
EMA/603042/2019
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

Ekesivy

International non-proprietary name: diclofenamide

Procedure No. EMEA/H/C/005141/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACZ	Acetazolamide
API	Active Pharmaceutical Ingredient
ASMF	Active substance master file
AUC	Area under the plasma concentration-time curve
BSE	Bovine Spongiform Encephalopathy
CL	Clearance
CL_H	Hepatic clearance
CL_R	Renal clearance
CQA	Critical Quality Attribute
CYP450	Cytochrome P450
DCP	Diclofenamide/Dichlorphenamide
DSC	Differential scanning chromatography
fu	Fraction unbound
GC	Gas chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High density polyethylene
HOP	Hypokalemic Periodic Paralysis
HPLC	High Performance Liquid Chromatography
HYP	Hyperkalemic Periodic Paralysis
ICH	International Conference on Harmonisation
IPC	In-process controls
IR	Infra-Red Spectroscopy
LOD	Loss on drying/Limit of detection
LOQ	Limit of quantification
MAD	Multiple ascending dose
MAH	Marketing Authorisation Holder
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
PDE	Permissible Daily Exposure
Ph. Eur.	European Pharmacopoeia
PP	Periodic Paralyses
PPP	Primary periodic paralyses
PPQ	Process performance qualification
QC	Quality control sample
QP	Qualified Person
RSD	Relative Standard Deviation
SAD	Single ascending dose
tau	Dosing interval
TSE	Transmissible Spongiform Encephalopathy
UDU	Uniformity of Dosage Units
ULOQ	Upper limit of quantification
USP	United States Pharmacopoeia
V	Volume of distribution
XRD	X-Ray Diffraction

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Ekesivy, an orphan medicinal product in the treatment of periodic paralysis;

Is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

- The overall absence of bridging data to the reference product in light of this Article 10(3) hybrid application
- The lack of description of the development of the dissolution method and that the discriminatory ability of the method has not been shown
- The absence of nonclinical data
- The quality of the pharmacokinetic documentation which lacks essential aspects of the diclofenamide pharmacokinetic profile
- The quality of the submitted documentation which raises uncertainties regarding the conduct and data analysis of the pivotal HYP-HOP study. The deficiencies are considered to preclude an adequate assessment of efficacy and safety
- The wording of the proposed indication in consideration of the studied population and the available data

Questions to be posed to additional experts

Inspection issues

GMP inspection(s)

No issues that would trigger a GMP inspection have been observed during the assessment of the module 3 documentation.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Diclofenamide is indicated for the *treatment of periodic paralysis*.

Primary periodic paralyses are a group of rare autosomal dominant genetic disorders caused by sporadic or inherited mutations in skeletal muscle sodium, calcium or potassium channels. They are part of the broader spectrum of *muscle channelopathies* that are caused by mutations in sodium, chloride, potassium, and calcium ion channels that result in increased or decreased sarcolemma excitability. Traditionally, channelopathies are divided into the nondystrophic myotonias and periodic

paralyses. The non-dystrophic myotonias (NDM) include myotonia congenita, paramyotonia congenita, and sodium channel myotonias. Primary periodic paralyses include hyperkalemic periodic paralysis (also called potassium-sensitive period paralysis), hypokalemic periodic paralysis, and Andersen–Tawil syndrome.

There are various conditions that associated with secondary periodic paralysis. In the diagnosis of primary periodic paralysis, secondary causes of hypo or hyperkalemia should be excluded (Phillips, L. & Trivedi, J.R. Neurotherapeutics (2018) 15: 954. https://doi.org/10.1007/s13311-018-00678-0).

2.1.2. Epidemiology

Estimated prevalences are 1 per 200,000 for hyperkalemic periodic paralysis, 1 per 100,000 for hypokalemic, and 1 per 1000,000 for Andersen-Tawil syndrome (Statland et al. Muscle Nerve. 2018;57[4]:522-30). According to another reference, hypokalemic periodic paralysis is the most common PP and has a prevalence of ~0.13 per 100,000 (Phillips, L. & Trivedi, J.R. Neurotherapeutics (2018) 15: 954).

2.1.3. Biologic features

In all forms of primary PP, there is aberrant depolarization which inactivates sodium channels and leads to muscle membrane inexcitability.

Hypokalemic periodic paralysis is mostly associated with mutations involving muscle calcium ion (*CACNA1S*, chromosome 1 ~60%) and sodium (*SCN4A*, chromosome 17 ~20%) channels. The clinical presentation is the same as the calcium or sodium channel mutations result in leakage current at the resting potential producing susceptibility to paradoxal depolarization of the skeletal muscle fiber and inexcitability in the setting of low extracellular K+.

Hyperkalemic periodic paralysis is associated with mutations in the sodium channel (*SCN4A* gene) on chromosome 17q23. These mutations are associated with gain of function changes, usually impaired channel inactivation.

Andersen-Tawil syndrome has in some cases been identified to be caused by mutations of the KCNJ2 gene which encodes the inward rectifier potassium channel Kir2.1 (Statland et al. Muscle Nerve. 2018;57[4]:522-30).

2.1.4. Clinical presentation, diagnosis

Diagnosis of primary periodic paralyses is based on history of attacks of flaccid paralysis, positive family history, characteristic ictal changes in serum potassium (high or low), prolonged exercise test, and exclusion of secondary causes of hypokalemia and hyperkalemia.

Most patients with primary periodic paralysis have inherited autosomal dominant disorders although sporadic cases have been reported. Genetic testing is the gold standard to confirm definite periodic paralysis, however, a significant number of patients (20-30%) will have no identifiable mutation.

Hypokalemic periodic paralysis is characterized by focal or generalized paralytic episodes of skeletal muscle which can last hours to days and are associated with concomitant hypokalemia (<2.5 mgEq/L). A variable myopathy develops in many individuals and may result in a progressive muscle weakness predominantly in proximal muscle groups of the lower limbs. Attack triggers may be carbohydrate-rich meals, alcohol and rest after strenuous exercise Statland et al. Muscle Nerve. 2018;57[4]:522-30).

Characteristic features of hyperkalemic periodic paralysis are attacks of limb weakness and an increase of serum potassium although some patients reportedly have normal serum potassium levels during

attacks. Administration of potassium may trigger an attack or worsen an ongoing episode. Attacks may also be triggered by potassium-rich food, rest after exercise fasting, exposure to cold, emotional stress or pregnancy. Attacks in hyperkalemic periodic paralysis tend to be more frequent and shorter in duration than hypokalemic disease. Approximately half of the patients experience muscle stiffness (Statland et al. Muscle Nerve. 2018;57[4]:522-30).

Andersen-Tawil syndrome is characterized by a triad of episodic flaccid muscle weakness, cardiac abnormalities, and distinctive skeletal features. This syndrome is not further discussed in detail as it formed an exclusion criterion for the pivotal and supportive studies.

Table 1: Clinical presentation of primary paralysis

Feature	HypoPP	HyperPP	Andersen-Tawil syndrome
Ictal K + level	Low	High/normal	Variable
Age at onset	Age 5–35 y	Before age 20 y	Age 2–18 y
Mean duration of episodes	>2 h	<2 h	1 to 36 h
Muscle stiffness	Absent	Moderate	Absent
Episodic weakness	Yes	Yes	Yes
Maximum weakness	Severe	Mild to severe	Moderate
Characteristic facies	Absent	Absent	Present
Arrhythmias	Absent	Absent	Long QT arrhythmia

From: Statland et al. Muscle Nerve. 2018;57[4]:522-30

2.1.5. Management

Treatment strategies involve patient education, and lifestyle changes to minimize triggers of periodic paralysis and potassium therapy (supplementation or avoidance).

Carbonic anhydrase inhibitors, in particularly acetazolamide and dichlorfenamide, have been used for almost 50 years as empiric treatment for both hyper and hypokalemic periodic paralysis. Treatment options are limited and based largely on anecdotal experience (see table below). In 2016, Keveyis dichlorphenamide 50 mg tablets were approved by FDA for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants.

Table 2: General approach to treatment for periodic paralysis

	HyperPP	HypoPP	Andersen-Tawil syndrome
Acute attack			
Non-pharmacological	Mild exercise; carbohydrates	Mild exercise at attack onset; potassium supplements	Mild exercise; carbohydrates (if attacks associated with hyperkalemia)
Potassium supplement†	Not applicable	Oral K + 1 mEq/kg up to 200 mEq/24h* Avoid slow release formulations	If attacks associated with low K+, oral K + 1 mEq/kg up to 200 mEq/12h* to normalize
Beta-2 agonist – salbutamol	2 puffs 0.1 mg	Not applicable	Not applicable
Prevention			
Non-pharmacological	Frequent high carbohydrate meals; Avoid: fasting; strenuous exercise; cold exposure; K + rich foods	Low sodium and carbohydrate diet; potassium supplements; avoid hyperosmolar states (dehydration, hyperglycemia)	
Acetazolamide	Adults: 125-1000 mg daily Children: 5-10 mg/kg/d	Adults: 125-1000 mg daily Children: 5-10 mg/kg/d	Adults: 125-1000 mg daily Children: 5-10 mg/kg/d
Dichlorphenamide	50-200 mg daily	50-200 mg daily	50-200 mg daily
Potassium supplement†	Not applicable	Oral K + 30-60 mEq/day; sustained released formulation may be preferred	Not applicable
K + sparing diuretic	Not applicable	Triamterene 50-150 mg/d Spironolactone 25-100 mg/d Eplerenone 50-100 mg/d	Not applicable‡
Hydrochlorothiazide	25-75 mg daily	Not applicable	Not applicable
Antiarrhythmics	Not applicable	Not applicable	Flecainide, beta-blockers or calcium channel blockers to prevent ventricular arrhythmias

Monitor ECG and potassium levels.

†*Total body potassium is not depleted in HypoPP, use caution with acute K^+ administration to avoid overshoot.*

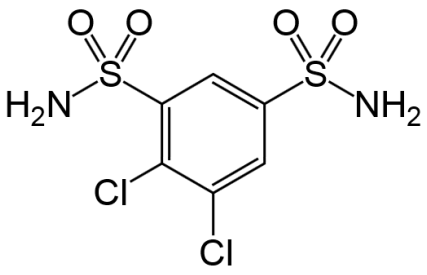
‡*Use of K-sparing diuretics should be individualized based on patient needs.*

From: Statland et al. Muscle Nerve. 2018;57[4]:522-30

In general, randomized trials in patients with primary periodic paralyses are limited by small patient populations (due to the rarity of the disease and consequent low patient enrolment) and high attrition rates. There is a need for additional studies to better understand efficacy and adverse events, including long-term follow-up, comparative efficacy of active treatments, as well as the effects of treatment on permanent muscle weakness.

2.2. About the product

Diclofenamide (4,5-dichlorobenzene-1,3-disulfonamide) is a sulfonamide and a carbonic anhydrase inhibitor of the meta-disulfamoylbenzene class with the following structural formula:



The mechanism of action of carbonic anhydrase inhibitors in periodic paralyses is incompletely understood. Carbonic anhydrase inhibitors increase the removal of bicarbonate, sodium and potassium through the urine. The systemic acidosis promoted by these drugs may reduce patients' susceptibility to period paralysis. Enhanced opening of calcium-activated K channels or reduction of intracellular sodium accumulation has also been proposed (Statland et al. Muscle Nerve. 2018;57[4]:522-30).

The proposed indication is treatment of periodic paralysis.

The proposed posology is as follows:

Initiate dosing at 50 mg twice daily. The initial dose may be increased or decreased based on individual response, at weekly intervals (or sooner in case of adverse reaction). The maximum recommended total daily dose is 200 mg. Prescribers should evaluate the patient's response to diclofenamide after 2 months of treatment to decide whether diclofenamide should be continued.

The proposed SmPC contains a contraindication and warnings related to the following safety issues:

-concomitant use of diclofenamide and high-dose acetylsalicylic acid (sections 4.3 and 4.4)

-risk for hypokalemia when diclofenamide is used in patients with conditions associated with hypokalemia or other drugs that may cause hypokalemia (section 4.4).

Concomitant use of diclofenamide with other drugs that cause metabolic acidosis may increase the severity of metabolic acidosis (section 4.4).

2.3. The development programme/compliance with CHMP guidance/scientific advice

The development program for diclofenamide included a single and multiple dose PK study in 36 healthy volunteers (DCPT-1531) and in vitro studies.

The Phase III program for dichlorphenamide (DCP) included a single pivotal efficacy study (HYP-HOP). In addition, the applicant submitted a supportive literature study by Tawil et al, Ann Neurol. 2000; 47[1]:46-73).

The developmental product does not have PRIME status.

No formal scientific advice was issued by CHMP for this medicinal product.

The reference product, Fenamide 50 mg tablets was authorised nationally in Italy with date of first authorisation on 19th February 1960. The therapeutic indication was treatment of glaucoma. The authorisation was withdrawn on 2 October 2014, for marketing reasons. According to the MS, the application contained bibliographical data and own clinical trials qualifying the application for a complete dossier, however, being an historical MA, this documentation would probably not be in line with current requirements concerning an application in accordance with art. 8(3).

The application is submitted under Article 10(3) of Directive 2001/83/EC. According to Article 9 of Regulation (EC) 1901/2006, Articles 7 & 8 of that regulation (which define its mandatory scope) do not apply to products authorised under this legal basis. Accordingly, no paediatric investigation plan is required.

2.4. General comments on compliance with GMP, GLP, GCP

No issues that would trigger a GMP inspection have been observed during the assessment of the module 3 documentation.

The applicant declares that the clinical trials included in this submission were conducted in accordance with Good Clinical Practice standards and in accordance with applicable regulatory clinical requirements.

According to the applicant, the clinical trials within this submission conducted outside the European Union (EU) meet the ethical requirements of Directive 2001/20/EC. These clinical trials are study

DCPT-1531 and study HYP-HOP. Both studies were conducted in the USA. The HYP-HOP study also included 2 EU sites, one in Italy and one in the UK).

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 10(3) of Directive 2001/83/EC, as amended – relating to applications for hybrid medicinal products.

The chosen reference product is: Fenamide

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA: Fenamide

- Product name, strength, pharmaceutical form: Fenamide 50 mg Tablet
- Marketing authorisation holder: Farmigea S.p.A.
- Date of authorisation: 19-02-1960
- Marketing authorisation granted by:
  - Member State (EEA): Italy
    - National procedure
- Marketing authorisation number: AIC n. 016626018

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Same as above

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Not applicable

Orphan designation

Ekesivy was designated as an orphan medicinal product EU/ 3/16/1677 on 2016-06-27 in the following condition: treatment of periodic paralysis.

Similarity with orphan medicinal products

The application did contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

There are no authorised orphan medicinal products for the proposed indication.

Information on paediatric requirements

Not applicable.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as tablets containing 50 mg of diclofenamide as active substance.

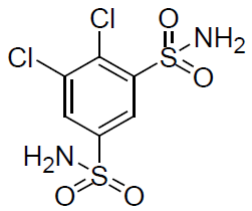
Other ingredients are: pregelatinized starch, lactose monohydrate and magnesium stearate.

The product is available in high density polyethylene (HDPE) bottles with polypropylene caps.

3.1.2. Active Substance

General Information

The INN for the drug substance is diclofenamide. The USP name for the substance is dichlorphenamide. The chemical structure is found below



The molecular formula is $C_6H_6Cl_2N_2O_4S_2$ and relative molecular mass 305.16. Other general properties are

Physical characteristics:	White or almost white powder
Solubility:	Soluble in alcohol, slightly soluble in ether, freely soluble in pyridine. Soluble in dilute solutions of sodium carbonate and sodium hydroxide. Diclofenamide is very slightly soluble in buffer solutions at pH=1.06, 2.99, 5.06, 7.00 (ca 0.35 mg/ml) and slightly soluble (1.54 mg/ml) at pH=9.00.
Melting range:	236.5-240 °C
pK_a-value:	7.4 and 8.6
Partition coefficient:	Log P = 1.03
Polymorphism	Only one solid form for diclofenamide is known in the literature.
Stereochemistry:	No potential isomerism.

An ASMF has been provided from the drug substance manufacturer.

Information about hygroscopicity of diclofenamide should be added. Discussion of polymorphism is based on literature rather than experimentation. It is acknowledged that 4 batches of API have had the same polymorphic form. However, the API is poorly soluble in aqueous media. Therefore, additional solid state studies should be conducted to demonstrate the absence of other potential forms. Information on particle size should be provided.

Manufacture, process controls and characterisation

The drug substance is manufactured by one manufacturer.

The overall control strategy including IPCs, starting material specifications is considered acceptable. Information on manufacture of the intermediate is currently collected in a "Technical package" in 3.2.S.2.3. This information should be split and included under the relevant sections.

The process is a standard process with no elements of Design of Experiments.

The molecular structure of diclofenamide has been confirmed by the following methods:

Elemental analysis, IR, MS, UV, ^{13}C-NMR and ^{1}H-NMR.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The proposed limits for related substances and residual solvents are in accordance with ICH limits and therefore acceptable. However, a question is raised regarding the validation of the related substances method. The limits for assay are acceptable and the method has been satisfactorily validated. The other methods are taken from the USP monograph for the active substance without any further description or justification. However, since USP monographs are not automatically accepted for substances in products on the Eu market, the chosen methods should be further justified. Provided that the specification will be accepted, the provided batch analyses data seems acceptable.

Diclofenamide is packed in double polyethylene (PE) bags. The internal bag, in direct contact with the active substance, is an Antistatic Transparent Polyethylene bag. The external bag is an Opaque Black Polyethylene (PE) bag. The container closure system has been satisfactorily described.

Stability

Stability studies in accordance with ICH guidelines have been performed. Six production scale batches and four pilot scale batches were included in the stability studies. Some of the early batches was packed in a slightly different polyethylene inner bag (not antistatic) but there are also data from the final container closure system. Data from up to 5 years studies have been provided. However, a question is raised to submit the latest available stability data for the largest scale batches.

Diclofenamide seems very stable and no trends are seen. However, there is an out of specification value for assay that the drug substance manufacturer has not commented on and a re-test period will not be assessed until this out of specification value has been satisfactorily commented on.

Forced degradation studies have been performed and it was found that the method is stability indicating and selective for the drug substance and its impurities.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Ekesivy tablets are round, white tablets with one side scored, and engraved with "D" above score and "50" below the score. The other side is engraved with "TARO". The tablets have a score line but no breakability studies have been performed. However, it is stated in the SmPC that the score line is not intended for breaking the tablet.

The information regarding the pharmaceutical development is very brief and not in line with what that is expected for a state-of-the-art application. This is probably due to that the product was first developed in the 1960s. Daranide (diclofenamide) 50 mg tablets was first approved by FDA on 01/01/1982 and was manufactured and marketed by Merck & Co (NDA #011366). On May 2003, Merck's Daranide was voluntarily discontinued for reasons not related to the safety or effectiveness of the product. This is confirmed by The FDA [Docket No. 2006P-0160] from August 6, 2007.

On May 2008 Taro has informed the FDA about transfer of ownership of NDA #11-366 from Merck& Co Inc. to Taro Pharmaceutical USA Inc. Today, both drug product and drug substance manufacturing is performed by Taro Pharmaceutical Industry Ltd. Israel. This development report summarizes the

activities performed by Taro within drug product's site transferring and main changes made to original Merck's Daranide during this period.

The product is applied according to Article 10(3) hybrid application, the chosen reference product is Fenamide, 50 mg, tablet that has been marketed by Farmigea S.p.A. on the Italian market. In the documentation in Module 3, there is no information about the reference product and no data that compares the applied product with the reference product. A multidisciplinary major objection is raised regarding the bridging between the applied product and the reference product.

No description of the development of the dissolution method has been provided. A dissolution procedure intended to be used as a routine control test for immediate release drug products should be robust, reproducible and discriminatory in order to assure a consistent product quality and detect product quality attributes, which, if altered, may affect the in vivo performance. Therefore, the development of the dissolution method should be further described by discussing the selection of dissolution medium, apparatus, stirring speed etc. and the discriminatory power of the method should be demonstrated. This question is raised as a major objection.

No information has been provided regarding the batches used in clinical studies. Furthermore, no dissolution profiles have been provided for batches used in clinical studies.

Some questions are asked related to product development: Diclofenamide is very slightly soluble in buffer solutions at pH=1.06, 2.99, 5.06, 7.00 (ca 0.35 mg/ml). Therefore, particle size of the active substance may influence dissolution of the tablets. This has not been discussed. This should be investigated, and a specification for particle size for diclofenamide should be established. Relevant details on milling of the API, including which screen is used, should be included in the relevant part of the dossier. The development of the dissolution test should be described, including a discussion of discriminatory properties. A discussion of the manufacturing process for the drug substance at Merck & Co vs the current process at Taro regarding the resulting particle size of diclofenamide should be given. The ease of opening of the tablet bottle by the relevant patient group should be discussed.

The tablets are packaged in HDPE bottles and polypropylene closure which seem suitable for their intended use.

It is also stated during development that instead of a microbial limit test in the drug product specification, water activity will be tested during stability. However, no test for water activity is included in the specification and no data for water activity has been provided neither at release nor shelf-life.

Manufacture of the product and process controls

The drug product is manufactured by the same manufacturer as for the drug substance.

The tablets are manufactured by a standard process including blending, wet granulation, wet milling, drying, dry milling, mixing and tablet compression by a rotary compression machine. No holding times are proposed. More details should be included in the manufacturing process, based on experience gained during process validation (which also included challenging the process). Questions on this are included in the list of questions below.

Process validation has been performed on six production scale batches of 150 000 tablets. Studied parameters were: loss on drying and bulk and tapped density during granulation and also bulk and tapped density of the final blend. During tablet compression the following parameters were studied: tablet weight, hardness, thickness, friability, dissolution and assay.

Critical quality attributes were evaluated during the process validation and all was concluded as low risk. In-process controls have been established to control moisture content, blend homogeneity and tablet weight, thickness, hardness and friability.

No design space is claimed.

The established in-process controls and the performed process validation is acceptable.

Product specification, analytical procedures, batch analysis

The specification includes relevant tests. The IR test for identity should be further described. A test for either water activity or microbial limit should be included unless further justified. The proposed limit for assay of 92.0 – 108.0 % at both release and shelf-life is not justified from batch and stability data and should be tightened to 95.0 % to 105.0 %. The omission of a test for microbial quality has not been satisfactorily justified.

The limits for related substances are in accordance with ICH requirements and are acceptable.

The dissolution limit seems unnecessarily wide for an immediate release tablet but cannot be assessed based on the current data since no description of the development of the method has been provided and no data for clinical batches.

The applicant states under justification of specification that the product complies with Elemental impurities requirements according to USP <232> and ICH Q3D but no risk assessment has been provided and this is therefore requested.

The analytical methods used has been satisfactorily described, except for the IR method.

The assay method has been acceptably validated. Questions are raised on the validation of the methods for related substances and dissolution.

Acceptable batch analyses data has been provided on production scale batches.

No discussion on impurities originating from the drug product has been provided and no risk assessment for elemental impurities. These are therefore requested.

The container/closure system used for Ekesivy, 50 mg, tablets consist of 45 ml white HDPE bottle and polypropylene child resistance cap with aluminium liner. Examples of Certificates of Analysis (CoA) of the primary packaging materials are enclosed in the documentation. The tests include e.g. IR identification and dimensions.

Stability of the product

Stability studies were performed in accordance with ICH guidance on four production scale batches. Three batches were packaged in bottles with 100 tablets in each and one batch in bottles with 60 tablets. Since the tablets were very stable, the bottles are identical for both pack sizes and there is not so big difference between 60 and 100 tablets, this is considered acceptable. The tests and methods are the same as intended for the marketed product. The tests performed were appearance, dissolution, assay and related compounds.

All results were within the specification limits and no trends were seen. Since all results are within the specification limits, the proposed storage condition of not above 25°C is not needed. This should be changed to no special precautions for storage. The proposed shelf-life of 3 years can be accepted.

No in-use stability study has been performed for opened bottles. This is acceptable and in compliance with the EMA Q&A since there are no indications that the drug product may be susceptible to

deterioration from the stability studies with unopened bottles. Therefore, no in-use shelf-life needs to be stated.

Forced degradation studies showed that the method is stability indicating and suitable for quantitative determination of diclofenamide and its related compounds (impurities and degradation products) during stability studies.

Since Ekesivy tablets are packed in white opaque HDPE bottles and since the tablets have shown to have no sensitivity to light during the stress studies (no degradation products appeared when exposed to UV Illumination for 24 hours the drug product remains stable respect of assay and purity), photostability study was considered redundant.

Post approval change management protocol(s)

Not applicable.

Adventitious agents

Not applicable.

GMO

Not applicable.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The information in the ASMF is generally acceptable. However, it is quite brief and is sometimes lacking the drug substance manufacturers own discussions and justifications of deviations. Therefore, some other concerns are raised in order to get a deeper understanding of the data provided. Furthermore, some of the analytical methods need to be further described, justified and validated.

In the restricted part of the ASMF there is a lack of information regarding the first step of the GMP synthesis and also about what happens before the start of synthesis. However, since the starting material is a small molecule and no especially critical steps have been identified in the synthesis, these questions are also raised as other concerns.

Since the drug substance manufacturer is the same as the drug product manufacturer, there are no additional questions on the control of the substance by the drug product manufacturer. However, since the audit that the QP declaration is based on is more than 3 years old and it was stated that a new audit was performed in December, an updated QP declaration should be provided.

No description of the development of the dissolution method has been provided. A dissolution procedure intended to be used as a routine control test for immediate release drug products should be robust, reproducible and discriminatory in order to assure a consistent product quality and detect product quality attributes, which, if altered, may affect the in vivo performance. Therefore, the development of the dissolution method should be further described and the discriminatory power of the method should be demonstrated. Since the drug substance has poor aqueous solubility and there are outstanding questions on particle size and polymorphism, this question becomes even more crucial and is therefore raised as a Major Objection.

No information has been provided regarding the batches used in clinical studies. Furthermore, no dissolution profiles have been provided for batches used in clinical studies.

There are several other concerns raised on the drug product specification, regarding limits that need to be tightened and tests that need to be justified. Two of the analytical methods used need to be further validated and a risk assessment for elemental impurities must be provided.

The tablets seem to very stable according to the provided stability data.

No paediatric formulation has been developed.

3.2. Non-clinical aspects

No new nonclinical studies have been performed. The MAA cross-refers to the reference product for all nonclinical aspects of the application. No bibliographic information on pharmacology and pharmacokinetics has been provided. For toxicology, the applicant presents publicly available toxicological information, which only reports LD50 values in different species. In addition, reference is made to a published study from 1967, showing teratogenic effects in rats. Teratogenic effects (fetal limb reduction defects) were reported following oral administration of diclofenamide to pregnant rats during organogenesis at 350 mg/kg/day.

3.2.1. Ecotoxicity/environmental risk assessment

The applicant refers to the product Fenamide, which has been approved in Italy and states:

"Based on the assumption that this hybrid product is intended to be used for the same active substance as is on the market, but with different indication, the approval of the referred product should not result in an increase of the total quantity of diclofenamide released into the environment. Therefore, it should not result in increase of risk to the environment during storage, distribution, use and disposal."

3.2.2. Discussion on non-clinical aspects

No nonclinical studies have been provided with this application. The applicant refers to the reference product Fenamide. Essentially no bibliographic documentation on the nonclinical safety has been provided. According to the Italian agency, the approval of Fenamide was based on clinical data and bibliographical information. Thus, it appears that nonclinical safety data for diclofenamide do not exist. Nonclinical safety data to support this application are required. The data may be derived from bibliographical information or study reports. Nonclinical data on genotoxicity, carcinogenic potential and reproductive and developmental toxicity are essential. If further documentation on clinical safety can be provided, further studies on general toxicity are not warranted. **(MO)**

The applicant's justification for not performing an ERA is not accepted. This product is currently not marketed in Europe, and this application concerns a new indication, not previously subject to an MAA. Therefore, the position of the applicant that an approval would not result in an increase of exposure to the environment is not correct. An Environmental Risk Assessment in accordance with CHMP guidance should be provided. **(OC)**

3.2.3. Conclusion on non-clinical aspects

Ekesivy cannot be recommended for approval from a nonclinical point of view, since a Major Objection has been raised.

3.3. Clinical aspects

Tabular overview of clinical studies

The applicant submitted a single and multiple dose PK study in 36 healthy volunteers (DCPT-1531). This was an open-label, dose-escalation, Phase 1 study to assess the safety and to characterize the pharmacokinetics of dichlorphenamide. Diclofenamide at 25, 50, 100, 200, and 400 mg tablets was dosed twice daily using 6 cohorts of 6 subjects.

The Phase III program for dichlorphenamide (DCP) includes a single pivotal efficacy study (HYP-HOP). In addition, the applicant submitted a supportive literature study (Tawil et al, Ann Neurol. 2000; 47[1]:46-73).

Table 3: Overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase III	Tawil-et-al 2000	5.3.5.1	To test the efficacy of dichlorphcnamidc in the treatment of episodic weakness in the periodic paralyses.	Two multicenter randomised, double blind, placebo-controlled cross-over trials: one involving participants with HypoPP, and the other involving participants with PSPP. In each trial, two eight-week treatment periods were separated by a washout period of at least nine weeks; participants were their own controls.	Test: dichlorphenamide tablets, 50 mg BID (100 mg/day).	31 PSPP Subjects 42Hypo PP Subjects	Hyperkalemic Periodic Paralysis (HYP or PSPP – potassium sensitive PP)* and Hypokalemic Period Paralysis(HO P or HypoPP)	two eight-week treatment periods were separated by a washout period of at least nine weeks	Complete; eCTD Annals of Neurology 2000;47(1): 46–53
Phase III	HYP HOP	5.3.5.1	To assess whether dichlorphenamide (DCP) lowers the rate of attacks of weakness in subjects with Hyperkalemic periodic paralysis (HYP) and hypokalemic period paralysis (HOP) as measured by participant self-report over the last 8 weeks of a 9-week double-	Multi-center, two arm, double-blind, placebo-controlled, parallel group, 9-week trials to compare the effects of dichlorphenamide vs. placebo in subjects with HYP and HOP. The 9-week phase was followed by a 1-year open label extension of DCP.	Test: dichlorphenamide tablets, 50 mg BID (100 mg/day).	21 HYP Subjects; 44 HOP Subjects		9-week followed by 52-week extension phase	Complete; eCTD

3.3.1. Pharmacokinetics

The present hybrid application contained 2 nonclinical *in vitro* studies and 1 clinical study contributing with new pharmacokinetic information about diclofenamide:

1) **Study DCPT-1612** – "Hepatic Metabolism and Metabolites of Diclofenamide in Human Liver Microsomes".

2) **Study DCPT-1530** – "Cytohrome P450 Induction and Inhibition Assessment of Diclofenamide".

3) **Study DCPT-1531** – Open-label, single- and multiple-dose PK study in healthy volunteers.

Bioanalytical method

Plasma samples from clinical study DCPT-1531 were quantified by high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS). The bioanalysis was conducted at Bio Pharma Services Inc, 4000 Weston Road, Toronto, Ontario, Canada, M9L 3A2. The bioanalytical method was validated prior to quantification of study samples. Assay was validated over the concentration range of 1 -1000 ng/mL for diclofenamide. Chlorfenamide was used as an internal standard.

Pharmacokinetic data analysis

Applicant has performed non-compartmental PK analysis on data obtained from the clinical study DCPT-1531 conducted in healthy volunteers receiving single ascending doses (SAD) and multiple ascending doses (MAD) of diclofenamide. This was the only clinical study providing new PK data.

Subjects in the first five cohorts (n = 30; or 6 subjects per cohort A-E) received a single oral dose of diclofenamide on Day 1. Cohort E was dosed in sub-cohorts E1 and E2 (n=3 per each sub-cohort). Depending on the cohort, subjects have received a single dose of diclofenamide of either 25, 50, 100, 200 or 400 mg.

Single-Dose Cohorts:

Cohort	Cohort Cumulative Days	Study Cumulative Days	Total Dose of Dichlorphenamide (# doses x dose/mg)
Cohort A	1-3	1	1 x 25mg = 25mg
Cohort B		2	1 x 50mg = 50mg
Cohort C		3	1 x 100mg = 100mg
Cohort D		4	1 x 200mg = 200mg
Cohort E1		5	1 x 400mg = 400mg
Cohort E2		9	1 x 400mg = 400mg

On the Day 3 (or Day 4 for cohort E), same study subjects were enrolled in a multiple-dose phase according to the table below. In this phase subjects have received a twice daily dose (tau=12h) of diclofenamide every day according to the cohort schedule, except on the last cohort day when the subjects have received one dose. The total number of doses for each subject in the multiple-dose phase was 9.

Multiple-Dose Cohorts:

Cohort	Cohort Cumulative Days	Study Cumulative Days	Total Dose of Dichlorphenamide (# doses x dose/mg)
Cohort A	3-7	3 - 7	9 x 25mg = 225mg
Cohort B		4 - 8	9 x 50mg = 450mg
Cohort C		5 - 9	9 x 100mg = 900mg
Cohort D		6 - 10	9 x 200mg = 1800mg
Cohort E1	4-8	8 - 12	9 x 400mg = 3600mg
Cohort E2		12 - 16	9 x 400mg = 3600mg

Figure 1. The mean plasma concentration profile for diclofenamide in linear scale plot (Single Ascending Dose).

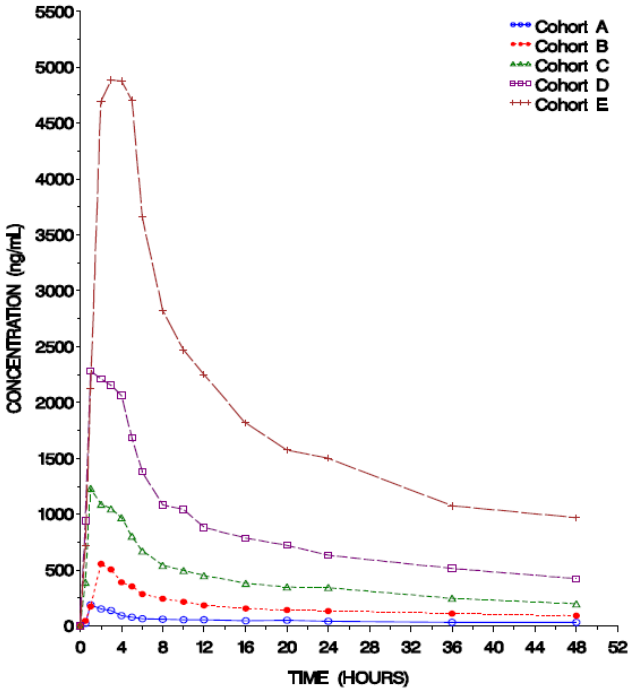


Figure 2. The mean plasma concentration profile for diclofenamide in semi-log scale (Single Ascending Dose).

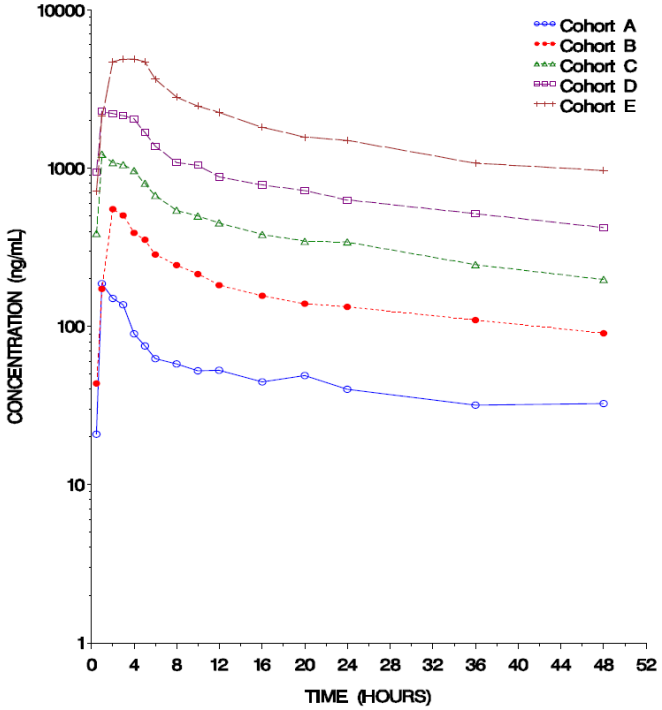


Figure 3. The mean plasma concentration profile for diclofenamide in linear scale plot (Multiple Ascending Dose).

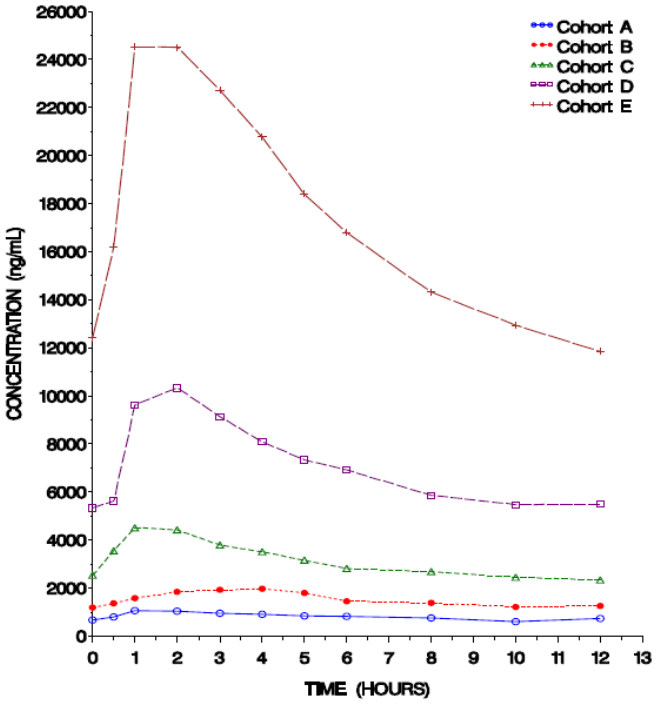


Figure 4. The mean plasma concentration profile for diclofenamide in semi-log scale (Multiple Ascending Dose).

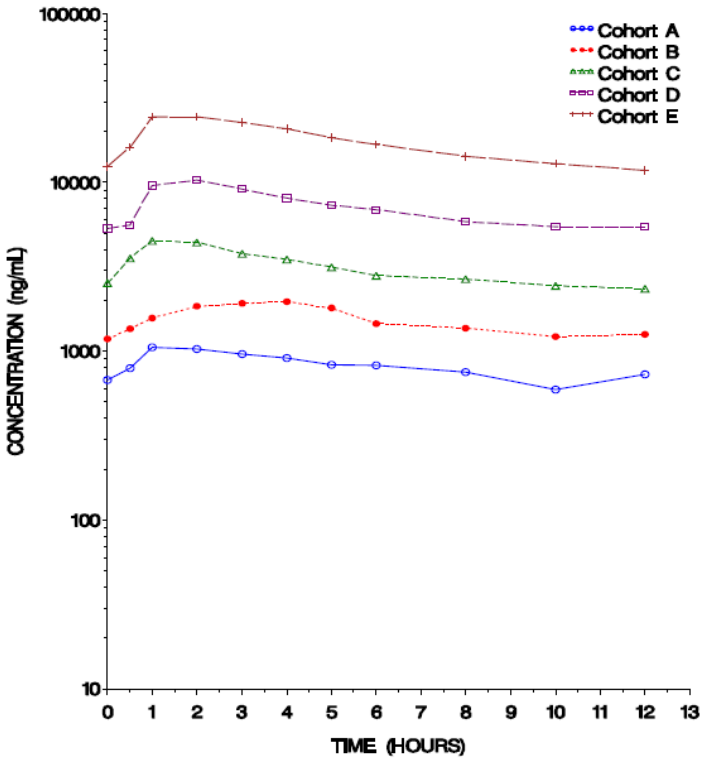


Table 4: Overview of PK parameters for diclofenamide obtained after single ascending dose (SAD) and multiple ascending dose (MAD)

Parameter	Cohort A 25 mg	Cohort B 50 mg	Cohort C 100 mg	Cohort D 200 mg	Cohort E 400 mg
SAD (dichlorphenamide)					
N=	6	6	6	6	6
Mean AUC_t (SD) (ng.h/mL)	2326.87 (731.08)	7896.93 (2055.10)	19118.64 (7317.16)	38131.96 (8248.89)	88243.08 (12615.58)
Mean AUC_{inf} (SD) (ng.h/mL)	4672.38 (1045.83)	14734.44 (4554.61)	28901.36 (13317.23)	66456.28 (26211.47)	143164.80 (17921.83)
Mean C_{max} (SD) (ng/mL)	297.63 (77.04)	709.02 (489.84)	1512.42 (909.27)	3029.64 (1209.3110)	6317.51 (1278.97)
Mean $T_{1/2}$ (SD) (h)	66.12 (23.56)	51.37 (23.92)	31.86 (11.39)	41.00 (17.29)	40.63 (7.12)
Median T_{max} (range) (h)	1.51 (1 - 3.12)	2.5 (2 - 5.02)	2 (1 - 4)	2 (0.5 - 4)	3 (2 - 5)
MAD (dichlorphenamide)					
N=	5	6	6	5	3
Mean AUC_{tau} (SD) (ng.h/mL)	10038.31 (3283.05)	18329.37 (6592.87)	37468.02 (13297.90)	84960.34 (34244.58)	207577.0 (62625.67)
Mean C_{max} (SD) (ng/mL)	1148.48 (239.16)	2219.37 (959.31)	4867.38 (1886.10)	10736.14 (4029.94)	26577.04 (5390.52)
Mean C_{min} (SD) (ng/mL)	726.47 (348.45)	1258.49 (410.31)	2341.43 (721.57)	5478.73 (2272.65)	11837.19 (6116.47)
Mean C_{avg} (SD) (ng/mL)	836.53 (273.59)	1527.45 (549.41)	3122.33 (1108.16)	7080.03 (2853.71)	17298.08 (5218.81)
Median T_{max} (range) (h)	2 (0.5 - 3)	3 (0.5 - 5)	1.5 (1 - 2)	2 (1 - 3)	1 (1 - 2)
Mean Flutuation (SD)	58.63 (42.35)	56.70 (22.40)	80.49 (25.93)	75.83 (16.73)	90.90 (28.36)
Mean Swing (SD)	75.31 (60.88)	69.66 (32.61)	108.24 (38.95)	99.11 (25.29)	148.92 (65.43)

Absorption and distribution

T_{max} obtained in study DCPT-1531 was in accordance with previously reported T_{max} for the reference product Fenamide. No further information about the absorption of diclofenamide is provided. There is no information on bioavailability nor the food influence on absorption of diclofenamide.

No data nor discussion on distributional aspects of diclofenamide are provided. Pharmacokinetic parameters relevant for distribution such as V, fu and blood-to-plasma concentration ratio are not known. No information about active transport of diclofenamide is available.

Elimination

Newly obtained half-life in the clinical study DCPT-1531 was in a range of 32-68 h, which was much longer in comparison to the half-life reported for the reference product Fenamide. There is no information available on CL of diclofenamide, neither as CL_R nor CL_H. No urine data were presented in order to evaluate contribution of urinary excretion for diclofenamide elimination.

Study DCPT-1612 implied no metabolism of diclofenamide *in vitro*.

Dose proportionality

There was more than proportional increase in AUC and C_{max} with increasing doses of diclofenamide, which was especially evident for AUC after the SAD study.

Table 5: Dose Proportionality Assessment of diclofenamide from dose range of 25 to 400 mg after SAD

Pharmacokinetic Parameter	Slope	95% CI for slope	Pvalue
LNAUCt	1.2859	1.1747 – 1.3972	<.0001
LNC_{max}	1.1101	0.9656 – 1.2545	<.0001

Table 6: Dose Proportionality Assessment of dichlorphenamide from dose range of 25 to 400 mg after MAD

Pharmacokinetic Parameter	Slope	95% CI for slope	Pvalue
LNAUCtau	1.0863	0.9172 – 1.2555	<0.0001
LNC_{max}	1.1331	0.9542 – 1.3120	<0.0001

Pharmacokinetics in target population

Pharmacokinetic data from target patient population is not available.

Pharmacokinetics in special populations

No data on pharmacokinetics in special patient populations is provided. According to the SmPC of Ekesivy, diclofenamide is contraindicated in patients with renal impairment and hepatic insufficiency.

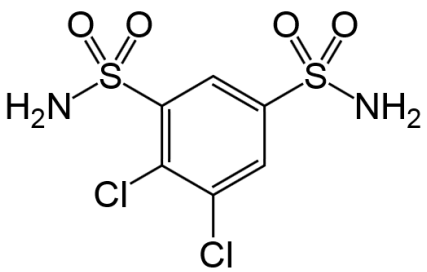
Interactions

In vitro study DCPT-1530 included experiments investigating diclofenamide's potential for the inhibition and induction of CYP450 enzymes. Results indicated no inhibition (at diclofenamide concentrations of up to 25.6 µM) nor induction (at diclofenamide concentrations of up to 80 µM) of all tested CYP450 enzymes. Data on time-dependent inhibition of CYP450 enzymes were not presented. No measurements of mRNA levels in the CYP450 induction experiments were performed.

No data about diclofenamide interactions with transporter proteins are available.

3.3.2. Pharmacodynamics

Diclofenamide (4,5-dichlorobenzene-1,3-disulfonamide) is a sulfonamide and a carbonic anhydrase inhibitor of the meta-disulfamoylbenzene class with the following structural formula:



The precise mechanism by which dichlorphenamide exerts its therapeutic effects in patients with periodic paralysis is unknown. Carbonic anhydrase inhibitors increase the removal of bicarbonate, sodium and potassium through the urine. This increases the acidity of the body (metabolic acidosis),

which may help normalise the function of the ion channels in muscle cells, thus regulating muscle contraction.

No PD or PK/PD studies were conducted by the applicant.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

In general, many important pharmacokinetic aspects of diclofenamide are insufficiently described, and many relevant pharmacokinetic parameters are not available. Applicant was referring to Fenamide as a reference product, which was approved for the treatment of glaucoma in 1960 when many aspects of modern pharmacokinetics were not required or not known. In addition, certain discrepancies between Ekesivy and the reference product Fenamide (e.g. large differences in half-life) were unexpectedly discovered by the applicant in the present application, which implies uncertainties and questions the relevance of the reference product. Therefore, the present hybrid application needs to be updated with detailed and precise summary of clinical pharmacology which will clearly discuss all relevant pharmacokinetic aspects of diclofenamide, and which will clarify data sources that could be based either on the published scientific literature, reference product or newly obtained experimental data. Furthermore, new additional data on insufficiently characterised pharmacokinetic aspects/parameters may be required (**LoQ**).

The link to the reference product Fenamide has not been discussed in the application. The applicant has not addressed whether the formulation of the test product, Ekesivy, is expected to result in the same plasma exposure as the reference product, Fenamide. In case the applicant wishes to refer to data from the reference product (e.g. regarding safety or pharmacokinetic aspects) the applicant needs to address the relative bioavailability between the two products, to support that data from the reference product are relevant to the current formulation **(LoQ).**

In the phase I study submitted, dicofenamide was quantified by LC-MS/MS method. However, some validation aspects need to be addressed in order to fulfil requirements of EMA's guideline on bioanalytical method validation (**LoQ**).

Apart from T_{max}, there is no more information available regarding the process of diclofenamide's absorption. There is no information about the food influence on diclofenamide's absorption (**LoQ**).

Distribution of diclofenamide is not discussed and no relevant parameters are available, e.g. volume of distribution, plasma protein binding, blood-to-plasma concentration ratio (**LoQ**).

Elimination of diclofenamide is not well-described and many aspects are considered unknown. In the SmPC of the reference product Fenamide it says that: "Elimination as unchanged substance occurs through the renal excretion and reaches 80% within 12 hours. Complete elimination occurs within 24 hours." This would mean that the half-life of diclofenamide is roughly around 4-5 hours. However, in the current application, results from the clinical study conducted in healthy volunteers indicated half-life of diclofenamide even up to 68 h. This discrepancy makes the overall reliability of the data on Fenamide questionable. Moreover, applicant has removed information about the urinary excretion from the current SmPC in comparison to previous SmPC text of the reference product. Therefore, the exact contribution of urinary excretion and metabolism in the elimination of diclofenamide is unknown at present (**LoQ**).

Applicant has conducted *in vitro* studies where no CYP450 mediated metabolism of diclofenamide was detected. The experiments however had technical drawbacks (see Pharmacokinetics AR). In case further *in vivo* investigations cannot prove that diclofenamide is entirely excreted unchanged via kidneys, more data on its metabolism may be needed. In that case certain experimental aspects need

to be addressed in order to generate reliable experimental data and to provide comprehensive investigation of the metabolism of diclofenamide (**LoQ**).

Further clarification on data obtained after single and repeated dosing are needed in terms of accumulation index and time-dependency for diclofenamide (**LoQ**).

There is no data provided on the use of diclofenamide in special patient populations. However, use of diclofenamide is suggested to be contraindicated in patients with renal impairment and hepatic insufficiency. Further explanations on the use of diclofenamide in special populations are needed, and it needs to be clarified in the SmPC at which degree of renal and hepatic impairment specific considerations have to be taken (**LoQ**).

In vitro experiments conducted to investigate interaction potential of diclofenamide for the inhibition and induction of CYP450 enzymes were inadequate. According to the EMA's guideline, concentrations of up to 50 x unbound C_{max} need to be tested to examine drugs interaction potential *in vitro*. Since the unbound fraction of diclofenamide in plasma was not determined, the concentration cut-off to be tested is 50 x $C_{max,tot}$ (assumption of the worst-case scenario with fu=1). Therefore, new *in vitro* experiments with diclofenamide concentrations of up to 800 µM (see section 2.1.10. of the pharmacokinetic AR) need to be conducted (**LoQ**). In addition, certain aspects like investigation of TDI CYP inhibition, transporter inhibition and measurement of mRNA levels in the CYP induction experiments need to be performed (**LoQ**).

If further *in vivo* data suggest a role of active renal secretion, *in vitro* experiments investigating active renal transport proteins with diclofenamide need to be performed (**LoQ**).

Pharmacodynamics

The mechanism of action of carbonic anhydrase inhibitors in periodic paralyses is incompletely understood. According to a recent review article, the systemic acidosis due to these drugs may reduce patients' susceptibility to period paralysis. Enhanced opening of calcium-activated K channels or reduction of intracellular sodium accumulation has also been proposed (Statland et al. Muscle Nerve. 2018;57[4]:522-30).

No studies related to primary or secondary pharmacology, or pharmacodynamics interactions were conducted by the applicant.

Diclofenamide promotes kaliuresis and non-anion gap metabolic acidosis by increasing urinary excretion of bicarbonate. The proposed SmPC contains a contraindication and warnings related to the following safety issues:

-concomitant use of diclofenamide and high-dose acetylsalicylic acid (sections 4.3 and 4.4)

-risk for hypokalemia when diclofenamide is used in patients with conditions associated with hypokalemia or other drugs that may cause hypokalemia (section 4.4).

Concomitant use of diclofenamide with other drugs that cause metabolic acidosis may increase the severity of metabolic acidosis (section 4.4).

No discussion on genetic differences in PD response was provided by the applicant and literature data is limited to small studies and anecdotal reports. For example, in a retrospective study (Matthews et al. Neurology. 2011;77[22]:1960-4), a total of 74 patients with hypokalemic periodic paralysis were genotyped. Overall, 46% of the total patient cohort (34 of 74) reported benefit from acetazolamide. There was a greater chance of benefit in patients with mutations in the calcium channel gene CACNA1S (31 responded of 55 total) than in those with mutations in sodium channel gene SCN4A (3 responded of 19 total).

No studies addressing the relationship between plasma concentration and effect were conducted.

No dose-response studies were conducted.

3.3.4. Conclusions on clinical pharmacology

Pharmacokinetics

In general, the characterisation of diclofenamide pharmacokinetics appears inadequate. Many relevant pharmacokinetic aspects/parameters are considered unknown and need to be addressed further. In addition, the link between the current formulation and the reference product appears unclear.

Pharmacodynamics

No PD or PK/PD studies were conducted.

Carbonic anhydrase inhibitors have been used empirically for the treatment of periodic paralysis. The mechanism of action is incompletely understood.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

No dose response studies were conducted.

The doses and twice-daily dosing regimen studied in the pivotal HYP-HOP study (see below) were chosen on the basis of the known posology, pharmacokinetics and adverse effects information, as presented in the SmPC for the reference product and the efficacy and safety results reported by the supportive literature study (Tawil et al, 2000).

The currently proposed posology section 4.2 states the following:

Initiate dosing at 50 mg twice daily. The initial dose may be increased or decreased based on individual response, at weekly intervals (or sooner in case of adverse reaction). The maximum recommended total daily dose is 200 mg. Prescribers should evaluate the patient's response to diclofenamide after 2 months of treatment to decide whether diclofenamide should be continued.

The recommendation for a maximum total daily dose of 200 mg refers to the single and multiple dose PK study in 36 healthy volunteers (DCPT-1531). This was an open-label, dose-escalation, Phase 1 study to assess the safety and to characterize the pharmacokinetics of dichlorphenamide. Diclofenamide at 25, 50, 100, 200, and 400 mg tablets was dosed twice daily using 6 cohorts of 6 subjects (see Clinical Pharmacology section). Twenty-four subjects reported at least 1 adverse event; 18 of these subjects were receiving more than 200 mg/day.

The 200 mg maximum dose is consistent with the maximum dose recommended for the reference product (Fenamide 50 mg tablets, for treatment of glaucoma).

In the proposed SmPC it is suggested to initiate dosing at 50 mg twice daily and then increase or decrease based on the individual response. There seems to be no documentation for this particular choice of dose for periodic paralysis. Furthermore, the rationale for allowing dose increases to 400 mg/day in the open-label phase of the study is not clear. The dose-response relationship should be further clarified. **(OC)**

Main study

Study HYP-HOP

Dichlorphenamide vs. Placebo for Periodic Paralysis

Study HYP-HOP was a Phase III, multicentre, randomized, double-blind, placebo-controlled parallel group study. This protocol was run as 2 separate (sub) studies, one in patients with hyperkalemic periodic paralysis (HYP) and one in patients with hypokalemic periodic paralysis (HOP). In each study, a 9-week double-blind treatment phase was followed by a one-year open label extension.

Methods

Study Participants

The pivotal HYP-HOP study was conducted at 10 sites in the United States, one site in the United Kingdom, and one site in Italy.

Enrolment criteria for HYP

The following diagnostic criteria were used for HYP:

1. Presence, in the subject or affected family member, of a mutation in the skeletal muscle sodium channel gene associated with HYP.
2. At least 2 attacks of tetraparesis or 1 attack with a family history of attacks of HYP.
3. Hyperkalemia, in the subject or affected family member, during a documented attack (spontaneous or induced).
4. Positive family history
5. Presence of myotonia or any 3 of the following clinical features:
   a. typical attack duration less than 2 hours
   b. onset before 30 years
   c. positive long exercise test (>40% decrement in CMAP)
   d. typical external triggers (rest after exercise, potassium load, fasting)
6. None of the following exclusions:
   a. unexplained long QT on ECG
   b. secondary HYP due to ingestion of potassium or of a potassium sparing diuretic
   c. adrenal insufficiency

Diagnostic categories

Genetically definite = 1 + 2 + 6

Clinically definite = 2 + (3 or 4) + 5 + 6

Clinically probable = 2 + 5 + 6

The following inclusion criteria were used for HYP patients:

All of the following criteria had to be met:

1. Genetically definite, clinically definite or clinically probable HYP as outlined above.
2. Male and female participants, age 18 and older who were able to comply with the study procedures.

3. Participants were required to have distinct regular episodes of weakness by history with an average frequency of ≥1 /week and <3/day either on or off treatment, whichever is higher.
4. Normal TSH and T4.
5. Pregnancy: Women: non-childbearing potential (i.e., postmenopausal or surgically sterile) or had to meet all of the following conditions:

   a. Use a medically accepted contraceptive regimen for at least 30 days before the baseline visit and agree to continue such use throughout the duration of the study and for 30 days after the final dose of study drug. Women had to be given a pregnancy test unless they were at least 2 years postmenopausal or surgically sterile.

The following exclusion criteria were used for HYP patients:

None of the following could be present:

1. Evidence for Andersen-Tawil syndrome (any one of the following 3 criteria)
   a. Prolonged QT interval or complex ventricular ectopy between attacks
   b. KIR 2.1 gene mutation
   c. Distinctive physical features (2 out of 5)
      - Low set ears
      - Short stature
      - Hypo-/micro-gnathia
      - Clinodactyly
      - Hypo-/hypertelorism
2. Coincidental renal, hepatic, restrictive or obstructive lung disease, active thyroid, or heart disease
3. Chronic, non-congestive, angle-closure glaucoma
4. Use of any of the following medications for reasons other than treatment of periodic paralysis: diuretics, antiarrhythmics, corticosteroids, beta-blockers, calcium channel blockers, antiepileptics, magnesium
5. History of life-threatening episodes of respiratory muscle weakness or cardiac arrhythmias during attacks
6. History of worsening symptoms with the use of CAI's
7. Any other neuromuscular disease

<u>Enrolment criteria for HOP</u>

The following diagnostic criteria were used for HOP:

1. Presence, in the subject or affected family member, of a mutation in the CACNLA3 gene or skeletal muscle sodium channel genes associated with HOP.
2. At least 2 attacks of tetraparesis or 1 attack with a family history of attacks of HOP.
3. Hypokalemia, in the subject or affected family member, during a documented attack (spontaneous or induced)
4. Positive family history
5. All of the following clinical features:

a. typical external triggers (rest, rest after exercise, carbohydrate load)
b. onset before 30 years of age
c. positive response to oral potassium intake
d. typical duration greater than 2 hours
e. positive long exercise test (>40% decrement in CMAP)

6. None of the following forms of secondary HOP: hyperthyroidism, renal and adrenal dysfunction, laxative abuse, diuretics abuse

Diagnostic categories

Genetically definite = 1 + 2 + 6

Clinically definite = 2 + (3 or 4) + 5 + 6

Clinically probable = 2 + 5 + 6

The following inclusion criteria were used for HOP patients:

All of the following criteria had to be met:

1. Genetically definite, clinically definite or clinically probable HOP as outlined above.
2. Male and female participants, age 18 and older who were able to comply with the study procedures.
3. Participants were required to have distinct regular episodes of weakness by history with an average frequency of ≥1 /week and <3/day either on or off treatment, whichever is higher.
4. Normal TSH and T4.
5. Pregnancy: Women: non-childbearing potential (i.e., postmenopausal or surgically sterile) or had to meet all of the following conditions:
   a. Use a medically accepted contraceptive regimen for at least 30 days before the baseline visit and agree to continue such use throughout the duration of the study and for 30 days after the final dose of study drug. Women had to be given a pregnancy test unless they were at least 2 years postmenopausal or surgically sterile.

The following exclusion criteria were used for HOP patients:

None of the following could be present:

1. Known mutation in the α subunit of sodium channel.
2. Evidence for Andersen-Tawil syndrome (any one of the following 3 criteria)
   a. Prolonged QT interval or complex ventricular ectopy between attacks
   b. KIR 2.1 gene mutation
   c. Distinctive physical features (2 out of 5)
      • Low set ears
      • Short stature
      • Hypo-/micrognathia
      • Clinodactyly
      • Hypo-/hypertelorism
3. Coincidental renal, hepatic, active thyroid disease, restrictive or obstructive lung disease, or heart disease
4. Chronic, non-congestive, angle-closure glaucoma

5. Use of any of the following medications for reasons other than treatment of periodic paralysis: diuretics, antiarrhythmics, corticosteroids, beta-blockers, calcium channel blockers, antiepileptics, magnesium
6. History of life-threatening episodes of respiratory muscle weakness or cardiac arrhythmias during attacks
7. History of worsening symptoms with the use of CAI's
8. Any other neuromuscular disease

The inclusion and exclusion criteria are overall considered acceptable. With regard to the exclusion criterion related to CAIs, it should be further clarified what is known today about which patients typically experience worsening of symptoms with intake of carbonic anhydrase inhibitors. **(OC)**

Also, it appears that patients with an intolerable number of attacks could have been excluded from participating in the study. It is not clear how many patients were subject to such exclusion and whether this could have created a selection bias. **(OC)**

For most HOP patients, the pathogenic mutation is located in the CACNA1S (Cav.1) gene. However, for some patients, it is SCN4A (e.g. Phillips, L. & Trivedi, J.R. Neurotherapeutics (2018) 15: 954. https://doi.org/10.1007/s13311-018-00678-0). In the current study, 3 HOP patients were enrolled with a sodium channel mutation. It should be clarified whether any other restrictions were implemented in the studies, e.g. for the sake of standardization. For example, known trigger factors in HOP patients include meals rich in carbohydrates whereas in HYP patients, ingesting small amounts of potassium could trigger an attack. **(OC)**

Treatments

For the first 9 weeks of the study, patients received either DCP or placebo. The dose depended on the dosage of periodic paralysis medication (if any) that the patient was taking at baseline, as summarized in the table below.

Table 7: Doses of study treatment based on medications taken before study start

Medication before start of study:	ACZ was taken by subject before study start	DCP was taken by subject before study start	No medication was taken by subject before study start
Study Dosage DCP/Placebo	20% of ACZ dosage before study start	DCP dosage before study start	50 mg, po bid

The rationale for the dosage equivalence between DCP and acetazolamide (ACZ) was empirical. Although the carbonic anhydrase inhibiting effects of DCP to ACZ are 30:1 in in vitro studies, how that translates into their relative in vivo potency is unclear. Most glaucoma studies comparing DCP to ACZ have used a 5:1 ratio.

The following procedure was used for reducing study drug dosage:

If patients experienced adverse effects that were intolerable, the site investigator reduced the dosage of study medication. Reductions were made in increments of 25 mg/bid from the DCP/Placebo bottle.

If AEs were still intolerable, and patients were in the 9-week phase, they were to be withdrawn from this phase, complete the visit scheduled for the end of the 9-week phase, and enter the open-label phase, in which all patients received active study medication.

Patients started the open-label phase at the same dosage that they were taking at the end of the 9-week phase.

Temporary dose suspensions were not permitted. If study drug was discontinued, patients continued to be followed for the entire 61 weeks.

In the open-label phase, if the patient reported no improvement, the dosage could be titrated upward as it would be in clinical practice. DCP was titrated by increments of 25 mg bid (maximum dosage 400 mg/day). Titrations upward were made no more frequently than once a week.

Pill bottles were brought to each visit for a count to check on whether participants were taking the study medication at the appropriate dosages.

Prior and concomitant therapy

Doses of ACZ or DCP may have been taken prior to study start. All pre-study treatments for periodic paralysis were discontinued at baseline; however, HOP participants were allowed to continue to use KCl supplements on an as needed basis for the treatment of acute attacks of weakness.

Objectives

The primary objective of the study was to assess whether DCP lowers the rate of attacks of weakness in HYP and HOP participants as measured by participant self-report over the last 8 weeks of a 9-week double-blind period.

The secondary objectives in the 9-week double-blind phase were as follows:

- To test whether a larger percentage of placebo-treated HOP participants reach the endpoint of acute worsening (increase in attack frequency or severity necessitating withdrawal from the initial nine-week treatment period, as judged by the enrolling investigator) than of participants taking DCP.
- To test whether the mean scores from the physical health and mental health summary scales of the SF-36 are significantly higher in HYP and HOP participants taking DCP than in HYP and HOP participants taking placebo.

In the open-label phase the objective was to test whether, after 52 weeks of treatment with DCP, HYP and HOP participants had a positive mean change from baseline in composite strength measures and muscle mass during attack-free intervals.

Assumptions for the sample size calculation were based on data from the initial trials of DCP in HYP and HOP participants (Tawil et al, 2000). For the HYP subjects, the mean +/- SD of attack rates was assumed to be:

- 3.7 +/- 3.8 for participants on placebo and
- 1.8 +/- 3.1 for participants on DCP not reaching the endpoint of acute worsening

(Acute worsening was assumed to occur in 3/24 patients on placebo and 2/23 patients on DCP). For the HOP subjects, the mean +/- SD of attack rates for participants not reaching the endpoint of acute worsening was:

- 1.8 +/- 2.3 for participants on placebo and
- 1.0+/- 1.8 for participants on DCP

Also, 15/35 HOP participants (43%) was assumed to reach the endpoint of acute worsening while on placebo, compared to 5/35 HOP participants (14%) on DCP.

Sample size was calculated for a Wilcoxon rank sum test. The calculations were performed using simulations. In order to detect these effects of DCP (vs. placebo) with power >85%, sample sizes of 64 HYP participants (32 per group) and 48 HOP participants (24 per group) were required.

Outcomes/endpoints

The primary efficacy measure in the initial 9-week phase for both the HOP Subjects and the HYP subjects was the average number of attacks per week over the final 8 weeks of follow-up (attack rate), as self-reported by the participants using (initially) a hand-held electronic LogPad diary produced by PHT corporation. The mode of capture of attack data was changed part-way through the study to an IVR telephone diary.

Participants were provided with an IVR telephone diary template and were educated on how to use the IVR system and the information to be reported. Participants reported attack frequency, length and severity daily for at least 4 weeks following the screening visit.

The secondary efficacy variables were as follows:

- An intolerable increase in attack frequency or severity necessitating withdrawal from the initial nine-week treatment period (in the trial for participants with HOP).
- The severity-weighted attack rate as self-reported by the participants in electronic or telephone diaries, for which the severity for each attack was scored (ranging from 1 to 10). The severity-weighted attack rate was defined as the sum of average attack severity across all distinct attacks over the final 8 weeks (weeks 2-9) of the double-blind treatment period divided by the number of weeks that the subject was followed.
- The total attack duration per week, defined as the sum of attack durations across all distinct attacks over the final 8 weeks (weeks 2-9) of the double-blind treatment period divided by the number of weeks that the subject was followed.
- Measures of muscle strength (quantitative myometry and manual muscle testing) and muscle mass (DEXA).
- Changes in health-related quality-of-life as measured by SF-36v2 subscale and summary scores.

As attack duration was not specified as efficacy variable in the protocol or SAP, it appears that this efficacy variable was analyzed post-hoc. This should be clarified. **(OC)**

Randomisation and blinding (masking)

Subjects were randomly assigned to receive placebo or DCP during the 9-week double-blind phase in ratio 1:1. Randomization was performed using a web randomization process. The computer-generated randomization plans (one for HYP and one for HOP) included stratification by site and current treatment at baseline (yes/no) and blocking.

The study was conducted in a double-blind manner. The participants, the site investigators, and the Program Oversight and CTCC staff did not know the treatment assignment. All drug bottles were identical in appearance with the exception of bottle code number affixed to the outside of the bottle.

The placebo tablets were formulated to match the dichlorphenamide 50 mg tablets in appearance. Each tablet was designed to be split so as to allow a placebo match with a dichlorphenamide 25 mg dose, which may be administered. A pill cutter and a weekly pillbox were provided to each participant by the site coordinators. The pill cutters were necessary for participants who had to halve the tablets in order to meet their individual dosing requirements.

Further clarification is needed regarding the content of the placebo tablets and the study blind. Given that the active and placebo tablets in this study were uncoated and not over-encapsulated (as was the case in the supportive Tawil study) and considering also that some subjects were already familiar with or using DCP treatment prior to entering the study, it is not clear whether potential differences in e.g. taste or other characteristics between the active and placebo treatments could have affected the study blind. This may in turn potentially have affected study outcomes, e.g. the process of assigning 'acute worsening' status to patients. **(MO)**

Statistical methods

Analysis of the primary endpoint

The attack rate from diary data was compared between DCP and placebo using Wilcoxon rank sum test. Acute worsening was imputed as the worst rank. The test was not stratified.

A 95% confidence interval for group difference in median attack rate was computed using nonparametric bootstrap.

It should be clarified whether all patients who experienced acute worsening were imputed with the same value and how ties were handled. **(OC)** In addition, the performance of the Wilcoxon sum rank test depends on various parameters such as sample size, difference in means and degree of skewness. Further clarifications are requested. **(OC)**

Analysis of secondary endpoints

Severity-weighted attack rates and total attack durations per week were compared between the placebo and DCP groups using Wilcoxon rank sum tests and bootstrap-based confidence intervals. The severity-weighted attack rate was calculated from self-reported average scores of attack severity, defined as the sum of average attack severity across all distinct attacks over weeks 2-9 divided by the number of weeks that the subject was followed.

The endpoint of acute worsening (HOP subjects only), the treatment group comparisons were performed using Fisher's exact test.

This test was specified in the SAP but this should be clarified as the CSR mentioned a conditional logistic regression model. **(OC)**

For other secondary outcome variables such as composite strength measures (maximum voluntary isometric contraction testing (MVICT) and manual muscle testing (MMT) scores), muscle mass (DEXA), tests of cognition and mood and quality of life (2 summary scales and 8 subscales of the SF-36), an analysis of covariance model was used with treatment group as the factor of interest, center and pre-trial treatment (none, ACZ, DCP) as stratification factors, and the baseline value of the outcome variable as a covariate.

Analysis populations

Prior to protocol amendment #5 (20 August 2008), the study had been designed as a 3-arm trial using acetazolamide as active comparator. Five enrolled patients randomized to acetazolamide were excluded (see further below under Results).

In the SAP (Version 2.0, 15 June 2013) a modified intent to treat population is described. All randomized subjects were to be included as randomized except for some modifications. According to the SAP, these modifications were specified after unblinding of data.

- Subject 5209 did not meet inclusion criteria and was excluded from all analyses.

- Two subjects from the same family (subject 5202 and 5203) had their study drug switched with each other and were analysed as treated instead of as randomised. The reason given for this allocation was for interpretation of safety data.

The latter modification was specified after the unblinding of the data. The analysis of the two subjects from the same family as treated violates the ITT principle. The modifications to the analysis population appear to originate from having a single analysis population for safety and efficacy analysis. The applicant should re-analyse the main efficacy results using an ITT population where all randomized subjects that fulfilled the inclusion criteria are analysed as randomized. **(MO)**

Also, including more than one patient from the same family may not be appropriate, since statistical methodology relies on the assumption that study subjects are independent. It is not clear from the documentation if there are more patients that are similarly clustered. **(OC)**

No separate safety population was defined.

Subgroups

Subgroup evaluation has not been undertaken quantitatively in this study due to the limited number of subjects. Qualitative assessments have been conducted on attack rate, severity weighted attack rate and attack duration in relation to age (younger than 40 years or 40 years and older), gender, pre-trial drug treatment and skeletal muscle calcium channel mutations R528H and R1239H. These assessments were only made for HOP subjects where the population assessed was large enough to make these categorizations.

Multiplicity

There was one primary endpoint and two secondary variables listed for HYP/HOP respectively. There were also "additional secondary outcome variables" specified.

No multiple testing procedure was specified.

Missing data

According to the section Analysis of the Primary Outcome Variable in the SAP, patients who reach the endpoint of acute worsening or who submit no diary data will have an attack rate higher than any other observed during the trial imputed. In the section Changes from the Protocol in the SAP it is stated that missing diaries for the primary analysis will be assumed to correspond to the subject not having an attack. A secondary analysis is added in this section, where missing diaries were removed from the calculation of attack rate, severity- weighted attack rate, and weekly attack duration resulting in a correspondingly smaller denominator.

Supportive and sensitivity analyses

No supportive or sensitivity analyses of the primary endpoint were reported.

Interim analyses

There was no interim analysis for efficacy.

Overall, the documentation provided on the statistical methodology was sparse and inconsistent. The submitted SAP is dated after unblinding and it is not clear which analyses were specified before unblinding. The secondary endpoint attack duration was not specified in the original protocol or the amendments and the section about subgroup analyses appears to be written after the end of the study. The date for database lock should be clarified. Handling of missing data in the primary endpoint (diary data) is described differently in different parts of the SAP (and study report) and it is unclear

whether appropriate methods were used. This is considered a major concern in relation to the quality of the study documentation and conduct. **(MO)**

Results

The first patient was enrolled on 23 April 2007 with the last patient completed 5 May 2013.

The most recent version of the protocol is version 1.6 (2010-03-18). The original protocol is dated 2006-09-27, followed by version 1.1 (2006-11-08); version 1.2 (2006-12-01); version 1.3 (2007-03-08); version 1.4 (2008-03-21); and version 1.5 (2009-08-20).

In addition to the removal of the acetazolamide (ACZ) treatment arm, several other implemented protocol changes may have had a relevant impact on the study including changes to the randomization stratification plan and diagnostic criteria. A structured discussion of the various amendments to the protocol is requested, further explaining the rationale for relevant changes and their potential impact, if any, on the study results. **(OC)**

In addition, some study subjects may also have participated in the supportive Tawil et al. study. This should be clarified. **(OC)**

Participant flow

A total of ninety (90) subjects were screened. Nineteen (19) subjects were screen failures. The most common reasons for screen failure were diagnostic uncertainties, patients not meeting certain inclusion criteria or patients unwilling or unable to meet protocol and/or travel requirements.

A total of 71 subjects were enrolled. Five of these subjects were excluded from all safety and efficacy analyses as these subjects were enrolled prior to the amended protocol version 1.5 (2009-08-20) and had been randomized to acetazolamide (ACZ). Prior to this amendment, the HYP-HOP trial was designed as a 3-arm study and these 5 (HOP) subjects (#2002, 2108, 9541, 9783, and 2401) had been randomized to treatment with acetazolamide (ACZ). In addition, one additional HOP subject (5209) was excluded from all analyses as he did not meet the inclusion criteria.

The remaining modified ITT population included in the summary tables below includes 21 HYP and 44 HOP patients. Of these, one HYP patient (2503) had been randomized to placebo during the 9-week blinded treatment phase and subsequently to ACZ for the extension phase. The data from this subject was subsequently only included with regard to the 9-week treatment phase.

Of the 21 enrolled HYP subjects, 4 (19%) withdrew from therapy over the course of the study, 3 during the blinded phase and 1 during the open-label phase. Three of the withdrawals were due to AEs, in all 3 cases while on active treatment with DCP.

Acute worsening was defined as an increase in attack frequency or severity necessitating withdrawal from the initial 9-week treatment period, as judged by the enrolling investigator.

In the HYP group,9 patients on DCP and 7 placebo patients completed the full 9-week double-blind phase as planned; 2 subjects randomized to placebo treatment experienced intolerable attacks and met the ‘acute worsening criteria’. These subjects were removed from the 9-week treatment phase and immediately started the 52-week open label treatment phase with DCP.

Patients with acute worsening received an imputed attack rate higher than any other observed during the trial (see table below).

Table 8: Disposition of HYP subjects

	DCP (N = 12)	Placebo (N = 9)	All (N = 21)
Completed 9-Week Phase	9 (75.0%)	9 (100%)	18 (85.7%)
Reached Endpoint of Acute Worsening[b]	0 (0.0%)	2 (22.2%)	2 (9.5%)
Withdrew from 9-Week Phase	3 (25.0%)	0 (0.0%)	3 (14.3)
Primary Reason for Withdrawal Adverse Event Withdrew Consent	 2 (66.7%) 1 (33.3%)	 0 (0.0%) 0 (0.0%)	 2 (66.7%) 1 (33.3%)
Entered 52-Week Open-label Extension Phase	9	8[a]	17[a]
Completed 52-Week Open-label Extension Phase	9	7	16
Withdrew from 52-Week Open-label Extension Phase	0	1	1
Primary Reason for Withdrawal Adverse Event	 0	 1	 1

[a] - Data from one subject was included in the 9-week phase, but not in the 52-week open-label extension phase as subject was randomized to ACZ in this phase.
[b] – Those subjects who reached the endpoint of acute worsening during the 9-week double blind phase had an early 9-week visit and moved directly to the 52-week open phase

Of the 44 enrolled HOP subjects, 13 (30%) withdrew from therapy over the course of the study, 3 during the blinded phase and 10 during the open-label phase. Most of the withdrawals were due to AEs during active treatment with DCP.

Overall, 22 patients on DCP and 14 placebo patients completed the full 9-week double-blind phase as planned. Five subjects randomized to placebo treatment experienced intolerable attacks and met the 'acute worsening criteria'. These subjects were removed from the 9-week treatment phase and immediately started the 52-week open label treatment phase with DCP.

Patients with acute worsening received an imputed attack rate higher than any other observed during the trial (see table below).

Table 9: Disposition of HOP subjects

	DCP (N = 24*)	Placebo (N = 20)	All (N = 44)
Completed 9-Week Phase	22 (91.7%)	19 (95%)	41 (93%)
Reached Endpoint of Acute Worsening[b]	0 (0.0%)	5 (25.0%)	5 (11.4%)
Withdrew from 9-Week Phase	2 (8.3%)	1 (5.0%)	3 (6.8%)
Primary Reason for Withdrawal			
Adverse Event	1 (50.0%)	0 (0.0%)	1 (33.3%)
Noncompliance	1 (50.0%)	0 (0.0%)	1 (33.3%)
Negative DNA Test	0 (0.0%)	1 (100.0%)	1 (33.3%)
Entered 52-Week Open-label Extension Phase	22	19	41
Completed 52-Week Open-label Extension Phase	17	14	31
Withdrew from 52-Week Open-label Extension Phase	5	5	10
Primary Reason for Withdrawal			
Adverse Event	5	3	8
Worsening Disease	0	2	2

[b] – Those subjects who reached the endpoint of acute worsening during the 9-week double blind phase had an early 9-week visit and moved directly to the 52-week open phase

*One subject (Subject ID #5209) completed the study, but was excluded from all analyses due to the protocol violation. The subject was enrolled against Inclusion Criteria #1.

Patients with acute worsening received an imputed attack rate higher than any other observed during the trial. Acute worsening was however judged by the enrolling investigator, but no standardized criteria were provided in the submitted documentation. This raises concern both regarding if it an appropriate level of clinical relevance is attributed to the event, and if there may have resulted in bias. It should be clarified what criteria were used to classify patients as having acute worsening. The 2 HYP and 5 HOP patients that met these criteria should be more fully described and the reason for early withdrawal clarified. **(MO)**

Baseline data

Baseline characteristics for the HYP and HOP subjects are summarized in the tables below.

Table 10: Baseline characteristics for HYP Subjects in the study

		DCP (N = 12)	Placebo (N = 9)	All (N = 21)
Age (Years)	N	12	9	21
	Mean (SD)	40.6 (10.3)	45.2 (17.7)	42.6 (13.7)
	Median	43.4	47.7	43.9
	Min, Max	19.5, 53.8	19.9, 68.2	19.5, 68.2
Gender				
Male	N (%)	6 (50.0%)	3 (33.3%)	9 (42.9%)
Female	N (%)	6 (50.0%)	6 (66.7%)	12 (57.1%)
Race				
White	N (%)	11 (91.7%)	6 (66.7%)	17 (81.0%)
Multiracial	N (%)	0 (0.0%)	1 (11.1%)	1 (4.8%)
Unknown	N (%)	1 (8.3%)	2 (22.2%)	3 (14.3%)
Treatment-Naïve				
Yes	N (%)	7 (58.3%)	4 (44.4%)	11 (52.4%)
No	N (%)	5 (41.7%)	5 (55.6%)	10 (47.6%)
Initial DCP Dosage (mg)	N	12	9	21
	Mean (SD)	95.8 (9.7)	83.3 (25.0)	90.5 (18.5)
	Median	100.0	100.0	100.0
	Min, Max	75.0, 100.0	50.0, 100.0	50.0, 100.0
Mutation				
Other Sodium Channel	N (%)	9 (75.0%)	5 (55.6%)	14 (66.7%)
Unknown	N (%)	3 (25.0%)	4 (44.4%)	7 (33.3%)
Attack Rate (missing diary = no attack)	N	11	9	20
	Mean (SD)	4.0 (4.0)	4.0 (2.9)	4.0 (3.5)
	Median	2.0	4.0	3.4
	Min, Max	0.0, 11.8	0.3, 8.3	0.0, 11.8

Attack Rate (missing diary not counted)	N	11	9	20
	Mean (SD)	6.1 (3.9)	5.2 (3.4)	5.7 (3.6)
	Median	7.0	6.6	6.8
	Min, Max	0.0, 12.2	0.3, 8.9	0.0, 12.2
Severity-weighted Attack Rate (missing diary = no attack)	N	11	9	20
	Mean (SD)	10.0 (12.2)	9.1 (8.1)	9.6 (10.3)
	Median	7.0	9.3	7.9
	Min, Max	0.0, 43.5	0.3, 26.3	0.0, 43.5
Severity-weighted Attack Rate (missing diary not counted)	N	11	9	20
	Mean (SD)	19.3 (18.1)	12.6 (11.8)	16.3 (15.6)
	Median	14.0	10.0	12.0
	Min, Max	0.0, 49.0	0.3, 38.7	0.0, 49.0
Manual Muscle Testing Score	N	12	9	21
	Mean (SD)	4.7 (0.3)	4.4 (0.5)	4.6 (0.4)
	Median	4.8	4.5	4.7
	Min, Max	4.1, 5.0	3.4, 5.0	3.4, 5.0

Table 11: Baseline characteristics for HOP Subjects in the study

		DCP (N = 24)	**Placebo (N = 20)**	**All (N = 44)**
Age (Years)	N	24	20	44
	Mean (SD)	44.8 (14.6)	44.0 (15.6)	44.5 (14.9)
	Median	45.5	44.5	45.0
	Min, Max	19.2, 76.2	18.9, 76.8	18.9, 76.8
Gender				
Male	N (%)	16 (66.7%)	16 (80%)	32 (72.7%)
Female	N (%)	8 (33.3%)	4 (20%)	12 (27.3%)
Race				
White	N (%)	20 (83.3%)	20 (100.0%)	40 (90.9%)
Multiracial	N (%)	1 (4.2%)	0 (0.0%)	1 (2.3%)
Unknown	N (%)	3 (12.5%)	0 (0.0%)	3 (6.8%)
Treatment-Naïve				
Yes	N (%)	6 (25.0%)	6 (30.0%)	12 (27.3%)
No	N (%)	18 (75.0%)	14 (70.0%)	32 (72.7%)
Initial DCP Dosage (mg)	N	24	20	44
	Mean (SD)	102.1 (44.8)	130.0 (101.8)	114.8 (76.5)
	Median	100.0	100.0	100.0
	Min, Max	25.0, 200.0	50.0, 500.0	25.0, 500.0

Mutation				
R528H	N (%)	10 (41.7%)	9 (45.0%)	19 (43.2%)
R1239H	N (%)	4 (16.7%)	4 (20.0%)	8 (18.2%)
Other Calcium Channel	N (%)	1 (4.2%)	1 (5.0%)	2 (4.5%)
Other Sodium Channel	N (%)	0 (0.0%)	3 (15.0%)	3 (6.8%)
Unknown	N (%)	9 (37.5%)	3 (15.0%)	12 (27.3%)
Attack Rate (missing diary = no attack)	N	24	19	43
	Mean (SD)	2.0 (2.3)	2.4 (2.2)	2.2 (2.2)
	Median	1.1	1.8	1.5
	Min, Max	0.0, 9.3	0.0, 7.0	0.0, 9.3
Attack Rate (missing diary not counted)	N	24	19	43
	Mean (SD)	3.0 (2.9)	3.9 (2.7)	3.4 (2.8)
	Median	2.2	4.2	3.1
	Min, Max	0.0, 12.3	0.0, 7.3	0.0, 12.3
Severity-weighted Attack Rate (missing diary = no attack)	N	24	19	43
	Mean (SD)	5.7 (6.7)	6.7 (6.1)	6.1 (6.4)
	Median	2.6	4.8	3.5
	Min, Max	0.0, 28.8	0.0, 22.8	0.0, 28.8
Severity-weighted Attack Rate (missing diary not counted)	N	24	19	43
	Mean (SD)	9.1 (9.2)	12.3 (10.7)	10.5 (9.9)
	Median	5.1	11.8	7.4
	Min, Max	0.0, 38.3	0.0, 42.0	0.0, 42.0
Manual Muscle Testing Score	N	24	20	44
	Mean (SD)	4.5 (0.5)	4.7 (0.3)	4.6 (0.4)
	Median	4.6	4.8	4.8
	Min, Max	3.3, 5.0	4.0, 5.0	3.3, 5.0

The characterization of the study population is considered to be unacceptably insufficient in particular in terms of treatment history. It is requested to clarify whether treatment-naïve means no history of prior treatment at all (such as potassium supplements), whether it means no history of prior treatment with carbonic anhydrase inhibitors, or whether treatment-naïve status pertains to a certain time period prior to entering the study. The prior treatment regimens of previously treated patients should be further described and summarized in more detail. It should also be clarified which subjects were already receiving DCP, and at what dose, at the time of enrolment into the study and to what treatment they were assigned. **(OC)**

The applicant is requested to clarify the respective diagnostic categories the patients were deemed to belong to on upon enrolment (genetically definite, clinically definite, or clinically probable) in relation to the detected mutations and patient characteristics. Reference is made to the inclusion criteria. **(OC)**

In addition, protocol deviations and any GCP noncompliance issues should be discussed. **(OC)**

Numbers analysed

A total of 21 HYP subjects were analysed for efficacy (9 placebo, 12 DCP).

A total of 44 HOP subjects were analysed for efficacy (20 placebo, 24 DCP).

Outcomes and estimation

Patients with HYP

Primary endpoint

The primary endpoint was the weekly attack rate, calculated over the final 8 weeks (Weeks 2-9) of the double-blind period.

For HYP patients, the baseline weekly attack rate was 4.0 (1.3, 6.0) median (interquartile range [IQR]) in subjects treated with placebo (N =9) and 2.0 (1.0, 7.5) in subjects treated with DCP (N = 11) (missing diary entries interpreted as no attack) (Table 14.2.2 of the CSR).

At week 9 of treatment (based on averages of weeks 2-9), the weekly attack rates were 4.8 (0.5, 7.1) in placebo and 0.9 (0.4, 1.5) in DCP treated HYP subjects respectively (missing diary entries interpreted as no attack).

The attack rate over the 9-week double blind phase of the study was not statistically different from placebo (**P=0.08**). In this analysis, 2 of the 9 subjects in the placebo group who had reached the endpoint of 'acute worsening' had been assigned an arbitrarily large attack rate.

Table 12: Treatment Effects on Diary Outcomes, Hyperkalemic Periodic Paralysis (HYP)

Variable	Treatment	Median (IQR)	Treatment Effect	95% CI	P-value
Attack rate[1]	DCP Placebo	0.9 (0.4, 1.5) 4.8 (0.5, 7.1)	-4.1	(NA, 0.9)	0.08
Attack rate[2]	DCP Placebo	3.9 (1.0, 6.9) 7.3 (6.2, 14.0)	-3.8	(NA, 3.3)	0.11
Severity-weighted attack rate[1]	DCP Placebo	1.0 (0.4, 2.9) 5.8 (1.4, 28.0)	-5.0	(NA, 1.2)	0.03
Severity-weighted attack rate[2]	DCP Placebo	3.1 (0.5, 14.9) 14.4 (7.1, 34.3)	-10.9	(NA, 7.2)	0.10
Weekly attack duration[1]	DCP Placebo	10.5 (2.5, 21.3) 39.4 (6.2, 139.4)	-25.8	(NA, 13.0)	0.26
Weekly attack duration[2]	DCP Placebo	21.7 (11.9, 73.8) 48.6 (13.6, 467.6)	-9.0	(NA, 46.2)	0.57

[1] Missing diary interpreted as no attack
[2] Missing diary interpreted as missing and not counted in the calculations

Treatment effect is computed as the median of the bootstrap distribution of the treatment group difference in median response. The 95% confidence interval (CI) is computed using the 2.5 and 97.5 percentiles of this bootstrap distribution. NA indicates that the 2.5 percentile of the bootstrap distribution of the treatment group difference in median response was not available because 2 out of the 9 subjects in the placebo group reached the endpoint of acute worsening and thus were assigned an arbitrarily large attack rate for purposes of analysis.

P-value is computed using a Wilcoxon rank sum test, with those who reached the endpoint of acute worsening (n = 2, both in the placebo group) assigned an arbitrarily large attack rate for purposes of analysis.

Over the 52-week unblinded treatment period, attack rate fell to 0.9 (0.0, 1.4) and 0.3 (0.1, 1.3) in placebo (N=7) and DCP treated HYP subjects (N=9), respectively at week 61 (averages of weeks 54-61) (missing diary entries interpreted as no attack).

In a secondary analysis, missing diary cards days were treated as days without data and the day removed from the calculation of attack rate (Table 14.2.3).

The baseline weekly attack rate was 6.6 (2.0, 7.6) median (interquartile range [IQR]) in subjects treated with placebo and 7.0 (3.0, 8.0) in subjects treated with DCP.

At week 9 of treatment (based on averages of weeks 2-9), the weekly attack rates were 7.3 (6.2, 14.0) and 3.9 (1.0, 6.9) in placebo and DCP treated HYP subjects respectively.

Statistical analysis of the data over the 9-week double blind phase, where attack rate is adjusted for missing diary days, shows that statistical significance was not reached for the reduction in attack rate during DCP treatment (**P=0.11**). Similarly, in this analysis, 2 of the 9 subjects in the placebo group who had reached the endpoint of acute worsening had been assigned an arbitrarily large attack rate.

Over the course of the extension treatment period, attack rate fell to 3.5 (0.0, 6.7) for placebo patients (N = 7) and was 5.4 (0.3, 7.0) in DCP treated HYP subjects (N = 9), respectively, at week 61 (averages of weeks 54-61).

The applicant should present a plot per treatment group showing the attacks per day per patient, indicating missing values and treatment discontinuations. **(OC)**

Intermediate missing values (missing diary entries) were imputed with a value higher than any other value observed during the trial. It should be clarified whether that value was chosen per patient or whether that value was the same for all intermediate missing data regardless treatment arm or previous attacks. **(OC)**

On the other hand, values from patients who drop-out from the study for other reasons than acute worsening were not imputed. Sensitivity analysis where the missing at random assumption is not applied should be provided, for example, placebo imputation or other methods. **(OC)**

The applicant is asked to investigate whether a negative binomial model that incorporates the stratification factors could be applied. Different strategies to handle missing unreported days, dropouts, and withdrawal due to acute worsening should be considered. **(OC)**

Supportive analyses using the per-protocol population should be presented. **(OC)**

Also, the DCP dose tested vs placebo depended on the baseline treatment and this is not accounted for in the analyses. The applicant should discuss this issue and present analyses for each baseline-treatment subgroup. **(OC)**

Also, patients were exposed to study drug for 9 weeks, but the first week of treatment was excluded from the analyses. This is not supported. Additional analyses for the primary and secondary endpoints, where the complete study period (9 weeks) are included should be presented. **(OC)**

Secondary endpoints from diary cards

Severity-weighted attack rate and duration of attack were used as secondary assessments of efficacy.

- **Severity-weighted attack rate**

The severity-weighted attack rate was calculated from self-reported scores of attack severity (scored as 1-10 with increasing severity) defined as the sum of average attack severity across all distinct attacks over the final 8 weeks (weeks 2-9) divided by the number of weeks that the subject was followed.

The baseline weekly severity-weighted attack rate was 9.3 (2.8, 12.3) in subjects treated with placebo (N = 9) and 7.0 (2.3, 13.5) in subjects treated with DCP (N = 11) (all values are median [IQR]) (missing diary entries interpreted as no attack) (Table 14.2.2 of the CSR).

At week 9 of treatment (averages of weeks 2-9), the weekly severity-weighted attack rates were 5.8 (1.4, 28.0) and 1.0 (0.4, 2.9) in placebo and DCP treated subjects, respectively (missing diary entries interpreted as no attack).

Statistical analysis of the data over the 9-week double blind phase of the study shows that the severity-weighted attack rate during DCP treatment was statistically different from that during placebo treatment (**P=0.03**).

In a secondary analysis, where attack rate is adjusted for missing diary days, statistical significance was not reached for the reduction in severity-weighted attack rate during DCP treatment (**P=0.10**).

- **Duration of attack**

The total attack duration per week was defined as the sum of attack durations across all distinct attacks over the final 8 weeks (weeks 2-9) divided by the number of weeks that the subject was followed.

The baseline weekly total attack duration was 21.5 (6.8, 49.8) hours in subjects treated with placebo and 51.8 (11.1, 79.2) in subjects treated with DCP (missing diary entries interpreted as no attack) (see Table 14.2.2). At week 9 of treatment (averages of weeks 2-9), the weekly total attack durations were 39.4 (6.2, 139.4) and 10.5 (2.5, 21.3) in placebo and DCP treated subjects, respectively.

Statistical analysis of the data over the 9-week double blind phase of the study shows that the attack duration during DCP treatment was not statistically different from that during placebo treatment (**P=0.26**);

In a secondary analysis, where attack rate was adjusted for missing diary days, attack duration during DCP treatment was not statistically different from that during placebo treatment **(P=0.57**).

Other secondary endpoints

Additional outcome variables for efficacy included changes from baseline to week 9 in the following:

- **Average MMT score**

The strength of each of 26 individual muscles was graded using a modified 13-point Medical Research Council scale ranging from 0-5.

The baseline average MMT score was 4.4 ± 0.5 in subjects treated with placebo and 4.7 ± 0.3 in subjects treated with DCP (mean ± SD). At week 9 of treatment, the change from baseline average MMT score was 0.00 ± 0.16 and 0.13 ± 0.26 in placebo and DCP treated HYP subjects, respectively. The 95% confidence interval and the P-value of 0.18 indicate that the increase in average MMT did not reach statistical significance.

- **Average MVICT scores and percent of predicted scores**

The strength of each of 10 muscles was measured using quantitative myometry and expressed either as the number of standard deviations from normal (Z-score) or the percent of predicted normal given the participant's age, gender, and height.

The baseline average MVICT Z-score was -2.9 ± 1.4 in subjects treated with placebo and -3.5 ± 2.4 in subjects treated with DCP (mean ± SD). At week 9 of treatment, the change from baseline average MVICT Z-score was 0.55 ± 0.76 and 0.78 ± 0.52 in placebo and DCP treated HYP subjects, respectively. The 95% confidence interval and the P-value of 0.44 indicate that the increase in average MVICT Z-score did not reach statistical significance.

The baseline average percent of predicted normal score was 68.8 ± 20.7 in subjects treated with placebo and 67.6 ± 26.3 in subjects treated with DCP. At week 9 of treatment, the change from

baseline average percent of predicted normal score was 10.17 ± 14.54 and 10.84 ± 8.27 in placebo and DCP treated HYP subjects respectively. No difference in the change from baseline average percent of predicted normal score was evident between the placebo and DCP treatments.

- **Lean body mass, as measured by dual-energy X-ray absorptiometry (DEXA)**

The baseline lean body mass was 46.6 ± 13.1 kg in subjects treated with placebo and 49.0 ± 12.7 kg in subjects treated with DCP (mean ± SD). At week 9 of treatment, the change from baseline lean body mass was -1.52 ± 1.47 kg and -1.31 ± 1.94 kg in placebo and DCP treated HYP subjects, respectively. The 95% confidence intervals and the P-value of 0.28 indicate that there was no significant difference between these changes.

- **Health-related quality of life scores as measured by the SF-36 (Version 2)**

Health-related quality of life scores were measured by the SF-36 (Version 2) questionnaire, including the physical and mental component summary scale and subscale scores. The baseline physical component summary score was 37.3 ± 11.7 in subjects treated with placebo and 41.0 ± 10.8 in subjects treated with DCP. The baseline mental component summary score was 45.9 ± 14.9 in subjects treated with placebo and 47.2 ± 9.7 in subjects treated with DCP. None of the health-related quality of life scores or subscores showed significant differences between treatments at week 9.

A number of clarifications related to the statistical analyses of the secondary endpoints are needed. **(OC)**

Changes from week 9 to week 61

Subjects completing weeks 35 and 61 were assessed for changes in MMT score, MVICT Z-score, and percent of predicted normal score; a total of 9 subjects treated with DCP and 8 subjects treated with placebo during the 9-week double blind phase were assessed at weeks 35 and 61. During this 52-week follow up period all subjects received DCP.

Subjects completing to week 61 were also assessed for changes in lean body mass using DEXA. A total of 9 subjects treated with DCP and 8 subjects treated with placebo during the 9-week double blind phase were assessed at week 61.

No relevant changes were observed.

In the open-label phase, if the patient reported no improvement, the dosage could be titrated upward. The applicant should discuss changes made to the DCP dosing during this phase. **(OC)** It is also not clear whether dose reductions or increases were accounted for in the analyses. **(OC)**

In addition, additional discussion is requested regarding the number of participating patients and duration of participation in the extension phase and how missing data and drop-outs were handled in the analyses. All patients who participated should be included in the analyses. **(OC)**

Patients with HOP

Primary endpoint

For HOP patients, the baseline weekly attack rate was 1.8 (0.5, 3.8) in subjects treated with placebo (N = 19) and 1.1 (0.5, 2.4) in subjects treated with DCP (N = 24) (missing diary entries interpreted as no attack) (see Table 14.2.30 of the CSR).

At week 9 of treatment (averages of weeks 2-9), the weekly attack rates were 2.4 (0.5, NA) and 0.3 (0.1, 1.6) in placebo and DCP treated HOP subjects, respectively. The upper quartile for the placebo group could not be calculated because more than 25% of placebo-treated subjects reached the

endpoint of acute worsening. Subjects who reached the endpoint of acute worsening during the 9-week double blind phase had an early 9-week visit and moved directly to the 52-week open phase.

Statistical analysis of the data over the 9-week double blind phase of the study shows that the attack rate during DCP treatment was significantly lower than that during placebo treatment (**P=0.02**); In this analysis, 5 of the 20 HOP patients in the placebo group who had reached the endpoint of acute worsening had been assigned an arbitrarily large attack rate.

Table 13: Treatment Effects on Diary Outcomes, Hypokalemic Periodic Paralysis (HOP)

Variable	Treatment	Median (IQR)	Treatment Effect	95% CI	P-value
Attack rate[1]	DCP Placebo	0.3 (0.1, 1.6) 2.4 (0.5, NA)	-2.2	(-6.8, -0.4)	0.02
Attack rate[2]	DCP Placebo	0.7 (0.2, 3.3) 4.4 (0.8, NA)	-3.9	(-7.4, -0.6)	0.02
Severity-weighted attack rate[1]	DCP Placebo	0.6 (0.2, 3.9) 5.7 (1.2, NA)	-5.2	(-25.2, -1.2)	0.02
Severity-weighted attack rate[2]	DCP Placebo	2.0 (0.6, 5.9) 8.7 (2.6, NA)	-7.9	(-25.6, -1.8)	0.03
Weekly attack duration[1]	DCP Placebo	2.7 (0.4, 13.4) 26.2 (4.0, NA)	-24.1	(-151.3, -4.6)	0.02
Weekly attack duration[2]	DCP Placebo	5.8 (0.6, 28.3) 32.3 (6.7, NA)	-29.1	(-148.3, -4.7)	0.02

[1] Missing diary interpreted as no attack
[2] Missing diary interpreted as missing and not counted in the calculations

NA indicates that the upper quartile of the distribution was not available because more than 25% of subjects in the placebo group reached the endpoint of acute worsening and thus were assigned an arbitrarily large attack rate for purposes of analysis.

Treatment effect is computed as the median of the bootstrap distribution of the treatment group difference in median response. The 95% confidence interval (CI) is computed using the 2.5 and 97.5 percentiles of this bootstrap distribution.

P-value is computed using a Wilcoxon rank sum test, with those who reached the endpoint of acute worsening (n = 5, all in the placebo group) or who did not provide post-baseline diary data (n = 1, DCP group) assigned an arbitrarily large attack rate for purposes of analysis.

Over the 52-week un-blinded treatment period, the attack rate was reduced to 0.2 (0.0, 1.0) and 0.0 (0.0, 0.1) in subjects treated with placebo (N = 14) and DCP (N = 17), respectively, at week 61 (averages of weeks 54-61) (missing diary entries interpreted as no attack).

The large number of missing diary entries is of concern. While no summary table of compliance of diary reporting was included in the CSR for HYP patients, the applicant provided one for HOP patients (inserted below). Only about 60% of the days did patients provide a diary entry. The clinical relevance of the primary outcome should be further substantiated in view of this. **(MO)**

HOP patients were allowed to continue using potassium supplements on an as-needed basis for the treatment of acute attacks of weakness. It is not fully clear whether treatment-naïve patients were using potassium supplements prior to randomization but presumably this was the case. The applicant should discuss this and describe whether there was an improvement in the need for potassium supplementation in this subgroup of patients who were randomized to DCP. **(OC)**

In a secondary analysis, missing diary cards were treated as days without data and the day removed from the calculation of attack rate (Table 14-2.31).

The baseline weekly attack rate was 4.2 (0.8, 6.5) median (interquartile range [IQR]) in subjects treated with placebo and 2.2 (0.9, 4.1) in subjects treated with DCP.

At week 9 of treatment (based on averages of weeks 2-9), the weekly attack rates were 4.4 (0.8, NA) and 0.7 (0.2, 3.3) in placebo and DCP treated HOP subjects respectively.

Statistical analysis of the data over the 9-week double blind phase, where attack rate is adjusted for missing diary days, is similar and the attack rate during DCP treatment was also significantly lower than that during placebo treatment (**P=0.02**). Similarly, in this analysis, 5 subjects in the placebo group who had reached the endpoint of acute worsening had been assigned an arbitrarily large attack rate.

Over the course of the extension treatment period, attack rate fell to 0.4 (0.0, 2.3) for placebo patients (N = 14) and 0.0 (0.0, 0.2) in DCP treated HOP subjects (N = 17), respectively, at week 61 (averages of weeks 54-61).

The applicant should present a plot per treatment group showing the attacks per day per patient, indicating missing values and treatment discontinuations. **(OC)**

Intermediate missing values (missing diary entries) were imputed with a value higher than any other value observed during the trial. It should be clarified whether that value was chosen per patient or whether that value was the same for all intermediate missing data regardless treatment arm or previous attacks. **(OC)**

On the other hand, values from patients who drop-out from the study for other reasons than acute worsening were not imputed. Sensitivity analysis where the missing at random assumption is not applied should be provided, for example, placebo imputation or other methods. **(OC)**

The applicant is asked to investigate whether a negative binomial model that incorporates the stratification factors could be applied. Different strategies to handle missing unreported days, dropouts, and withdrawal due to acute worsening should be considered. **(OC)**

Supportive analyses using the per-protocol population should be presented. **(OC)**

Also, the DCP dose tested vs placebo depended on the baseline treatment and this is not accounted for in the analyses. The applicant should discuss this issue and present analyses for each baseline-treatment subgroup. **(OC)**

Also, patients were exposed to study drug for 9 weeks, but the first week of treatment was excluded from the analyses. This is not supported. Additional analyses for the primary and secondary endpoints, where the complete study period (9 weeks) are included should be presented. **(OC)**

Secondary endpoints from diary cards

- **Severity-weighted attack rate**

The baseline weekly severity-weighted attack rate was 4.8 (2.3, 10.5) in subjects treated with placebo (N = 19) and 2.6 (1.9, 8.0) in subjects treated with DCP (N = 24) (all values are median (IQR)) (missing diary entries interpreted as no attack) (see Table 14.2.30).

At week 9 of treatment (averages of weeks 2-9), the weekly severity-weighted attack rates were 5.7 (1.2, NA) and 0.6 (0.2, 3.9) in placebo and DCP treated HOP subjects, respectively. The upper quartile for the placebo group could not be calculated because more than 25% of placebo-treated subjects reached the endpoint of acute worsening (missing diary entries interpreted as no attack).

While the use of a Fisher exact test for the comparison of the proportions is endorsed, it should be clarified how dropouts and intermediate missing values were handled. **(OC)**

Statistical analysis of the data over the 9-week double blind phase of the study shows that the severity weighted attack rate during DCP treatment was significantly lower than that during placebo treatment (**P=0.02**).

In a secondary analysis, where attack rate is adjusted for missing diary days, severity weighted attack rate during DCP treatment was significantly lower than that during placebo treatment (**P=0.03**).

- **Duration of attack**

The total attack duration per week was defined as the sum of attack durations across all distinct attacks over the final 8 weeks (weeks 2-9) divided by the number of weeks that the subject was followed.

The baseline weekly total attack duration was 13.5 (2.6, 47.5) in subjects treated with placebo and 9.3 (3.9, 14.8) in subjects treated with DCP (missing diary entries interpreted as no attack) (see Table 14.2.30). At week 9 of treatment (averages of weeks 2-9), the weekly total attack durations were 26.2 (4.0, NA) and 2.7 (0.4, 13.4) in placebo and DCP treated subjects, respectively.

Statistical analysis of the data over the 9-week double blind phase of the study shows that the attack duration during DCP treatment was significantly shorter than that during placebo treatment (**P=0.02**).

In a secondary analysis, where attack rate was adjusted for missing diary days, the attack duration during DCP treatment was significantly shorter than that during placebo treatment (**P=0.02**).

Other secondary endpoints

- **Average MMT score**

The baseline average MMT score was 4.7 ± 0.3 in subjects treated with placebo and 4.5 ± 0.5 in subjects treated with DCP (mean ± SD). At week 9 of treatment, the change from baseline average MMT score was -0.08 ± 0.15 and 0.05 ± 0.21 in placebo and DCP treated HOP subjects, respectively. The 95% confidence interval and the P-value of 0.08 indicate that the group difference in change in average MMT score was not statistically significant.

- **Average MVICT scores and percent of predicted scores**

The baseline average MVICT Z-score was -3.4 ± 1.4 in subjects treated with placebo and -3.3 ± 1.6 in subjects treated with DCP (mean ± SD). At week 9 of treatment, the change from baseline average MVICT Z-score was -0.27 ± 0.58 and -0.08 ± 0.92 in placebo and DCP treated HOP subjects, respectively. The 95% confidence interval and the P-value of 0.34 indicate that the group difference in change in average MVICT Z-score was not statistically significant.

The baseline average percent of predicted normal score was 70.2 ± 14.1 in subjects treated with placebo and 72.4 ± 18.3 in subjects treated with DCP (mean ± SD). At week 9 of treatment, the change from baseline average percent of predicted normal score was -2.94 ± 7.20 and -0.81 ± 11.27 in placebo and DCP treated HOP subjects, respectively. Group differences in change from baseline average percent of predicted normal score were not statistically significant.

- **Lean body mass, as measured by dual-energy X-ray absorptiometry (DEXA)**

The baseline lean body mass was 52.8 ± 11.8 kg in subjects treated with placebo and 51.4 ± 12.0 kg in subjects treated with DCP (all values are mean ± SD – Table 14.1.2). At week 9 of treatment, the change from baseline lean body mass was 0.44 ± 2.39 kg and -0.78 ± 1.65 kg in placebo and DCP treated HOP subjects, respectively (P-value of 0.05).

- **Health-related quality of life scores as measured by the SF-36 (Version 2)**

Differences in favour of DCP were observed in the physical component summary score and in five subscales.

Table 14: Change in SF36 from baseline to week 9

Scale	Adjusted group mean		Difference (DCP-Placebo)	95% CI for difference	p-value
	DCP	Placebo			
Physical component summary score	4.68	-2.61	7.29	(2.26, 12.32)	0.006
Mental component summary score	-0.96	-6.52	5.56	(-0.69, 11.81)	0.08
Physical functioning subscale	4.93	-6.94	11.87	(2.36, 21.38)	0.02
Role-physical subscale	14.62	-8.93	23.55	(10.51, 36.59)	0.0008
Bodily pain subscale	6.02	-12.25	18.27	(2.88, 33.66)	0.02
General health subscale	5.27	-3.60	8.88	(-1.00, 18.75)	0.08
Vitality subscale	2.43	-12.54	14.97	(4.48, 25.46)	0.006
Social functioning subscale	9.46	-12.81	22.26	(8.78, 35.74)	0.002
Role-emotional subscale	0.08	-10.72	10.81	(-2.77, 24.39)	0.12
Mental health subscale	-2.25	-9.68	7.43	(-2.36, 17.21)	0.13

A number of clarifications related to the statistical analyses of the secondary endpoints are needed. **(OC)**

Changes from week 9 to week 61

In subjects treated with DCP in the double-blind initial 9-week phase the change from week 9 MMT score values at weeks 35 and 61 were -0.04 ± 0.21 and 0.05 ± 0.18, respectively. In subjects treated with placebo during the 9-week double-blind phase the change from week 9 values at weeks 35 and 61 were 0.12 ± 0.19 and 0.10 ± 0.16, respectively. The change to week 61 for all subjects was statistically significant (P=0.04). None of the changes in MVICT Z score and percent predicted normal score were statistically significant.

In subjects treated with DCP in the double blind initial 9-week phase, the change in lean body mass from week 9 values at week 61 was -0.99 ± 1.97. In subjects treated with placebo during the 9-week double blind-phase the change from week 9 values at week 61 was -3.41 ± 3.90. The change between weeks 9 and 61 in DCP treated subjects was not statistically significant. In subjects treated with placebo in the 9-week double blind phase of the study and then treated with DCP for 52 weeks, the change in lean body mass was statistically significant (P=0.02).

In the open-label phase, if the patient reported no improvement, the dosage could be titrated upward. The applicant should discuss changes made to the DCP dosing during this phase. **(OC)**

It is also not clear whether dose reductions or increases were accounted for in the analyses. **(OC)**

In addition, additional discussion is requested regarding the number of participating patients and duration of participation in the extension phase and how missing data and drop-outs were handled in the analyses. All patients who participated should be included in the analyses. **(OC)**

Ancillary analyses

Subgroup analyses

Qualitative assessments have been conducted on attack rate, severity weighted attack rate and attack duration in relation to age (younger than 40 years or 40 years and older), gender, pre-trial drug treatment and skeletal muscle calcium channel mutations R528H and R1239H. These assessments were only made for HOP subjects where the population assessed was large enough to make these categorizations.

Given the limited sample size, no conclusions can be drawn.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15: Summary of efficacy for trial HYP-HOP

Title: Dichlorphenamide vs. Placebo for Periodic Paralysis			
Study identifier	<code>		
Design	A multi-center, double-blind, placebo-controlled, parallel group, nine-week trial to compare the effects of dichlorphenamide vs. placebo in HYP and HOP subjects.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		9 wks 4 wks 52 wks
Hypothesis	Superiority		
Treatments groups	**HYP Patients (N=21)** Dichlorphenamide (DCP)		DCP, 9 wks, N=12
	Placebo		Placebo, 9 wks, N=9
Endpoints and definitions	Primary endpoint	Weekly attack rate	Average number of attacks per week over the final 8 weeks of follow-up (wks 2-9) as self-reported by patients

	Secondary	Severity-weighted attack rate	Sum of average attack severity across all distinct attacks over weeks 2-9 of the double-blind treatment period divided by the number of weeks patient was followed
	Secondary	Total attack duration per week	Sum of attack durations across all distinct attacks over weeks 2-9 of the double-blind treatment period divided by the number of weeks that the patient was followed
Database lock	unknown		

Results and Analysis (HYP patients)

Analysis description	**Primary Analysis**		
Analysis population and time point	other: modified ITT		
Descriptive statistics and estimate variability	**HYP subjects**	**DCP**	**Placebo**
	Number of subjects	12	9
	Weekly attack rate (median [IQR])*	0.9 (0.4, 1.5)	4.8 (0.5, 7.1)
Effect estimate per comparison	Primary endpoint*	Comparison groups	DCP vs. placebo
		Treatment effect	-4.1
		95% CI	(NA, 0.9)
		P-value Wilcoxon rank sum test	0.08
Descriptive statistics and estimate	Weekly attack rate (median [IQR])**	3.9 (1.0, 6.9)	7.3 (6.2, 14.0)
Effect estimate per comparison	Primary endpoint**	Comparison groups	DCP vs. placebo
		Treatment effect	-3.8
		95% CI	(NA, 3.3)
		P-value Wilcoxon rank sum test	0.11
Notes	*missing diary data interpreted as no attack **missing diary data interpreted as missing and not counted In both analyses, 2 of 9 placebo subjects reached endpoint of acute worsening and were assigned an arbitrarily large attack rate.		

Results and Analysis (HOP patients)

Analysis description	**Primary Analysis**		
Analysis population and time point description	other: modified ITT		
Descriptive statistics and estimate variability	**HOP subjects**	**DCP**	**Placebo**
	Number of subjects	24	20
	Weekly attack rate (median [IQR])*	0.3 (0.1, 1.6)	2.4 (0.5, NA)
Effect estimate per comparison	Primary endpoint*	Comparison groups	DCP vs. placebo
		Treatment effect	-2.2
		95% CI	(-6.8, -0.4)
		P-value Wilcoxon rank sum test	0.02
Descriptive statistics and estimate variability	Weekly attack rate (median [IQR])**	0.7 (0.2, 3.3)	4.4 (0.8, NA)
Effect estimate per comparison	Primary endpoint**	Comparison groups	DCP vs. placebo
		Treatment effect	-3.9
		95% CI	(-7.4, -0.6)
		P-value Wilcoxon rank sum test	0.02
Notes	*missing diary data interpreted as no attack **missing diary data interpreted as missing and not counted In both analyses, 5 of 20 placebo subjects reached endpoint of acute worsening and were assigned an arbitrarily large attack rate.		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

No studies in special populations were conducted.

The proposed SmPC (section 4.2) states:

Elderly

The risk of falls and of metabolic acidosis is greater in elderly patients.

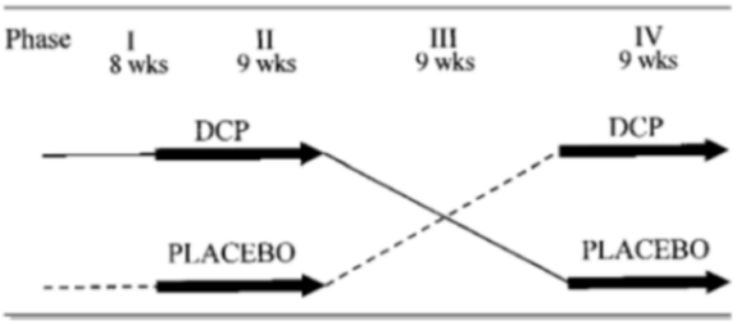
Paediatric population

Safety and effectiveness in pediatric patients have not been established.

Supportive study(ies)

As a supportive study, the applicant submitted a literature reference from a study published in 2000 with a study protocol dated from 1993 (Tawil et al, Ann Neurol. 2000; 47[1]:46-73).

The reference summarizes 2 multicenter, randomized, double-blind, placebo-controlled crossover trials, one in 42 subjects with hypokalemic periodic paralysis and one in 31 subjects with potassium-sensitive (hyperkalemic) periodic paralysis (PSPP). The study was organized by the Working Group on Periodic Paralysis (PP) and conducted at 7 sites in the United States to study the efficacy of DCP in the treatment of episodic weakness in primary periodic paralyses.



Three weeks before the end of the 8-week run-in period, subjects were randomly assigned to one of two treatment sequences (placebo/DCP or DCP/placebo). The active drug and placebo were crushed and repackaged into identical gelatine capsules, each containing 25 mg of active drug or placebo.

Subjects already taking ACZ during the run-in phase for treatment of their periodic paralysis were assigned to take DCP or placebo at one-fifth of their ACZ dosage in mg. Subjects taking DCP at baseline were assigned to continue with the same dosage of study medication. For all other subjects, the assigned dosage was 50 mg orally twice daily. During Phase III as during Phase I, subjects took their usual PP medication (pre-study treatment).

The primary outcome variable for PSPP was the attack rate. Secondary outcome variables included severity-weighted attack rate and the preferred treatment (Phase I, II, III or IV).

Data from the first week of each treatment phase (Phases II and IV) were omitted from the attack rate calculation to eliminate the possibility of a carry-over effect from Phases I and III in patients taking either DCP or ACZ at baseline.

The primary outcome variable in the HypoPP population was the occurrence of an intolerable increase in attack frequency or severity, necessitating withdrawal from the treatment phase as judged by the enrolling investigator in conjunction with the subject. Secondary outcome variables included attack rate, severity-weighted attack, and preferred treatment.

The subjects were analysed as randomised. However, analysis of the endpoint and attack rates was performed using a complete case analysis, including only subjects for whom data were available for both treatment points.

All tests were 2-tailed and used a significance level of 0.05. For the HypoPP trial, primary endpoint rates (occurrence of an intolerable increase in attack frequency or severity, necessitating withdrawal from treatment) were compared between DCP and placebo conditions by using the Mainland-Gart test for cross over data with the mid-p value method for approximation of the discrete distribution.

In the PPSP study, the primary endpoint was attack rate. Attack rates and severity-weighted attack rates were compared using Wilcoxon rank sum test. Subjects who reached the intolerable increase in attack rate endpoint were assigned the attack rate value of 99.

Thirty-one PSPP subjects were enrolled with 15 assigned to the placebo/DCP sequence and 16 to the DCP/placebo sequence. Twenty-four (77.4%) of the 31 randomized subjects completed both treatment phases. Of these, 21 either reached the endpoint or had complete diary data for attack rate determination.

Forty-two HypoPP subjects were enrolled, with 22 assigned to the placebo/DCP sequence and 20 assigned to the DCP/placebo sequence. Thirty-four of the 42 randomized subjects completed both treatment phases. Of these, 32 either reached the endpoint or had complete diary data for attack rate determination.

PSPP

For the 16 subjects who had attack rate data for both treatment phases, the mean improvement in attack rate on DCP relative to placebo was 2.3 ± 2.9 attacks per week (P = 0.006, Wilcoxon rank sum test). Five subjects reached the endpoint of acute worsening in one of the two treatment phases (2 while taking DCP and 3 while taking placebo). When these subjects were included in the analysis the treatment comparison remained significant (P = 0.04). The mean improvement in severity-weighted attack rate on DCP relative to placebo was 4.6 ± 5.7 (P = 0.003, Wilcoxon rank sum test). When subjects who reached the endpoint were included, the comparison remained significant (P = 0.02).

HypoPP

Of the 34 subjects who completed both treatment phases, 15 reached the endpoint in a treatment phase, including 2 who reached the endpoint in both phases. Of the 13 subjects who exhibited a preference, 11 subjects reached the endpoint while on placebo and 2 while on DCP (P = 0.02, Mainland-Gart test). Three other subjects reached the endpoint, 2 while on placebo and 1 while taking DCP, but withdrew from the trial before completing the other treatment phase.

For the 17 subjects who had attack rate data for both treatment phases, the mean improvement in attack rate on DCP relative to placebo was 0.9 ± 1.4 attacks per week (P = 0.02, Wilcoxon rank sum test). When subjects who reached the endpoint in at least one of the treatment phases were included in the analyses, the comparative improvement was also significant (P = 0.001). The mean improvement in severity-weighted attack rate for DCP relative to placebo was 1.1 ± 1.5 (P = 0.01, Wilcoxon rank sum test). When subjects who reached the endpoint in at least one of the treatment phases were included, the mean improvement was also significant (P = 0.007).

More details on this supportive study and a number of clarifications are requested. **(OC)**

3.3.6. Discussion on clinical efficacy

The applicant is seeking approval for Ekesivy (diclofenamide) 50 mg tablets. Dichlophenamide is a carbonic anhydrase inhibitor. The proposed indication is treatment of periodic paralysis. The proposed initial dose is 50 mg twice daily. The maximum recommended total daily dose is 200 mg.

Primary periodic paralyses are rare autosomal dominant genetic neuromuscular disorders associated with mutations in the skeletal muscle sodium, calcium and potassium channels. Primary period

paralysis is characterized by acute episodes of flaccid muscle weakness and variations in serum potassium levels. Primary periodic paralyses include hypokalemic paralysis, hyperkalemic paralysis and Andersen-Tawil Syndrome. There are also closely related diseases with overlapping features including paramyotonia congenital (PMC) and normokalemic periodic paralysis. Treatment options include avoidance of triggers, potassium supplementation to address hypokalemia. In addition, carbonic anhydrase inhibitors have been used as empiric treatment for both hypo and hyperkalemic periodic paralysis. The mechanism of action is not fully understood (Statland et al. Muscle Nerve. 2018;57[4]:522-30; Greig. Drugs. 2016; 76:501-7).

Ekesivy was designated as an orphan medicinal product EU/3/16/1677 on 27-06-2016. At the time of designation, periodic paralysis affected approximately 0.2 in 10,000 people in the European Union (EU).

The legal basis for the current application is an Article 10(3) hybrid application using Fenamide Tablets containing 50 mg dichlorphenamide as the reference product. Fenamide was authorised nationally in Italy with date of first authorisation on 19th February 1960. The therapeutic indication was treatment of all clinical forms of glaucoma. The authorisation was withdrawn on 2 October 2014, for marketing reasons.

There are no guidelines for the study of the treatment of periodic paralyses. No formal scientific advice was issued by CHMP for this medicinal product.

To support the efficacy of Ekesivy in the proposed indication, the applicant submitted a double-blind placebo-controlled trial (HYP-HOP).

In addition, the applicant submitted a supportive study in the form of a published literature reference (Tawil et al, Ann Neurol. 2000; 47[1]:46-73).

Design and conduct of clinical studies

No dose-response studies were conducted by the applicant. The proposed 50 mg twice daily dose is based on the supportive literature study by Tawil et al. in which this dosing regimen was used. In addition, the safety of dichlorphenamide maximum dose of 200 mg per day is supported by a small PK study DCPT-1531 in healthy volunteers and the posology in the Fenamide SmPC (one 50 mg tablet from one to four times daily).

The pivotal HYP-HOP study was a multi-center, double-blind, placebo-controlled, parallel group trial in adult subjects with a genetically definite, clinically definite or clinically probable diagnosis of hyperkalemic period paralysis (HYP) or hypokalemic periodic paralysis (HOP) conducted at sites in the United States (10), the United Kingdom (1) and Italy (1). The protocol was run as 2 separate (sub) studies, one in HYP and one in HOP patients.

The first treatment stage where subjects received either DCP or placebo lasted a maximum of 9 weeks. Following completion of the 9-week double-blind phase all subjects moved to the 52-week open label extension phase where all subjects received DCP. The patient's starting dosage depended on the dosage of periodic paralysis medication (DCP or ACZ, if any) that he or she was taking at baseline.

The primary analysis compared attack rates between groups in a pairwise fashion using Wilcoxon rank sum tests. Overall, 21 HYP and 44 HOP patients were included in the modified ITT population.

Some of the data in the pivotal HYP-HOP study suggests that treatment with DCP may be efficacious in treating patients with primary periodic paralysis. The primary endpoint of the trial, attack rate, was reduced following treatment with DCP, relative to placebo. The same was the case for some of the secondary endpoints, including severity weighted attack rate and attack duration. Statistical

significance was largely restricted to the HOP subjects but the HYP subject group included very few patients. HOP subjects also reported improvements in functional physical parameters. Reduction in rate, severity and duration of attack as well as improvements in QoL could be considered as potentially meaningful improvements for a patient population for which no approved treatment options exist.

However, major issues and other concerns have been identified related to the perceived quality of the documentation and conduct of the HYP-HOP study. These need to be addressed by the applicant (see the RSI for clinical MO and a listing of OCs);

- **The study blinding**

The active and placebo tablets in this study were uncoated and not over-encapsulated (as was the case in the supportive Tawil study). About half of the enrolled subjects were not treatment naïve and may have been using DCP prior to study start. Considering that thus a considerable portion of subjects were already familiar with or using DCP treatment prior to entering the study, it is not clear whether potential differences in e.g. taste or other characteristics between the active and placebo treatments could have affected the study blind for the patients and/or investigators. For example, paraesthesia is a characteristic, well known and frequently occurring ADR after treatment with ACZ and DCP and may have jeopardised the blinding.

Attack rate was the primary endpoint of the trial. Patients with acute worsening, as judged by the investigator, received an imputed attack rate higher than any other observed during the trial. No standardized criteria for acute worsening were included in the protocol. It appears conceivable that bias might be introduced by prior knowledge of assigned treatment affecting this type of evaluation.

- **Amendments to the study design**

The original protocol was dated 27 September 2006 and was followed by 6 amendments. The HYP-HOP study was initially a 3-arm trial including an acetazolamide (ACZ) treatment arm. Five subjects who were enrolled prior to this protocol implementation received ACZ during the blinded treatment phase and were excluded from the safety and efficacy analyses with no data provided. Several other protocol amendments were implemented including e.g. changes to the randomization stratification plan, changes to diagnostic criteria made and the possibility that patients previously enrolled in the supportive Tawil et al. study also participated in this HYP-HOP study. The rationale for the various amendments, date of implementation, and potential impact on study outcome needs to be discussed.

- **Documentation of the statistical analysis plan**

The submitted SAP is dated after unblinding and it is not clear from the documentation what analyses were specified before unblinding. The date for database lock could not be retrieved. Attack duration appears to be a post-hoc analysis. A SAP version dated prior to unblinding should be provided, together with a structured discussion of any relevant changes made, the implemented dates for these changes, and numbers of patients affected.

- **Extent of missing data**

The primary efficacy measure in the initial 9-week phase for both the HOP Subjects and the HYP Subjects was the average number of attacks per week over the final 8 weeks of follow-up (attack rate), as self-reported by the participants using (initially) a hand-held electronic LogPad diary produced by PHT corporation. The mode of capture of attack data was changed part-way through the study to an IVR telephone diary. Subjects were expected to provide daily self-report data on attacks throughout the 9-week double-blind treatment period, even if no attack occurred on a particular day. There was, however, a substantial amount of missing diary day entries for HOP patients, whereas no compliance data for HYP patients were included in the dossier at all. However, HOP patients on average only

reported approximately 60% of days with a diary entry, at baseline, during the double-blind treatment period as well as during the extension.

- **Handling of missing data**

Handling of missing data is inconsistently documented in different parts of the SAP and study report. Some sections state that missing diary entries were assumed to correspond to subjects no having an attack. Other sections state that patients with no data will have an attack rate higher than any other observed during the trial imputed. Yet additional, secondary analyses were performed where days with missing data were removed from any calculations. All together this leaves considerable uncertainty about what analysis is to be regarded as pre-specified and what methods were used in the actual analysis. The applicant should clearly outline, and justify with documentation, how missing diary data were handled, as well as missing data related to other efficacy variables and explain which analyses were prespecified and which ones, if any, were post-hoc analyses.

The applicant is also asked to submit supplementary sensitivity analyses challenging the assumptions of the used analysis method(s) and provide what appears to be the originally specified analysis, where participants who submitted no diary data are assigned an attack rate that was higher than any other observed during the trial.

- **Power of the study**

In order to detect effects of DCP (vs. placebo) in attack rate with power >85%, sample sizes of 64 HYP participants (32 per group) and 48 HOP participants (24 per group) were estimated to be required. However, the actual sample sizes were smaller, particularly for HYP. A total of only 21 HYP patients and 44 HOP patients were analysed for efficacy. Thus, in particular given the very small group of HYP patients enrolled, a thorough justification for including this subgroup in a treatment indication would be required.

- **Characterization of the enrolled study population**

The inclusion and exclusion criteria for HYP and HOP patients can overall be agreed (assuming some other concerns regarding the exclusion criteria are addressed). However, the respective diagnostic categories the patients were actually deemed to belong to on upon enrolment (genetically definite, clinically definite, or clinically probable) should be further clarified.

Also, patients' respective treatment history and concomitant treatments should be further clarified. For the first 9 weeks of the study, the participant's dosage depended on the dosage of periodic paralysis medication (if any) that the participant was taking at baseline, including DCP or ACZ. Approximately half of patients were treatment naïve but a clear definition of what this means is missing. Thus, it is not clear whether treatment naïve patients actually had a prior history of using carbonic anhydrase inhibitors or whether this pertains to a certain time period prior to entering the study. HOP patients were allowed to continued potassium supplements to treat their attack symptoms but it is not clear whether the use of these supplements, for example, can be assumed to have had a preventive effect on the rate or severity of additional attacks.

Efficacy data and additional analyses

The primary efficacy measure in the initial 9-week phase for both the HOP Subjects and the HYP subjects was the average number of attacks per week over the final 8 weeks of follow-up (attack rate), as self-reported by the participants. Secondary efficacy variables (descriptive endpoints) included an intolerable increase in attack frequency or severity necessitating withdrawal from the initial nine-week treatment period (in the trial for participants with HOP), severity-weighted attack rate, attack duration, measures of muscle strength and mass, and changes in health-related QoL (SF-36 v2).

In patients with HYP, statistical significance was neither demonstrated for the primary endpoint nor most of the secondary endpoints. Only 21 patients were enrolled (9 placebo, 12 DCP) and only 16 completed the 9-week double-blind treatment phase. The baseline weekly attack rate was 4.0 (1.3, 6.0) in subjects treated with placebo and 2.0 (1.0, 7.5) in subjects treated with DCP (median [IQR]). At week 9 of treatment (averages of weeks 2-9), the weekly attack rates were 4.8 (0.5, 7.1) and 0.9 (0.4, 1.5) in placebo and DCP treated HYP subjects respectively. This weekly attack rate showed a trend associated with DCP treatment (P=0.08) in the primary analysis but this was based on an analysis where missing data were non-conservatively imputed as 'no attack' and 2 out of the 9 subjects in the placebo group reached the endpoint of acute worsening and thus were assigned an arbitrarily large attack rate for purposes of analysis. Secondary analyses where missing diary cards days were removed from the calculations were not significant.

In patients with HOP, the primary endpoint in the trial, weekly attack rate, showed a statistically significant improvement with DCP treatment (P=0.02) over the course of 9 weeks, both in the primary and secondary analysis. The baseline weekly attack rate was 1.8 (0.5, 3.8) in subjects treated with placebo and 1.1 (0.5, 2.4) in subjects treated with DCP. At week 9 of treatment (averages of weeks 2-9), the weekly attack rates were 2.4 (0.5, NA) and 0.3 (0.1, 1.6) in placebo and DCP treated HOP subjects, respectively. The reduction in attack rate appeared to be maintained over the extension period. A secondary analysis where missing diary cards were removed from the analysis also showed a statistically significant reduction in attack rate with DCP treatment compared to placebo (P=0.02). However, 5 of the 20 placebo patients were assigned an artificially high attack rate as they reached a criterion of acute worsening.

Acute worsening was defined as an increase in attack frequency or severity necessitating withdrawal from the initial 9-week treatment period, as judged by the enrolling investigator. Identification of these subjects and further clarification as to whether any standardized criteria were applied is requested.

As also outlined above, as a significant proportion of diary data were missing, the handling of missing data is unclear, and additional sensitivity analyses are requested, no further conclusions can be drawn at this stage.

As an additional issue the applicant's analyses in this study appear to violate the ITT principle. One HOP subject (5209) was excluded from all analyses due to protocol violations. In addition, 2 subjects from the same family had their respective study drug switched and were analysed 'as treated' instead of 'as randomized'. It is considered that the main efficacy analyses should be generated using an ITT population.

In HOP patients, additional analyses of secondary endpoints of severity-weighted attack rate and attack duration showed that these were reduced by DCP treatment compared to placebo during the 9-week double blind phase of the study (both P=0.02). HOP subjects also reported improvements in functional physical parameters. However, these analyses should be viewed as descriptive. Also, attack duration appears to be a post-hoc defined efficacy outcome variable. Reduction in rate, severity and duration of attack as well as improvements in QoL could be considered as potentially meaningful outcome measures for a patient population for which no approved treatment options exist. However,

the clinical relevance of these reported improvements is currently not clear. In addition, for both substudies (HYP and HOP), the attack rate for DCP was already lower than placebo at baseline. This does not seem to have been taken into account in the analyses or interpretation of the results.

Subgroups for HOP patient related to age (younger than 40 years or 40 years and older), gender, pre-trial drug treatment and skeletal muscle calcium channel mutations R528H and R1239H were summarized. As the number of patients was small, no meaningful conclusions can be drawn.

In the open-label phase, if the patient reported no improvement, the dosage could be titrated upward. The applicant should discuss changes made to the DCP dosing during this phase for HYP and HOP patients.

As a supportive study, the applicant submitted a literature reference from a study published in 2000 with a study protocol dated from 1993. The reference summarizes 2 multicenter, randomized, double-blind, placebo-controlled crossover trials, one in 42 subjects with hypokalemic periodic paralysis (HypoPP) and one in 31 subjects with potassium-sensitive (hyperkalemic) periodic paralysis (PSPP). The primary outcome of the HypoPP trial was the occurrence of an intolerable increase in attack severity or frequency. The primary outcome in the PSPP trial was the number of attacks per week. In the HypoPP trial, 34 of the 42 subjects (81.0%) enrolled completed both phases of the trial. Of these, 13 showed a preference for one of the two treatments in terms of the endpoint (DCP or placebo) and 11 preferred DCP. In the PSPP trial, 24 of the 31 subjects (77.4%) completed both treatment phases. For 16 subjects who had attack rate data for both treatment phases, the mean improvement in attack rate on DCP relative to placebo (2.3 ± 2.9) was statistically significant.

As the study had a crossover design which included a return to baseline treatment in between the two study drug treatment phases as well as different primary endpoints for the respective hypo and hyperkalemic subgroups, the presence of various cross over effects cannot be excluded. Also, the relative datedness of this article, lack of source data, extent of missing data in a small sample size, and short treatment period likely limit the relevance of this study to support the pivotal HYP-HOP study. More details on this study and a number of clarifications are requested. **(OC)**

In conclusion, there are significant deficiencies in the quality of the submitted documentation, which raises uncertainties regarding the conduct and data analysis of the pivotal HYP-HOP study. Overall, these deficiencies are considered to preclude an adequate assessment of efficacy and include concerns about the study blind, criteria for acute worsening, documentation of the statistical analyses, and the extent and handling of missing data. Also, the clinical relevance of the reported improvements in attack rate, severity and duration of attack, as well as QoL should be further substantiated and justified. **(MO)**

In addition to the formulated fundamental concerns related in particular to the documentation and conduct of the pivotal HYP-HOP study, the proposed indication, treatment of periodic paralysis, is substantially broader than the population studied, which is 2 subgroups of patients with primary period analysis. Patients with secondary periodic paralysis (e.g. due to diuretics) have not been studied, nor patients with e.g. Andersen-Tawil syndrome. No paediatric patients were included in the studies. Accordingly, the wording of any indication should be limited to adults. Data in HYP patients were very limited and no statistically significant treatment effects were demonstrated. There is thus no clear indication that treatment with DCP in this population is beneficial. Overall, the indication should be further justified and revised as appropriate. It should be discussed whether further support for the HYP subgroup or other subgroups could be lent by extrapolation from the HOP patient population. **(MO)**

3.3.7. Conclusions on clinical efficacy

Major issues have been identified in relation to the quality of the submitted documentation which raises uncertainties regarding the conduct and data analysis of the pivotal HYP-HOP study. In addition, the clinical relevance of the reported outcome measures as well as the proposed indication are insufficiently justified. Also, a number of other concerns have been formulated (see List of Questions). These major issues and other concerns preclude a conclusion on clinical efficacy at current.

3.3.8. Clinical safety

Patient exposure

- **Study of healthy volunteers, PK study (DCPT-1531)**

In the study of 36 healthy volunteers 25 completed the study. Ten were withdrawn for AEs and 1 due to non-compliance. Withdrawal due to AE was associated with increased dose.

Table 16: Disposition of the 36 healthy volunteers

Cohort (number of *volunteers*)	**A** (n=6)	**B** (n=6)	**C** (n=6)	**D** (n=6)	**E** (n=6)	**F** (n=6)
Dose	25 mg x 2	50mg x 2	100 mg x 2	200 mg x 2	400 mg X 2	400 mg X 2
No of subjects treated	6	6	6	6	6	6
No of subjects withdrawn due to AE	0	0	0	1	3	6
No of subjects dismissed due to non-compliance	1	0	0	0	0	0

Source Clinical overview and clinical summary

The multiple-dose healthy volunteer PK study investigated not only those doses proposed for clinical use (maximum 200 mg/day) but also higher doses (up to 800 mg/day) to characterise the safety profile in that range.

Subjects in the first five cohorts (n=6 per cohort) received a total of 10 doses. (First and last day one dose and the other days two doses).

Based on the adverse events observed during the multiple dose phase of Cohort E, the investigator and sponsor agreed to add an additional cohort (Cohort F) using a dose titration approach. This cohort (also of 6 subjects) was dosed in accordance with the table below.

Table 17: Summary of healthy volunteers' total exposure in study DCPT-1531

Subject number	**Cohort**	**Total number doses**	**Daily dose**	**Total exposure**	**Completed study**	
					Yes	**No**
01-06	A	10 [a]	≤200mg	250 mg	5	1[a]
07-12	B	10		500 mg	6	
13-18	C	10		1000 mg	6	
19-24	D	10[b]		2000 mg	5	1[b]
25	E	1	>200mg	400 mg		1
26	E	1		400 mg		1
27	E	10		4000 mg	1	
28	E	10		4000 mg	1	
29	E	1		400 mg		1
30	E	10		4000 mg	1	
31	F	25	Ascending daily	6900 mg		1

32	F	19	doses	4500 mg		1
33	F	23		6100 mg		1
34	F	16		3300 mg		1
35	F	25		6900 mg		1
36	F	11		1500 mg		1

Source: Clinical summary table 15

[a] One of the patients in cohort A took only 6 doses (total exposure 150 mg) and dismissed due to non-compliance.
[b] One of the patients in cohort D took only 1 dose (total exposure 200 mg)

HYP-HOP study

Patients with HYP

In the 9-week double blind phase, the mean dosage of DCP was 77.1 mg/day and overall compliance with DCP was 91.1%. In the 52-week double blind phase, the mean dosage of DCP was 100 mg/day and overall compliance with DCP was 80.8 %.

Table 18: Summary of Study Drug Administration During the 9-Week Double Blind Phase and the 52-Week Extension Phase in HYP Subjects

Study Drug Administration During the 9-Week Double Blind Phase in HYP Subjects				
		Placebo (N=9)	DCP (N=12)	All (N=21)
Days on Treatment	N	9	12	
	Mean (days)	49.3	60.1	
	Median (days) Range (days)	64.0 8.0-67.0	64.0 12.0-78.0	
Week 9 Dosage	N	9	12	
	Mean (mg/day)	83.3	77.1	
	Median(mg/day) Range (mg/day)	100.0 50.0-100.0	87.5 0.0-100.0	
Overall Compliance	N	9	12	
	Mean (%)	95.1	91.1	
	Median (%) Range (%)	94.5 87.5-100.0	94.2 56.4-100.04	
Study Drug Administration During the 52-Week Extension Phase in HYP Subjects				
		"Placebo" (N=8)	DCP (N=9)	
Days on Treatment	N	8	9	17
	Mean (days)	363.6	368.6	366.2
	Median (days) Range (days)	362.5 357.0-371.0	371.0 314.0-425.0	364.0 314.0-425.0
Week 61 Dosage	N	7	9	16
	Mean (mg/day)	103.6	97.2	100.0
	Median (mg/day) Range(mg/day)	100.0 75.0-150.0	100.0 50.0-200.0	100.0 50.0-200.0
Overall	N	8	9	17
	Mean (%)	78.7	82.7	80.8

Compliance	Median (%) Range (%)	77.6 38.9-100.0	82.5 45.6-100.0	82.5 38.8-100.0

Source: Clinical Study Report-HYP-HOP Table 14 and 15

In the open label 52-week extension phase subjects in the "placebo" group were treated with placebo in the initial 9-week phase.

Patients with HOP

In the 9-week double blind phase, the mean dosage of DCP was 93.8 mg/day and overall compliance with DCP was 92.4 %. In the 52-week double blind phase, the mean dosage of DCP was 116.9 mg/day and overall compliance with DCP was 83.7 %.

Table 19: Summary of Study Drug Administration During the 9-Week Double Blind Phase and the 52-Week Extension Phase in HOP Subjects

Study Drug Administration During the 9-Week Double Blind Phase in HOP Patients				
		Placebo (N=20)	DCP (N=24)	All (N=44)
Days on Treatment	N	20	24	
	Mean (days)	53.1	62.8	
	Median (days) Range (days)	64.0 3.0-71.0	64.0 9.0-79.0	
Week 9 Dosage	N	20	24	
	Mean (mg/day)	107.5	93.8	
	Median(mg/day) Range (mg/day)	100 0.0-300.0	100 0.0-200.0	
Overall Compliance	N	20	24	
	Mean (%)	90.8	92.4	
	Median (%) Range (%)	97.9 44.4-100.0	99.0 49.2-100	
Study Drug Administration During the 52-Week Extension Phase in HOP Patients				
		"Placebo" (N=18)	DCP (N=22)	All (N=40)
Days on Treatment	N	18	22	40
	Mean (days)	332.5	313.6	322.1
	Median (days) Range (days)	364.0 78.0-430.0	363.5 25.0-371.0	364.0 25.0-430.0
Week 61 Dosage	N	14	17	31
	Mean (mg/day)	121.4	113.2	116.9
	Median (mg/day) Range (mg/day)	100.0 50.0-300.0	100.0 50.0-250.0	100.0 50.0-300.0
Overall Compliance	N	18	22	40
	Mean (%)	89.0	79.3	83.7
	Median (%) Range (%)	93.9 50.0-100.0	85.7 30.6-100.0	87.9 30.6-100.0

Source: Clinical Study Report-HYP-HOP Table 16 and 17

In the open label 52-week extension phase subjects in the "placebo" group were treated with placebo in the initial 9-week phase.

In the HYP-HOP trial daily doses could exceed the recommended daily dose of 200 mg/day. The applicant is requested to inform how many patients were treated with a daily dose of 50mg, 100mg, 200mg, 250mg and 300mg (OC).

The supportive study by Tawil et al.

This literature reference reported 2 multicenter, randomized, double-blind, placebo-controlled, crossover trials with DCP treatment, one trial in hypokalemic PP patients (HypoPP) and one in potassium-sensitive PP (PSPP) patients.

In each trial, two 8-week treatment periods were separated by a washout period of at least 9 weeks.

Forty-two patients with hypokalemic periodic paralysis were enrolled, with 22 assigned to the placebo/DCP sequence and 20 assigned to the DCP/placebo sequence.
Thirty-one patients with PSPP were enrolled, with 15 assigned to the placebo/DCP sequence and 16 assigned to the DCP/placebo sequence.

Table 20: DCP dosage in the HypoPP and PSPP patients

DCP dosage (%)	Hypo PP (N=42)	PSPP (N=31)
50mg/day	3 (7.1)	5 (16.1)
100mg/day	31 (73.8)	25 (80.6)
150mg/day	5 (11.9)	0
200mg/day	2 (4.8)	1 (3.2)
300mg/day	1(2.4)	0

Hypo PP=hypokalemic periodic paralysis.
PSPP= potassium sensitive periodic paralysis (including hyperkalemic PP and paramyotonia congenita with PP)

Summary of exposure

Healthy volunteers were exposed to increasing doses up to 400 mg x 2 with a total of 10 dosing occasions (some single patients on additional occasions). In the HYP-HOP study 16 HYP patients and 31 HOP patients completed the 52-week extension phase. Median dose in the extension phase was 100mg/day (range 50-300mg/day). Beyond that 73 patients (including patients with paramyotonia congenita) were included in the study by Tawil et al planned to be exposed for 8 weeks. The applicant is asked to inform how many patients were treated for at least 26 weeks and 52 weeks respectively and provide the total DCP exposure expressed as patient years. **(OC)**

Adverse events

- **Study of healthy volunteers, PK study (DCPT-1531)**

Thirty-six volunteers took part in the study of whom 24 reported at least one adverse event; 18 of these were receiving at least 200 mg/day. There was a clear association between increasing dose and numbers of AR reported. Totally 149 AEs were recorded, out of which 140 were classified as mild, seven as moderate and two were unclassified. A relationship to study medication was noted in 129 cases.

A total of 10 subjects were withdrawn from the study due to adverse events, one from a 200 mg twice-daily cohort and the other 9 from 400 mg twice-daily cohorts. One subject had a SAE (rash).

Table 21: Overview of all adverse events reported in healthy volunteers

Cohort	**A**	**B**	**C**	**D**	**E**	**F**
Dose (mg twice daily)	**25**	**50**	**100**	**200**	**400**	**400**
No of subjects treated	6	6	6	6	6	6
Total number of AEs*	1	3	16	36	42	50
No of AEs related to study medication	0	2	14	33	39	40
No of serious AEs	0	0	0	0	0	1
No of subjects with at least 1 AE	1	1	4	6	6	6
No of subjects with at least 1 related AE	0	1	3	6	6	6
No of subjects with at least 1 serious AE	0	0	0	0	0	1
No of subjects withdrawn due to AE	0	0	0	1	3	6

Source: Summary of Clinical Safety. Table 19
** the rapporteur finds the total number of AE to be 148.*

The most affected body system was the nervous system with 10 subjects reporting paraesthesia and 7 dizziness. Other events reported from the CNS were dysgeusia, headache, insomnia, irritability and mental impairment. Also, psychiatric symptoms (lethargy and euphoric mood) developed in the study population. Events frequently reported from other body systems were dyspnoea and blood potassium decreased.

The only AEs occurring at a dose less than or equal to the proposed maximum clinical dose (200 mg per day) were:

- Dyspepsia (1 case at 100 mg/day)
- Oral hypoaesthesia (1 case at 100 mg/day)
- Paraesthesia (2 cases at 200 mg/day)
- Blood potassium decreased (1 case at 200 mg/day)
- Pain in extremity (1 case at 200 mg/day)

HYP-HOP study

Patients with HYP

The table below presents an overview of adverse events reported by HYP patients. A total of 81 AEs were reported by 17 patients. 67 of the AEs were assigned as related by the investigator. Of the total AEs the majority were assessed as mild (31) or moderate (43) in intensity with 6 severe intensity events. Out of the total AEs the outcome was recovered for the majority (58) and 21 were under treatment or observation and the outcome for one AE was unknown.

There was 1 SAE (rash) in the 9-week double blind phase. This was in the DCP group and was considered related to treatment.

Table 22: Overview of all adverse events in HYP patients during the 9-week double blind and the 52-week extension period

Category[a]	Description	DCP (n=12**)		Placebo (n=9**)		Overall (n=21**)	
		No. events	% (No subjects)	No. events	% (No. subjects)	No. events	% (No subjects)
All AE		60	75 (9)	21*	89 (8)	81*	81 (17)
All related		38	67 (8)	12	67 (6)	50	67 (14)
All SAE		1	8 (1)	0	0	1	5 (1)
AE	Mild	22	50 (6)	9	78 (7)	31	62 (13)

Intensity	Moderate	32	75 (9)	11	67 (6)	43	71 (15)
	Severe	6	25 (3)	0	0	6	14 (3)
AE Outcome	Recovered	50	57 (8)	8	67 (6)	58	56 (14)
	Under	10	25 (3)	11	67 (6)	21	43 (9)
	Sequelae	0	0	0	0	0	0
	Fatal	0	0	0	0	0	0
	Unknown	0	0	1	11 (1)	1	5 (1)

source: summary of clinical safety table 21
[a] Subjects may fall in to more than 1 category
** For 2 AEs in the DCP group there was no AE related term recorded*
*** Numbers missing in summary of clinical safety table 21, inserted by the rapporteur.*

- **9-week double-blind phase**

The most common AEs were reported for the nervous system SOC. Of these the most common was paraesthesia. The only other AEs that occurred in more than one subject were nausea, weight decreased, confusional state and rash.

Table 23: Incidence of adverse events in HYP patients in the 9-week double-blind phase

System	AE	Relation to Study Medication	Placebo (N=9)	DCP (N=12)	All Subjects (N=21)
Gastrointestinal	Nausea	Possibly	0 (0.0%)	2 (16.7%)	2 (9.5%)
Investigations	Weight decreased	Unrelated	0 (0%)	1 (8.3%)	1 (4.8%)
	Weight decreased	Possibly	0 (0%)	1 (8.3%)	1 (4.8%)
Nervous	Paraesthesia	Probably	3 (33.3%)	5 (41.7%)	8 (38.1%)
	Paraesthesia	Possibly	0 (0.0%)	2 (16.7%)	2 (9.5%)
	Paraesthesia	Definitely	0 (0.0%)	1 (8.3%)	1 (4.8%)
Psychiatric	Confusional state	Possibly	0 (0%)	1 (8.3%)	1 (4.8%)
	Confusional state	Probably	0 (0%)	1 (8.3%)	1 (4.8%)
Skin	Rash	Possibly	0 (0%)	1 (8.3%)	1 (4.8%)
	Rash	Probably	0 (0%)	1 (8.3%)	1 (4.8%)

Source: summary of clinical safety table 24. The title of table 24 is "Incidence of adverse events in HYP patients in the HYP-HOP study, 9-week double blind phase" seems incorrect and don´t correspond to the text and table 14.3.1.2 in the CSR.

- **52-week extension phase**

In the 52-week extension period 12 of 17 subjects (70.6%) had AEs. The most common AEs were reported for the nervous system SOC. Of these the most common was paraesthesia. The only other AE that occurred in more than 1 patient was memory impairment. Relatively few AEs were reported from the HYP patients participating in a relatively long study (9+52 weeks). **(OC)**

Table 24: Incidence of adverse events in HYP patients in the 52- week open-label phase

System	AE	Relation to Study Medication	Placebo (N=8)	DCP (N=9)	All Subjects (N=17)
Nervous	Paraesthesia	Probably	4 (50.0%)	2 (22.2%)	6 (35.3%)
	Paraesthesia	Possibly	1 (12.5%)	1 (11.1%)	2 (11.8%)
	Paraesthesia	Definitely	0 (0%)	1 (11.1%)	1 (5.9%)
	Memory impairment	Possibly	1 (12.5%)	0 (0%)	1 (5.9%)
	Memory impairment	Probably	1 (12.5%)	0 (0%)	1 (5.9%)

Source: summary of clinical safety table 25. The title of table 25 is "Incidence of adverse events in HYP patients in the HYP-HOP study, 52-week open-label phase" seems incorrect and" don´t correspond to the text and table 14.3.1.9 in the CSR.
Subjects in the placebo group were treated with placebo in the initial 9-week phase and with DCP in the open label 52-week extension phase. The subjects in the DCP group were treated with active substance both in the initial 9-week and in the open label 52-week extension phase.

Patients with HOP

The table below presents an overview of adverse events reported by HOP patients. A total of 219 AEs were reported by 36 patients. 103 of the AEs were assigned as related by the investigator. Of the total AEs the majority was mild (163), 49 were moderate and there were 7 severe events. Of the AEs the majority (165) recovered, 53 were under treatment or observation and the outcome for 1 AE was unknown.

In total there were 4 SAEs. There was one SAE (humerus fracture) in the 9-week double blind phase, which was in the placebo group and was considered unrelated to treatment. There were 3 SAEs in the 52-week extension phase with 2 neoplasms (thyroid cancer and adenocarcinoma of pancreas) in the placebo group (treated with placebo the first 9-weeks and with DCP in the 52- week extension phase). These were considered unrelated to treatment, as well as one case of cauda equina syndrome.

Table 25: Overview of all adverse events in HOP patients during the 9-week double blind and the 52-week extension period

Category[a]	Description	DCP (n=24)		Placebo (n=20)		Overall (n=44)	
		No. events	% (No subjects)	No. events	% (No. subjects)	No. events	% (No subjects)
All AE		137	83 (20)	82	80 (16)	219	82 (36)
All related AE		62	75 (18)	41	60 (12)	103	68 (30)
All SAE		0	0 (0)	4	15 (3)	4	7 (3)
AE Intensity	Mild	103	71 (17)	60	70 (14)	163	70 (31)
	Moderate	31	67 (16)	18	55 (11)	49	61 (27)
	Severe	3	4 (1)	4	15 (3)	7	9 (4)
AE	Recovered	109	103 (20)	56	75 (15)	165	80 (35)

Outcome	Under treatment/observation	28	46 (11)	25	55 (11)	53	50 (22)
	Sequelae	0	0	0	0	0	0
	Fatal	0	0	0	0	0	0
	Unknown	0	0	1	5 (1)	1	2 (1)

Source: summary of clinical safety table 20
[a] Subjects may fall in to more than 1 category
** For 2AEs in the DCP group there was no AE related term recorded*

- **9-week double-blind phase**

In the 9-week double blind period 31 of 44 subjects (70.5%) had AEs with 24 of 44 subjects (54.5%) with related AEs. The most common AEs belonged to the nervous system SOC with the most common being paraesthesia and cognitive disorder.

Table 26: Incidence of adverse events in HOP patients in the 9-week double-blind phase

System	AE	Relation to Study Medication	Placebo (N=20)	DCP (N=24)	All Subjects (N=44)
Eye/Vision	Visual disturbance	Unlikely	1 (5.0%)	1 (4.2%)	2 (4.5%)
Gastrointestinal	Diarrhoea	Possibly	1 (5.0%)	1 (4.2%)	2 (4.5%)
General	Fatigue	Possibly	0 (0.0%)	2 (8.3%)	2 (4.5%)
	Fatigue	Probably	0 (0.0%)	1 (4.2%)	1 (2.3%)
Infections	Nasopharyngitis	Unrelated	2 (10.0%)	0 (0.0%)	2 (4.5%)
Injury/poisoning	Fall	Unlikely	2 (10.0%)	0 (0.0%)	2 (4.5%)
Musculoskeletal	Muscle spasms	Unlikely	0 (0.0%)	1 (4.2%)	1 (2.3%)
	Muscle spasms	Possibly	0 (0.0%)	2 (8.3%)	2 (4.5%)
	Muscle twitching	Unrelated	0 (0.0%)	1 (4.2%)	1 (2.3%)
	Muscle twitching	Unlikely	0 (0.0%)	1 (4.2%)	1 (2.3%)
Nervous	Cognitive disorder	Possibly	1 (5.0%)	2 (8.3%)	3 (6.8%)
	Cognitive disorder	Probably	1 (5.0%)	1 (4.2%)	2 (4.5%)
	Cognitive disorder	Definite	0 (0.0%)	2 (8.3%)	2 (4.5%)
	Headache	Unlikely	1 (5.0%)	1 (4.2%)	2 (4.5%)
	Headache	Unrelated	0 (0.0%)	1 (4.2%)	1 (2.3%)
	Headache	Possibly	0 (0.0%)	2 (8.3%)	2 (4.5%)
	Paraesthesia	Unrelated	0 (0.0%)	1 (4.2%)	1 (2.3%)
	Paraesthesia	Possibly	0 (0.0%)	2 (8.3%)	2 (4.5%)
	Paraesthesia	Probably	1 (5.0%)	6 (25.0%)	7 (15.9%)
	Dizziness	Possibly	0 (0.0%)	2 (8.3%)	2 (4.5%)
	Dysgeusia	Probably	0 (0.0%)	3 (12.5%)	3 (6.8%)
	Hypoaesthesia	Unrelated	0 (0.0%)	1 (4.2%)	1 (2.3%)
	Hypoaesthesia	Possibly	0 (0.0%)	2 (8.3%)	2 (4.5%)
	Lethargy	Unrelated	0 (0.0%)	1 (4.2%)	1 (2.3%)
	Lethargy	Probably	0 (0.0%)	1 (4.2%)	1 (2.3%)
Psychiatric	Confusional state	Probably	0 (0.0%)	2 (8.3%)	2 (4.5%)

Source: summary of clinical safety Table 22. The title of table 22 is "Incidence of adverse events in HOP patients in the HYP-HOP study, 9-week double blind phase" seems incorrect and don´t correspond to the text and table 14.3.1.15 in the CSR.

In the DCP group 9/24 (37 %) suffered from paraesthesia (assigned as related in 8 of 24 subjects) to compare with 1/20 (5%) in the placebo group. Cognitive disorders were reported by 5 DCP treated patients and by 2 patients treated with placebo. These were considered related to treatment. Muscle spasm and muscle twitching was assigned in 5 (21%) patients in the DCP group versus 0 (0%) in the placebo group.

- **52-week extension phase**

In the 52-week extension phase 32 of 40 subjects (80%) had AEs with 23 of 40 subjects (57.5%) with related AEs. The most common AEs were reported for the nervous system SOC, with the most common being paraesthesia and cognitive disorder. Muscle spasm were reported by 3 patients.

Table 27: Incidence of adverse events in HOP patients in the 52-week open-label phase

System	AE	Relation to Study Medication	Placebo (N=18)	DCP (N=22)	All Subjects (N=40)
Gastrointestinal	Constipation	Possibly	1 (5.6%)	1 (4.5%)	2 (5.0%)
	Diarrhoea	Probably	1 (5.6%)	0 (0.0%)	1 (2.5%)
	Diarrhoea	Unrelated	0 (0.0%)	1 (4.5%)	1 (2.5%)
	Gastroesophageal reflux disease	Unrelated	1 (5.6%)	0 (0%)	1(2.5%)
	Gastroesophageal reflux disease	Possibly	0 (0%)	1 (4.5%)	1(2.5%)
General	Fatigue	Possibly	1 (5.6%)	2 (9.1%)	3 (7.5%)
	Fatigue	Probably	0 (0%)	1 (4.5%)	1 (2.5%)
	Oedema peripheral	Unlikely	1 (5.6%)	0 (0%)	1 (2.5%)
	Oedema peripheral	Possibly	0 (0%)	1 (4.5%)	1 (2.5%)
Infections	Nasopharyngitis	Unrelated	1 (5.6%)	2 (9.1%)	3 (7.5%)
Injury/poisoning	Fall	Unlikely	2 (11.1%)	2 (9.1%)	4 (10.0%)
	Fall	Unrelated	1 (5.6%)	1 (4.5%)	2 (5.0%)
	Fall	Possibly	0 (0%)	1 (4.5%)	1 (2.5%)
Musculoskeletal	Muscular weakness	Unrelated	1 (5.6%)	0 (0.0%)	1 (2.5%)
	Muscular weakness	Probably	1 (5.6%)	0 (0.0%)	1 (2.5%)
	Pain in extremity	Unrelated	1 (5.6%)	0 (0.0%)	1 (2.5%)
	Pain in extremity	Unlikely	1 (5.6%)	1 (4.5%)	2 (5.0%)
	Pain in extremity	Possibly	1 (5.6%)	0 (0.0%)	1 (2.5%)
	Muscle spasms	Unrelated	0 (0.0%)	1 (4.5%)	1 (2.5%)
	Muscle spasms	Possibly	0 (0.0%)	2 (9.1%)	2 (5.0%)
Nervous	Paraesthesia	Probably	4 (22.2%)	6 (27.3%)	10 (25.0%)
	Paraesthesia	Possibly	1 (5.6%)	1 (4.5%)	2 (5.0%)
	Cognitive disorder	Probably	3 (16.7%)	2 (9.1%)	5 (12.5%)
	Cognitive disorder	Possibly	1 (5.6%)	2 (9.1%)	3 (7.5%)
	Cognitive disorder	Definite	1 (5.6%)	0 (0%)	1 (2.5%)
	Dysgeusia	Probably	1 (5.6%)	3 (13.6%)	4 (10.0%)
	Headache	Possibly	1 (5.6%)	1 (4.5%)	2 (5.0%)
	Headache	Unlikely	0 (0%)	1 (4.5%)	1 (2.5%)
	Lethargy	Unrelated	0 (0%)	1 (4.5%)	1 (2.5%)
	Lethargy	Probably	0 (0%)	1 (4.5%)	1 (2.5%)

Psychiatric	Confusional state	Probably	0 (0.0%)	2 (9.1%)	2 (5.0%)
Renal	Nephrolithiasis	Probably	0 (0.0%)	2 (9.1%)	2 (5.0%)
	Nephrolithiasis	Possibly	1 (5.6%)	0 (0.0%)	1 (2.5%)
Skin	Rash	Possibly	0 (0.0%)	2 (9.1%)	2 (5.0%)

Source: summary of clinical safety Table 23. The title of table 23 is "Incidence of adverse events in HOP patients in the HYP-HOP study, 52-week double blind phase" which seems incorrect and don´t correspond to the text and table 14.3.1.23 in the CSR.
Subjects in the placebo group were treated with placebo in the initial 9-week phase and with DCP in the open label 52-week extension phase. The subjects in the DCP group were treated with active substance both in the initial 9-week and in the open label 52-week extension phase.

Tables 23, 24, 26 and 27 above presents low numbers of AEs and relatively few organ systems are represented even in the 52- week extension phase (only paraesthesia and memory loss is reported among HYP patients). Furthermore, the numbers don´t correspond to the text and tables in the CSR. **(OC)**. The overviews of AEs (AEs table 22 and 25) should preferably present placebo and active treated patients separately in the 9-week double-blind phase **(OC)**.

- **The supportive study by Tawil et al.**

Patients with primary PPs were divided into two diagnostic groups, HypoPP and PSPP. The latter group included hyperkalemic PP and paramyotonia congenita with PP.

Forty-two patients with hypokalemic periodic paralysis were enrolled, with 22 assigned to the placebo/DCP sequence and 20 assigned to the DCP/placebo sequence.

In the placebo-group only one patient reported an AE (dizziness). In the DCP group HypoPP patients had AEs related to the nervous system, gastrointestinal tract and skin. Paraesthesia was the most frequently reported AE (42%). Cognitive disorders, rash and anorexia was reported in almost 20%.

Table 28: Adverse events in HypoPP patients in Tawil et al. (2000)

Symptom	DCP	Placebo
Abdominal discomfort	2 (5%)	0
Anorexia	7 (18%)	0
Dysgeusia	2 (5%)	0
Diarrhoea	5 (13%)	0
Dizziness	5 (13%)	1 (3%)
Pruritus	6 (16%)	0
Skin rash	7 (18%)	0
Paraesthesia	16 (42%)	0
Flank pain	2 (5%)	0
Cognitive	8 (21%)	0

Source: clinical overview table 10

Thirty-one patients with PSPP were enrolled, with 15 assigned to the placebo/DCP sequence and 16 assigned to the DCP/placebo sequence. Like in the HypoPP sub study paresthesia and cognitive disorders were the most frequently reported AEs in the PSPP sub study.

Table 29: Adverse events in Potassium Sensitive Periodic Paralysis (PSPP)patients (hyperkalemic PP and paramyotonia congenita with PP) in Tawil et al. (2000)

Symptom	DCP	Placebo
Anorexia	4 (14%)	0
Dysgeusia	5 (17%)	0
Diarrhoea	6 (21%)	0
Dizziness	5 (17%)	0

Pruritus	2 (7%)	1 (4%)
Skin rash	5 (17%)	1 (4%)
Paraesthesia	11 (38%)	2 (8%)
Flank pain	2 (7%)	0
Cognitive	7 (24%)	1 (3%)

Source: Clinical overview Table 11

Serious adverse events and deaths

Deaths

There were no deaths in either study.

Serious adverse events

SAEs for each study are presented below.

- **Study of healthy volunteers, PK study (DCPT-1531)**

One subject dosed with 400 mg twice daily developed a rash, which necessitated hospital treatment. This event, which was considered treatment-related, subsequently resolved.

- **HYP-HOP study**

Patients with HYP

There was one SAE (rash) in the DCP group, which occurred in the 9-week double-blind period and was considered by the applicant as possibly related to treatment. Time to onset was 27 days. The subject was permanently removed from the trial and recovered from the event.

There was no SAE in the 52-week extension phase.

Patients with HOP

There was one SAE, humerus fracture, in the 9-week double blind phase. Time to onset was 35 days. This was in the placebo group and was deemed unrelated to treatment.

In the 52-week extension period there were further three serious AEs, all deemed unrelated to treatment:

- *Thyroid cancer*, no action was taken with study medication and the subject remained under observation. (The patient had placebo in the 9-week double blind phase).
- *Adenocarcinoma of pancreas,* subject was permanently removed from the trial and remained under observation. (The patient had placebo in the 9-week double blind phase).
- *Cauda equine syndrome*, no action was taken with study medication and the subject remained under observation. (The patient had placebo in the 9-week double blind phase).

- **The supportive study by Tawil et al.**

Clear information about SAE in the DCP phase is missing.

Laboratory findings, vital signs and additional safety measurements

- **Study of healthy volunteers, PK study (DCPT-1531)**

Laboratory findings

Chemistry panel and haematology was analysed at screening and at D 7 in cohorts A-E.

In cohort F chemistry panel and haematology was analysed at screening and at D16. In addition, electrolyte test and liver function tests were analysed at check in and then daily D1-13.

The applicant states that three laboratory results were flagged as "clinically significant" during this study, all relating to post-study serum potassium concentrations:

- 2.8 mmol/L in a Cohort C subject who had received 100 mg twice daily
- 2.5 mmol/L in a Cohort E subject who had received 400 mg twice daily
- 2.8 mmol/L in a Cohort F subject who had received 400 mg twice daily

In the CSR 10 of 36 subjects (all 10 in cohort C, E, F) had at least one post study potassium value < lower normal limit. The applicant should clarify the conclusion of "three clinical significant laboratory results" and also provide information about bicarbonate. **(OC)**

Vital signs

Cardiac flutter, presyncope and hypotension was reported by healthy volunteers in the highest dose cohorts (400 mg x 2). The applicant is asked to provide the narratives. **(OC)**

- **HYP-HOP study**

Laboratory findings

Laboratory parameters were measured at baseline, at the end of the 9-week double blind phase and at the end of the 52-week extension phase (61 weeks) in all subjects.

Most subjects were within the normal range of *haematology parameters* at baseline and remained within normal range at 9 and 61 weeks for both the placebo and DCP groups.

The majority of the *clinical chemistry parameter*s measured were within normal ranges at baseline and except for occasional variation remained within the normal range at 9 and 61 weeks for both the placebo and DCP groups.

However, there was a reduction in bicarbonate levels and potassium levels in the DCP subjects. Furthermore, there are many uncertainties surrounding "random glucose tests". The applicant is invited to clarify "increased blood glucose" in relation to known diabetes and the amount of missing data. Only 7/62 possible tests at screening were available. **(OC)**

It is noted that changes in laboratory parameters are not included in the AE tables in the summary of clinical safety **(OC).**

Bicarbonate

According to the applicant a reduction in bicarbonate levels were seen in the DCP subjects at the 9-week visit with 46% of HYP subjects and 41% of HOP subjects who were normal at baseline with low levels of bicarbonate at 9 weeks (and no effect in the placebo subjects). At 61 weeks 27% of HYP

subjects and 6% of HOP subjects who were normal at baseline had "low" bicarbonate levels. There are no reports of AE concerning low bicarbonate. **(OC)**

Table 30: Bicarbonate levels (mmol/L)

	HYP					
	Placebo (n=9)			***DCP (n=12)***		
	Screening	***Week 9***	***Week 61*** *(placebo week 0-9, DCP week 9-52) **	***Screening***	***Week 9***	***Week 61***
N	9	8	6	10	11	7
Median	25.0	25.0	19.0	23.5	20.0	21.0
Range	20.0-26.0	21.0-28.0	13.0-21.0	18.0-28.0	18.0-24.9	20.0-24.0
	HOP					
	Placebo (n=19)			***DCP (n=22)***		
	Screening	***Week 9***	***Week 61*** *(placebo week 0-9, DCP week 9-52) **	***Screening***	***Week 9***	***Week 61***
N	15	17	14	20	23 (?)*	17
Median	21.0	23.0	21.0	22.0	20.0	20.0
Range	13.0-30.0	19.0-28.0	17.0-24.0	18.0-28.0	16.0-26.0	15.0-23.0

Source: Clinical study report table 14.3.4 and 14.3.4.7
Reference:20-31 mmol/L
**MPA comment*

Potassium

There was a decrease in potassium levels in only the HYP subjects at 9 weeks (in 8% of subjects) and at 61 weeks in 20% of subjects

Table 31: Potassium levels (mmol/L)

	HYP					
	Placebo (n=9)			***DCP (n=12)***		
	Screening	***Week 9***	***Week 61*** *(placebo week 0-9, DCP week 9-61) **	***Screening***	***Week 9***	***Week 61***
N	9	8	6	10	11	7
Median	3.7	3.9	3.6	4.2	4.0	4.3
Range	3.5-4.7	3.6-4.7	3.0-4.1	3.8-4.7	3.3-4.5	3.3-4.7
	HOP					
	Placebo (n=19)			***DCP (n=22)***		
	Screening	***Week 9***	***Week 61*** *(placebo week 0-9, DCP week 9-61) **	***Screening***	***Week 9***	***Week 61***
N	15	17	14	20	22	17
Median	4.2	4.2	3.9	4.0	3.9	4.0
Range	3.3-4.6	3.7-5.2	3.3-4.7	3.6-4.6	3.4-4.6	3.4-4.6

*Source: Clinical study report table 14.3.*4.1 *and 14.3.4.7*
Reference:3.6-5.2 mmol/L

Vital signs

A slight reduction in systolic and diastolic blood pressure was observed after 9 weeks of treatment in both the HYP and HOP subjects. This was not consistently evident in subjects receiving placebo in the double-blind phase then receiving DCP in the 52-week open-label phase and it was also not sustained

in subjects undergoing continuous treatment with DCP beyond week 9 (subjects treated with DCP in the initial double-blind phase). The decrease in mean blood pressure noted in DCP treated subjects during the double-blind phase were < 6mmHg and did not take into account changes in medication required for entry into the trial.

A reduction in body weight was noted over the 9-week double-blind phase of the trial in both HYP and HOP subjects. Weight reduction accentuated slightly, with a maximum mean decrease of 3.98 kg in HYP subjects and 2.60 kg in HOP subjects observed at 35 weeks, in subjects treated with DCP from week 9 onwards. At week 61 the mean reduction was 1.2-2.4 kg.

Additional safety measurements.
Possible changes in attention and psychomotor speed were assessed by application of the Symbol-Digit Modalities Test and the Trail Making Test. Changes in mood state were assessed using the POMS scale. According to the applicant no notable or clinically significant differences were seen between the DCP and placebo treatments in either the HYP or HOP subjects. However, in section 4.7 in the proposed SmPC the applicant states that the psychomotor speed assessment in clinical trials suggest a drug related effect on the ability to drive and use machines **(OC).**

Safety in special populations and situations

No studies in special populations, age groups or in pregnancy or lactation have been performed. However, the applicant is requested to present the number of exposed patients > 65 years in the HYP-HOP study **(OC).**

No studies of intrinsic factors, extrinsic factors, withdrawal or rebound, drug abuse or studies on effects on ability to drive have been performed.

Immunological events

No studies of antibody formation have been conducted.

DCP is a sulphonamide derivative. In section 4.3 in the proposed SmPC the applicant states that fatalities associated with the administration of sulfonamides have occurred due to adverse reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Pulmonary involvement can occur in isolation or as part of a systemic reaction. Therefore, hypersensitivity to sulphonamides is a contraindication for use of DCP, and consequently included in section 4.3 in the proposed SmPC.

According to the applicant hypersensitivity, anaphylactic and idiosyncratic reactions have been identified during post-approval use of diclofenamide. The applicant is requested to present a discussion of whether immunological events may be expected **(OC).**

Safety related to drug-drug interactions and other interactions

No direct studies of drug interactions have been performed. However, according to the applicant the negative results of the *in vitro* metabolism and CYP450 induction/inhibition studies make such interactions unlikely.

The proposed SmPC contains contraindications and warnings related to concomitant use of diclofenamide and high-dose acetylsalicylic acid (sections 4.3, 4.4 and 4.5). **(OC)**

Diclofenamide promotes hypokalemia and metabolic acidosis by increasing urinary excretion of potassium and bicarbonate. Consequently, the proposed SmPC includes warnings and precautions for use in patients with other conditions associated with hypokalemia or acidosis as well as in patients receiving other medicinal products that may cause hypokalemia (e.g. diuretics and laxatives) or

metabolic acidosis. However, the applicant is asked to discuss interactions with antiarrhythmics, beta-blockers, calcium channel blockers, antiepileptics and magnesium which were contraindicated in the HYP-HOP study and not included in the proposed SmPC **(OC).**

Discontinuation due to AES

- **Study of healthy volunteers, PK study (DCPT-1531)**

A total of ten of the 36 (=27%) healthy volunteers discontinued from the study because of adverse events, one from a 200 mg twice-daily cohort and the other 9 from 400 mg twice-daily cohorts. All subjects had at least 2 AEs. (It was not specified which AE was the main reason for discontinuation). The most common AEs were paraesthesia/hypoesthesia, mental/memory impairment, dizziness, weight decrease, and blood potassium decreased. One subject had a SAE (rash).

- **HYP-HOP study**

Overall, there was no clear pattern in AEs leading to withdrawal from the study. The applicant should inform whether there were any cases of
1) temporary discontinuation
2) temporary or permanent dose-reductions due to AE(s) **(OC)**

Patients with HYP

- **9-week double-blind phase**

  One HOP patient treated with DCP discontinued the study in the 9-week phase due to an SAE (rash) and another due to several AEs (rash, dry mouth, anorexia, weight decreased and dyspnoea).

- **52-week extension phase**

  One patient discontinued due to an AE (paraesthesia, polyneuropathy).

Patients with HOP

- **9-week double-blind phase**

  One patient in the DCP group withdrew due to an AE (cognitive disorder and malaise).

- **52-week extension phase**

  Seven patients withdrew due to AEs and one due to an SAE (adenocarcinoma).

Post marketing experience

The applicant informs that no post-marketing data are available. The applicant should confirm that this also includes post-marketing information from
1) the US where DCP is approved for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants
2) Italy where DCP (Fenamide) has been approved for the treatment of glaucoma. **(OC)**
In the event that post-marketing data is available from the US and/or Italy, this should be presented. **(OC).** The applicant is requested to discuss if there are post approval data evaluating a possible carcinogenic effect of DCP alternative carbon anhydrase inhibitors **(OC)**

3.3.9. Discussion on clinical safety

Safety database

Safety-data are derived from two proprietary studies and one supportive literature reference.

The proprietary studies were one PK study phase I study in 36 healthy volunteers (DCPT-1531) and the pivotal phase III study, the HYP-HOP trial, which included 21 patients with hyperkalemic periodic paralysis (HYP) and 44 patients with hypokalemic periodic paralysis (HOP). In the HYP-HOP study a 9-week double-blind treatment phase was followed by a one-year open label extension.

The supportive study was a literature reference dated 2000, by Tawil et al. (Tawil et al, Ann Neurol. 2000; 47[1]:46-73). No safety conclusion can be drawn on the supportive study since source data are missing and the information presented in the reference is incomplete. However, the types of reported AEs seem in line with those in the pivotal study.

A low proportion of patients in the HYP-HOP study (23/65=36%) were treatment naïve, which enhances the likelihood of including patients who tolerate the treatment **(OC).** Furthermore, a history of worsening symptoms with the use of CAI was an exclusion criterion. Despite this selective recruitment, 67% of the HYP - HOP patients had at least one related AE and AEs were the most common reason for discontinuation. About 15-20% of the HYP and HOP patients discontinued due to AEs.

The number of patients (n=65) in the HYP-HOP study is considered acceptable in this orphan setting. The therapy appears to be intended to be prophylactic as well as symptomatic (reduce the rate as well as severity and duration of attacks) and therefore the need for long- term treatment is likely. However, no long-term safety data is available from patients with PP. Chronic metabolic acidosis may adversely affect several organ systems including the musculoskeletal system. (In addition, some HOP- patients may develop myopathy resulting in permanent weakness). Furthermore, hypokalemia increases the tendency for cardiac arrhythmias in patients with digitalis treatment, ischemic heart disease and impaired left ventricular function. The applicant is invited to discuss and justify long term treatment with DCP with regard to chronic metabolic acidosis and development of skeletal muscle wasting and also with regard to hypokalemia and risk of cardiac arrhythmias. **(MO)**

Genetics

The proposed indication by the applicant is periodic paralysis without further specification. There are many different variants of periodic paralysis. A major safety issue is the uncertainty arising from an extrapolation to variants of the disease that are not included in the studies. Furthermore, not all patients in the study had genetically definitive diagnosis of HYP or HOP periodic paralysis. Despite that genetic testing was not mandatory, known mutation in the α subunit of sodium channel was an exclusion criterion for HOP patients. Patients with Andersen Tawil syndrome (potassium channel mutation) characterised by periodic paralysis, life threatening ventricular arrhythmias (and a variety of facial features) was also excluded from the study. Genetic testing is the gold standard to confirm definite periodic paralysis, although all periodic paralysis patients do not currently have an identifiable mutation. Most hypokalemic periodic paralysis patients have mutations in calcium (~60%) and sodium (~20%) channels. Hyperkalemic periodic paralysis (and paramyotonia congenita) is associated with mutations in the sodium channel.

Beyond the risk of arrhythmia in Andersen Tawil syndrome, the applicant should discuss the potential risk of malignant arrhythmias in other types of periodic paralysis, since there may be a phenotypic and genotypic overlap between cardiac and skeletal muscle sodium channelopathies (SCN4A variants) and Brugada syndrome. [Bissay 2016]. The indication needs to be further justified. **(MO)**

Special populations

Symptoms of periodic paralysis debuts in childhood and during adolescence. The included patients in the HYP-HOP study were all adults, without severe comorbidities or important concomitant medicines and all having normal s-creatinine levels, as per exclusion criteria. This distinguishes them from the population with periodic paralysis.

There are no studies in special populations, not in children, not in elderly and not in patients with renal impairment, which is a safety concern. According to the applicant "renal impairment" is a contraindication, but a definition of the degree of impairment is missing. **(OC)**

According to the applicant (in the proposed SmPC), foetal death is reported as an AE from post-marketing experiences and teratogen effects (foetal limb reduction) were reported in rat studies. Consequently, there are uncertainties regarding contraceptives and use in pregnant women/women of childbearing potential/pregnancy prevention programme. The applicant is invited to further clarify these data. **(OC)**

Adverse events

The types of AEs reported in the study in healthy volunteers and in the HYP-HOP study was in agreement with the expected safety profile based on the approved indication in glaucoma patients and in agreement with the class effect of CAI. It was demonstrated in the dose escalating study (healthy volunteers) that many AEs were dose related, had a short time to onset (except rash) and were reversible at withdrawal. There was no obvious difference in the incidence of AEs between the HYP and HOP patients.

Overall, adverse events from the nervous system, paraesthesia and cognitive impairment dominated.

Paraesthesia are characteristic, well known and frequently occurring ADR after treatment with ACZ and DCP and may have jeopardised the blinding. Other AEs known from the reference-product such as anorexia, nauseas, weight loss, hypokalaemia, acidosis, nephrolithiasis and rash were also reported from the current studies. Hypokalemia was frequent, especially in the healthy volunteers and the event appeared to be dose dependent. Subnormal levels of bicarbonate were frequently reported from HYP and HOP patients, but this information is missing from healthy volunteers. No long-term safety data is available from this population. Of special interest is chronic metabolic acidosis and association to muscular wasting and effects on other organ systems. **(MO)**

Most AEs were assessed by the investigator as mild to moderate in intensity. Two SAE (both rash) were related to the medical product. Additional four SAE (fracture, malignancy x2 and cauda equina syndrome) were assessed as probably not related to DCP. There were no deaths. Serious idiosyncratic side effects are rare, but still a clearly defined risk considering DCP is a sulphonamide derivate. No such events occurred in the study.

To summarise, the AE profile observed in the pivotal HYP-HOP study seems to be in line with the known safety profile of DCP. However, due to incomplete and sometimes contradictory data presentation further assessment is needed following clarification by the applicant. **(OC)**

3.3.10. Conclusions on clinical safety

Adverse events in the current studies did not differ markedly from that seen in glaucoma patients treated with DCP or Acetazolamide. AEs from the nervous system (paraesthesia and cognitive disorders) dominated and many AEs appeared to be dose dependent.

In patients with PP there are concerns regarding long-term effects of secondary acidosis on skeletal muscle and other organs. Furthermore, the indication includes patients with different mutations affecting different ion channels and presumed different safety profiles, which seems especially important regarding the potential risk of cardiac arrhythmias in combination with hypokalemia. Also, no studies have been performed in special populations, such as the elderly or in patients with renal impairment.

The quality of the submitted documentation raises questions about the conduct of the studies and currently the submitted data do not allow a thorough safety assessment.

3.4. Risk management plan

The Safety Specification (Part II, SI-SVIII) from RMP version 0.1 dated 26 Nov 2018 is assessed below. The approval of the proposed RMP is on hold, pending the full assessment of this hybrid application, however, some brief comments are given below.

Safety Specification

The rapporteur considers the data presented in the RMP as follows:

- **Epidemiology of the indications and target population**

The RMP outline of the epidemiology is without remarks.

- **Clinical trial exposure**

See section 4.2.

- **Populations not studied in clinical trials**

  - Renally impaired patients

Assessor's comment:

Subjects with renal impairment were excluded from the clinical study performed.

Pending the outcome of the safety assessment, this deficiency may be added as a safety concern and addressed in the SmPC (LoQ).

- **Post-authorisation experience**

No post-marketing data are available for the proposed indication.

- **Identification of safety concerns in the RMP submission**

Risks considered important for inclusion in the list of safety specification

Important identified risks

  - Hypersensitivity, anaphylactic and idiosyncratic reactions
  -

Assessor's comment:

'Hypersensitivity and anaphylactic reactions' should be separate from 'idiosyncratic reactions' as they have completely different mechanisms.

The safety concern is addressed in section 4.4 in the SmPC, and routine pharmacovigilance may be considered sufficient; however, the inclusion into the RMP of the proposed safety concern is on hold, pending the outcome of the full safety assessment.

  - Concomitant use with high dose of acetylsalicylic acid (Aspirin)

Assessor's comment:

In line with GVP module V, rev 2, only those risks should be addressed in the safety specification that are adverse clinical outcomes.

Thus, although the outcome of the full safety assessment is pending, the risk of 'concomitant use with high dose of acetylsalicylic acid' should be specified and further discussed, including a rational for inclusion (See Safety section and LoQ).

- Metabolic acidosis

Assessor's comment:

The rational for including 'metabolic acidosis' as an important identified risk is acknowledged.

The inclusion into the RMP of the proposed risk is on hold, pending the outcome of the full safety assessment for this procedure (See Safety section and LoQ).

Important potential risks

- Use in patients with hepatic insufficiency
- Use in patients with severe pulmonary diseases

Assessor's comment:

In line with GVP module V, rev 2, only those risks should be addressed in the safety specification that are adverse clinical outcomes.

Thus, although the outcome of the full safety assessment is pending, the important potential risks for patients with hepatic insufficiency and severe pulmonary disease, respectively, should be specified and further discussed, including a rational for inclusion (See Safety section and LoQ).

- Hypokalaemia

Assessor's comment:

The safety concern of hypokalaemia is acknowledged; however, since the risk of hypokalaemia may impact the benefit risk balance, the applicant should consider upgrading this safety concern to an important identified risk.

The assessment of this risk is on hold, pending the outcome of the full safety evaluation for this procedure (See Safety section and LoQ).

Missing information

- Use during pregnancy and lactation

Assessor's comment:

No data is available. Teratogenic effects have been reported in non-clinical studies following oral administration.

The applicant has proposed routine pharmacovigilance with a warning in 4.6 that diclofenamide should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

The full assessment of this topic is on hold, pending the outcome of the full safety evaluation for this procedure (See safety section and LoQ).

- Use in paediatric population

Assessor's comment:

The safety has not been established in paediatric population. Children and adolescents were not included in the clinical study. No data is available. The sought indication is for adults only.

The relevance of this missing information is questioned, pending the outcome of the full benefit/risk evaluation.

Topics not elsewhere discussed as safety concerns by the applicant

- **Long-term safety**

Assessor's comment:

Long-term safety data are missing, specifically with regard to the potential consequences of chronic metabolic acidosis, and development of muscular wasting. Pending the outcome of the MAH response to the LoQ, 'long term safety data' may be considered for inclusion in the RMP as missing information.

- **Interactions**

Assessor's comment:

The use of concomitant medication was very limited in the clinical study and no direct interactions studies were performed and the applicant is invited to disuss the risks of interactions. Pending the outcome of the full safety assessment, potential pharmacokinetic and pharmacodynamic interactions might be considered for inclusion in the safety specification.

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP v 0.1, dated 26 Nov 2018, in support of the new indication for treatment of periodic paralysis.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity, anaphylactic and idiosyncratic reactions Concomitant use with high dose of acetylsalicylic acid (Aspirin) Metabolic acidosis
Important potential risks	Use in patients with hepatic insufficiency Use in patients with severe pulmonary diseases Hypokalaemia
Missing information	Use during pregnancy and lactation Use in paediatric population

Assessor's comment:

Having considered the data in the safety specification, some brief comments were given on the RMP; however, due to the major objections raised, the full assessment of the safety specification is on hold, , as the full benefit/risk evaluation for this procedure is pending

3.4.2. Discussion on safety specification

The presentation of the safety data in the dossier was generally poor resulting in major objections and numerous other concerns. Accordingly, the Rapporteur considers that the safety specification cannot be fully assessed at this stage.

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification, the rapporteur considers that assessment of the safety concerns above listed are on hold, as the full benefit/risk evaluation for this procedure is pending

3.4.4. Pharmacovigilance plan

No post-authorisation study is planned by the applicant.

The applicant proposes only routine pharmacovigilance activities to address the safety concern. No additional pharmacovigilance activities are proposed.

The evaluation of the pharmacovigilance plan is on hold, pending the response to the LoQ and the full assessment of the safety specification. Thus, the proposed post-authorisation pharmacovigilance plan may need to be further considered, in line with the Company’s responses to the CHMP Major Objections and Other Concerns.

3.4.5. Risk minimisation measures

Table V.1 Routine Risk minimisation measures

Safety concern	Routine risk minimisation measures
Hypersensitivity, anaphylactic and idiosyncratic reactions	*Routine risk communication:* • **SPC section 4.8 and PL section 4** inform that rash, pruritus and some serious adverse reactions like: hypersensitivity, anaphylaxis, idiosyncratic reactions were reported with diclofenamide use. • **SPC section 4.4** warn that fatalities associated with the administration of sulfonamides have occurred due to adverse reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Pulmonary involvement can occur in isolation or as part of a systemic reaction. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • **SPC section 4.3 and PL section 2** warn that patients known to be allergic to diclofenamide or other sulfonamides or any of the other ingredients of this medicine must not take Ekesivy • **SPC section 4.4 and PL section 2** - recommendation that Diclofenamide should be discontinued at the first appearance of skin rash or any sign of immune-mediated or idiosyncratic adverse reaction *Other routine risk minimisation measures beyond the Product Information:* • **Legal status:** prescription only medicine (POM).

Concomitant use with high dose of acetylsalicylic acid(aspirin)	*Routine risk communication:* • **SPC section 4.4** inform that anorexia, tachypnoea, lethargy, and coma have been reported with concomitant use of Diclofenamide and high-dose acetylsalicylic acid. • **SPC section 4.5** inform that Diclofenamide may cause an elevation in salicylate levels in patients receiving acetylsalicylic acid. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • **SPC section 4.3 and PL section 2** warn that concomitant use of diclofenamide and high dose acetylsalicylic acid (aspirin) is contraindicated. • **SPC section 4.4** - recommend that Diclofenamide should be used with caution in patients receiving low dose aspirin. *Other routine risk minimisation measures beyond the Product Information:* • **Legal status** :prescription only medicine(POM)
Metabolic acidosis	*Routine risk communication:* • **SPC section 4.2** inform that the risk of metabolic acidosis is greater in elderly patients. • **SPC section 4.4 and PL section 2, 4** warns that Diclofenamide can cause hyperchloremic non-anion gap metabolic acidosis. • **SPC section 4.4** warns that concomitant use of Diclofenamide with other drugs that cause metabolic acidosis may increase the severity of metabolic acidosis. • **SPC section 4.8**: metabolic acidosis is included among serious adverse events that have been identified during post-approval use of Diclofenamide for which is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • **SPC section 4.3**- warns that severe pulmonary disease is a

Safety concern	Routine risk minimisation measures
	contraindication due to limiting compensation to metabolic acidosis caused by Diclofenamide. • **SPC section 4.4** recommends baseline and periodic measurement of serum bicarbonate during Diclofenamide treatment. *Other routine risk minimisation measures beyond the Product Information.* • **Legal status**: prescription only medicine (POM).
Use in patients with hepatic insufficiency	*Routine risk communication:* • **SPC section 4.3 and PL section 2** -Diclofenamide is contraindicated in patients with hepatic insufficiency as it may aggravate hepatic encephalopathy. *Other routine risk minimisation measures beyond the Product Information.:* • **Legal status:** prescription only medicine (POM).
Use in patients with severe pulmonary diseases	*Routine risk communication:* • **SPC section 4.3 and PL section 2** inform that-Diclofenamide is contraindicated in patients with severe pulmonary disease, in which limiting compensation to metabolic acidosis caused by Diclofenamide can occur. *Other routine risk minimisation measures beyond the Product Information* • **Legal status**: prescription only medicine (POM).
Hypoalemia	*Routine risk communication:* • **SPC section 4.4 and PL section 4** warn that Diclofenamide can cause hypokalaemia by increasing potassium excretion. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • **SPC section 4.4** recommend baseline and periodic measurement of serum potassium during Diclofenamide treatment. • **SPC section 4.4** recommend to consider reducing the dose or discontinuing Diclofenamide if hypokalemia develops or persists.

Safety concern	Routine risk minimisation measures
	• **SPC section 4.8**: hypokalemia is included among serious adverse events that have been identified during post-approval use of Diclofenamide for which is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure *Other routine risk minimisation measures beyond the Product Information :* • **Legal status**: prescription only medicine (POM).
Using during pregnancy and lactation	*Routine risk communication:* • **SPC section 4.6** warns that there are no adequate and well-controlled studies with Diclofenamide in pregnant women. • **SPC section 4.6** warns that Teratogenic effects (foetal limb reduction defects) were reported following oral administration of Diclofenamide to pregnant rats during organogenesis at 17 times the maximum recommended human dose. • **SPC section 4.6** inform that it is not known whether Diclofenamide is excreted in human milk. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • **SPC section 4.6** recommends that Diclofenamide should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. • **SPC section 4.6** recommends that caution should be exercised when Diclofenamide is administered to a nursing woman. *Other routine risk minimisation measures beyond the Product Information:* • **Legal status:** prescription only medicine (POM).
Use in paediatric population	*Routine risk communication:* • **SPC section 4.2 and PL section 2** inform that safety and effectiveness of Diclofenamide in pediatric patients have not been established. *Other routine risk minimisation measures beyond the Product Information:* • **Legal status:** prescription only medicine.

The applicant proposes only routine risk minimisation measures. This is acceptable at present; however, this is pending the assessment of the MAH's responses to the list of questions.

The applicant is requested to reflect all references to SmPC/PL sections and recommendation for specific clinical measures/monitoring to address the risks (e.g. hypokalaemia) and missing information in line with the CHMP (Co)-Rapps conclusions on the PI (**OC**).

In addition, if applicable, the MAH should mention the sections of the PIL addressing the different safety concerns; the specific clinical measures/monitoring information for patients in the PL should also be included.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.1 is currently not acceptable; a revised document is awaited, together with satisfactory responses to the list of questions. Further details are provided in the endorsed Rapporteur assessment report and in the list of questions in section 6.

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the fact that this is new indication with a new patient population compared to previously approved indication, the CHMP is of the opinion that the already existing entry in the EURD list for diclofenamide needs to be amended as follows: the PSUR cycle for the medicinal product should follow a half-yearly cycle.

4. Significance of paediatric studies

N/A.

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The applicant is seeking approval for Ekesivy (diclofenamide) 50 mg tablets. Diclofenamide is a carbonic anhydrase inhibitor. The proposed indication is *treatment of periodic paralysis*. The proposed initial dose is 50 mg twice daily. The maximum recommended total daily dose is 200 mg.

Primary periodic paralyses (PPP) are a group of rare autosomal dominant genetic disorders caused by sporadic or inherited mutations in skeletal muscle sodium, calcium or potassium channels. The conditions are characterized by acute episodes of flaccid muscle weakness and variations in serum

potassium levels. They are part of the broader spectrum of *muscle channelopathies*. Primary periodic paralyses include *hyperkalemic periodic paralysis* (potassium-sensitive period paralysis), *hypokalemic periodic paralysis*, and *Andersen–Tawil syndrome*.

The prevalence of hyperkalemic periodic paralysis is less than 1:200,000 and is caused by mutations in the *SCN4A* gene on chromosome 17. Hypokalemic periodic paralysis has a prevalence of ~0.13 per 100,000. It is caused by mutations involving mostly the muscle calcium (*CACNA1S*, chromosome 1) or, less frequently, the sodium channel genes (SCN4A, chromosome 17) (Phillips et al. 2018). In the absence of an identified mutation (~30% of patients), disease subtypes are distinguished based on clinical presentation, serum potassium levels during attacks and patterns of abnormalities on long exercise testing (Statland et al. 2018).

5.1.2. Available therapies and unmet medical need

There are no approved therapies for the treatment of primary periodic paralysis.

Treatment options are limited and based largely on anecdotal experience. They include lifestyle changes (avoidance of triggers) and potassium therapy (supplementation or avoidance). Acute attacks are treated with oral potassium chloride in hypokalemic periodic paralysis, and inhaled salbutamol or glucose/insulin therapy in hyperkalemic periodic paralysis (Greig. Drugs. 2016; 76:501-7). Patients with Andersen-Tawil syndrome frequently also require treatment with antiarrythmic agents.

Carbonic anhydrase inhibitors (acetazolamide [ACZ], dichlorphenamide [DCP]) have been used for many years as empiric treatment for periodic paralysis. The mechanism of action is not fully understood. Promotion of systemic acidosis possibly reduces patient susceptibility to period paralysis.

Periodic paralysis is associated with significantly impaired quality of life due to muscle weakness, myotonia and fatigue. Patients present with intermittent attacks of muscle weakness but the majority manifest persistent myopathy later in life. Also, many patients with hyperkalemic periodic paralysis develop muscle stiffness between attacks. There is a need to optimize and identify new treatment options in these patients to minimize symptoms and prevent permanent muscle weakness.

5.1.3. Main clinical studies

The main evidence of efficacy submitted is a single Phase III, multicentre, randomized, double-blind, placebo-controlled parallel group study (HYP-HOP), run as 2 separate (sub) studies, one in patients with hyperkalemic periodic paralysis (HYP) and one in patients with hypokalemic periodic paralysis (HOP). Patients with Andersen-Tawil syndrome were excluded.

In each substudy, a 9-week double-blind treatment phase was followed by a one-year open label extension. The primary objective was to assess whether DCP lowers the rate of attacks of weakness as measured by participant self-report over the double-blind period.

The primary endpoint was the weekly attack rate, calculated over the final 8 weeks (Weeks 2-9) of the double-blind period.

A total of 21 HYP subjects were analysed for efficacy (9 placebo, 12 DCP). A total of 44 HOP subjects were analysed for efficacy (20 placebo, 24 DCP).

In addition, as a supportive study, the MAH submitted a published literature reference (Tawil et al, Ann Neurol. 2000; 47[1]:46-73). The article summarizes 2 multicenter, randomized, double-blind, placebo-controlled crossover trials, one in 42 subjects with hypokalemic periodic paralysis (HypoPP) and one in 31 subjects with potassium-sensitive (hyperkalemic) periodic paralysis (PSPP). In each trial, two 8-week treatment periods were separated by a washout period of at least 9 weeks. The primary

outcome of the HypoPP trial was the occurrence of an intolerable increase in attack severity or frequency. The primary outcome in the PSPP trial was the number of attacks per week.

5.2. Favourable effects

For **HYP** patients, the baseline weekly attack rate was 4.0 (1.3, 6.0) median (interquartile range [IQR]) in subjects treated with placebo (N =9) and 2.0 (1.0, 7.5) in subjects treated with DCP (N = 11) (missing diary entries interpreted as no attack).

At week 9 of treatment, the weekly median attack rates were 4.8 (0.5, 7.1) in placebo and 0.9 (0.4, 1.5) in DCP treated HYP subjects respectively (missing diary entries interpreted as no attack).

The attack rate over the 9-week double blind phase of the study was not statistically different from placebo. In a secondary analysis where missing diary cards days were treated as days without data and the day removed from the calculation of attack rate, the attack rate over the 9-week double blind phase of the study was also not statistically different from placebo. Neither did this additional analysis have a numeric impact on the effect size.

Over the 52-week unblinded treatment period, attack rate fell to 0.9 (0.0, 1.4) and 0.3 (0.1, 1.3) in placebo (N=7) and DCP treated HYP subjects (N=9), respectively at week 61 (averages of weeks 54-61) (missing diary entries interpreted as no attack).

Severity-weighted attack rate and duration of attack over the 9-week blinded period were used as secondary assessments of efficacy.

Using the primary analysis strategy (missing diary entries as no attack) the median severity-weighted attack rate during DCP treatment was statistically different from that during placebo treatment (**P=0.03**) (-5.0; 95% CI: NA, 1.2). When missing diary cards were removed from the calculations, the median difference was -10.9 (NA, 7.2) (**P=0.10**).

Attack duration during DCP treatment was not statistically different from placebo in either of the analyses.

For **HOP** patients, the baseline weekly attack rate was 1.8 (0.5, 3.8) in subjects treated with placebo (N = 19) and 1.1 (0.5, 2.4) in subjects treated with DCP (N = 24) (missing diary entries interpreted as no attack).

At week 9 of treatment (averages of weeks 2-9), the weekly attack rates were 2.4 (0.5, NA) and 0.3 (0.1, 1.6) in placebo and DCP treated subjects, respectively (missing diary entries interpreted as no attack).

The attack rate over the 9-week double blind phase of the study was statistically different from placebo (**P=0.02**). The difference in median attack rate was -2.2 (95% CI: -6.8, -0.4).

Over the 52-week un-blinded treatment period, the attack rate was reduced to 0.2 (0.0, 1.0) and 0.0 (0.0, 0.1) in subjects treated with placebo (N = 14) and DCP (N = 17), respectively, at week 61 (averages of weeks 54-61) (missing diary entries interpreted as no attack).

In a secondary analysis, missing diary cards days were treated as days without data and the day removed from the calculation of attack rate.

The baseline weekly attack rate was 4.2 (0.8, 6.5) median (interquartile range [IQR]) in subjects treated with placebo and 2.2 (0.9, 4.1) in subjects treated with DCP.

At week 9 of treatment (based on averages of weeks 2-9), the weekly attack rates were 4.4 (0.8, NA) and 0.7 (0.2, 3.3) in placebo and DCP treated HOP subjects respectively.

In this analysis, statistical significance was reached for the reduction in attack rate during DCP treatment (**P=0.02**). The difference in median attack rate was -3.9 (95% CI: -7.4, -0.6).

Over the course of the extension treatment period, attack rate fell to 0.4 (0.0, 2.3) for placebo patients (N = 14) and 0.0 (0.0, 0.2) in DCP treated HOP subjects (N = 17), respectively, at week 61 (averages of weeks 54-61).

Using the primary analysis strategy (missing diary entries as no attack) the median severity-weighted attack rate during DCP treatment was statistically different from that during placebo treatment (**P=0.02**) (-5.2; 95% CI: -25.2, -1.2). When missing diary cards were removed from the calculations, the median difference was -7.9 (-25.6, -1.8) (**P=0.03**).

Statistical analysis of the data over the 9-week double blind phase of the study shows that the attack duration during DCP treatment was significantly shorter than that during placebo treatment (**P=0.02**) (missing diary entries interpreted as no attack). In the second analysis where attack rate was adjusted for missing diary days, the attack duration during DCP treatment was also significantly shorter than that during placebo treatment (**P=0.02**).

In both the HYP and HOP patient populations, additional secondary outcome variables were assessed. These included changes from baseline to Week 9 in average MMT score; average MVICT score and percent of predicted score; lean body mass (DEXA), and health-related QoL (SF-36 v2).

In general, changes in these outcomes for DCP compared to placebo were not statistically significant for either population. However, changes in favour of DCP were observed in the physical component summary score and five subscales of SF-36 in the population of patients with HOP.

Regarding the supportive Tawil et al. study, in the HypoPP trial, 34 of the 42 subjects (81.0%) enrolled completed both phases of the trial. Of these, 13 showed a preference for one of the two treatments in terms of the endpoint (DCP or placebo) and 11 preferred DCP. In the PSPP trial, 24 of the 31 subjects (77.4%) completed both treatment phases. For 16 subjects who had attack rate data for both treatment phases, the mean improvement in attack rate on DCP relative to placebo (2.3 ± 2.9) was statistically significant.

5.3. Uncertainties and limitations about favourable effects

The active and placebo tablets in this study were uncoated and not over-encapsulated (as was the case in the supportive Tawil study). About half of the enrolled subjects were not treatment naïve and may have been using DCP prior to study start. Considering that thus a portion of subjects were already familiar with or using DCP treatment prior to entering the study, it is not clear whether potential differences in e.g. taste or other characteristics between the active and placebo treatments could have affected the study blind for the patients and/or investigators.

Attack rate was the primary endpoint of the trial. Patients with acute worsening, as judged by the investigator, received an imputed attack rate higher than any other observed during the trial. No standardized criteria for acute worsening were included in the protocol. It appears conceivable that bias might be introduced by prior knowledge of assigned treatment affecting this type of evaluation.

The submitted SAP is dated after unblinding and it is not clear from the documentation what analyses were specified before unblinding. The date for database lock could not be retrieved. Attack duration appears to be a post-hoc analysis. A SAP version dated prior to unblinding should be provided,

together with a structured discussion of any relevant changes made, the implemented dates for these changes, and numbers of patients affected.

The primary efficacy measure was the attack rate, as self-reported by the participants. There was a substantial amount of missing diary day entries, however. No compliance data for HYP patients were included in the dossier. However, HOP patients on average only reported approximately 60% of days with a diary entry, both in the double-blind treatment period as well as during the extension. This raises uncertainty about the conclusions that can be drawn.

In addition, the handling of missing data is unclear due to inconsistent documentation in different parts of the SAP and study report. At this time, it is not known which analysis is to be regarded as pre-specified and whether appropriate methods were used in the actual analysis. In addition, the population used for the primary analysis for efficacy was not according to the ITT principle.

Patients' respective treatment history and concomitant treatments should be further clarified. For the first 9 weeks of the study, the participant's dosage depended on the dosage of periodic paralysis medication (if any) that the participant was taking at baseline, including DCP or ACZ. Approximately half of patients were treatment naïve but a clear definition of what this means is lacking. Thus, it is not clear whether treatment naïve patients actually had a prior history of using carbonic anhydrase inhibitors or whether this pertains to a certain time period prior to entering the study. HOP patients were allowed to continued potassium supplements to treat their attack symptoms but it is not clear whether the use of these supplements, for example, can be assumed to have had a preventive effect on the rate or severity of additional attacks.

The primary endpoint of the trial, attack rate, was reduced following treatment with DCP, relative to placebo. The same was the case for some of the secondary endpoints, including severity weighted attack rate and attack duration (post-hoc). Statistical significance was largely restricted to the HOP subjects. HOP subjects also reported improvements in functional physical parameters. Reduction in rate, severity and duration of attack as well as improvements in QoL might be considered as potentially meaningful outcome measures for a patient population for which no approved treatment options exist. However, it is not clear what would constitute a clinically relevant improvement. In addition, for both substudies (HYP and HOP), the attack rate for DCP was already lower than placebo at baseline. This does not seem to have been taken into account in the analyses or interpretation of the results.

The proposed indication is '*treatment of periodic paralysis*.' This wording is substantially broader than the population studied, which is 2 subgroups of patients with hyper/hypokalemic primary periodic paralysis. Patients with secondary periodic paralysis (e.g. due to thyrotoxicosis) have not been studied, nor patients with Andersen-Tawil syndrome. The data in HYP patients are limited. Also, no paediatric patients were included in the clinical studies.

The supportive study had a crossover design which included a return to baseline treatment in between the two study drug treatment phases as well as different primary endpoints for the respective hypo and hyperkalemic subgroups, the presence of various cross over effects cannot be excluded. Also, the datedness of the article (with a study protocol dating to 1993), lack of source data, extent of missing data, small sample size, and short treatment period limit the conclusions that can be drawn.

5.4. Unfavourable effects

Paraesthesia

Paraesthesia was reported by 10 (28%) of 36 healthy volunteers. The event was dose dependent, with two cases occurring at the proposed maximum clinical dose of 200mg/ day and the other 8 at higher doses. Time to onset was short and the symptoms were reversible.

In the HYP-HOP study paraesthesia was reported by 8 (66.7%) of HYP patients on active treatment and 3 (33.3%) on placebo in the 9-week phase and overall by 9 (52.9%) in the 52-week extension phase. The corresponding numbers in HOP patients were 9 (37.5%) on active treatment and 1 (5%) on placebo in the 9-week phase and 12 (30%) in the 52-week extension phase. In the supportive study by Tawil et al paraesthesia was reported by 11 (38%) in the active group and 2 (8%) in the placebo group in the PSPP sub study as well as 16 (42%) in the active and 0 in the placebo group in the HOP sub study.

Paraesthesia led to withdrawal of one HYP patient on DCP treatment in the 9-week phase and one HYP patient in the 52 week-extension phase of the HYP-HOP study. One HOP patient withdrew due to several AEs including paraesthesia.

Cognitive disorder

Mental impairment was reported by 3 (8%) of 36 healthy volunteers. Three of the volunteers who discontinued due to AEs reported mental impairment or memory impairment as one of several reasons. The volunteers were all in the highest dose cohorts (400mg x 2).

In the HYP-HOP study cognitive disorder was reported by 5 (20.8%) of HOP patients on active treatment and 2 (10.0%) on placebo in the 9-week phase. One HOP patient with DCP treatment discontinued from the 9-week phase due to cognitive disorder and malaise. Cognitive disorder was reported by 9 (20.0 %) HOP patients in the 52-week extension phase. In two of them the AEs were judged as severe by the investigator.

Memory impairment was reported by 2 HYP patients (11.8%) in the 52-week extension phase.

In the supportive study by Tawil et al cognitive symptoms were reported by 7 (24%) in the active group and 1 (3%) in the placebo group in the PSPP sub study. Number of reports were 8 (21%) in the active group and 0 in the placebo group in the HOP sub study.

Hypokalemia

All healthy volunteers had normal values at baseline (reference 3.6-5.2 mmol/L), but post study 10 (27%) had at least one value < lower normal limit. Six of the subjects were from cohort E and F exposed to the highest doses (400mg x2). Time to onset was short (days). Information about potassium supplement or potassium treatment is missing.

In the HYP-HOP study potassium supplement was allowed. There was a decrease in potassium levels in only the HYP subjects at 9 weeks (in 8 % of subjects) and at 61 weeks (in 20% of subjects). The lowest values were 3.3 at week 9 and 3.0 at week 61.

Metabolic acidosis

A reduction in bicarbonate levels was seen in the DCP subjects at 9-week with 46% of HYP subjects and 41% of HOP subjects who were normal at baseline with low levels of bicarbonate at 9 weeks (and no effect in the placebo subjects). At 61 weeks 27% of HYP subjects and 6% of HOP subjects who were normal at baseline had low bicarbonate levels. The lowest values were 13 mmol/L in the HYP population and 15 mmol/L in the HOP population (Reference bicarbonate:20-31 mmol/L).

Muscle spasms and twitching

In the 9-week phase of the HYP-HOP study muscle spasm or twitching was reported by 5 HOP patients on active treatment but in no patient on placebo in the 9-week phase.

Rash

Two cases of SAE were reported. (One HYP patient and one healthy volunteer). Two more HYP patients and two HOP patients on active treatment had AEs (rash). One patient on placebo had rash.

In the supportive study by Tawil et al 7 (18%) HOP patients and five (17%) PSPP patients on active treatment had rash. One on placebo had rash.

Idiosyncratic reactions

DCP is a sulphonamide derivative. No cases of idiosyncratic reactions were reported.

Hypersensitivity and anaphylactic reactions

According to the applicant hypersensitivity and anaphylactic reactions have been identified during post-approval experience of DCP (frequency unknown). In the study of healthy volunteers two potential hypersensitive AEs were reported, urticaria and swelling face. No details are known. **(OC)**

Nausea, anorexia, dysgeusia and weight loss

Nausea, anorexia, dysgeusia and weight loss were reported in the HYP-HOP study, more commonly by patients on active treatment than those on placebo. Weight was repeatedly measured in the HYP-HOP study. A reduction in body weight was noted over the 9-week double-blind phase of the trial in both HYP and HOP subjects compared with placebo. Weight reduction accentuated slightly, with a maximum mean decrease of 3.98 kg in HYP subjects and 2.60 kg in HOP subjects observed at 35 weeks (all patients treated with DCP from week 9 onwards). At week 61 the mean reduction was 1.2-2.4 kg.

Nephrolithiasis

CAI block the resorption of sodium bicarbonate in the proximal tubule and as a consequence urinary pH is increased. Long term treatment increases the risk for the development of calcium phosphate calculi due to this metabolic alteration. For Acetazolamide the side effect is regarded as less common (≥ 1/1000, < 1/100). There were three reports of Nephrolithiasis in HOP patients in the 52- week extension phase.

5.5. Uncertainties and limitations about unfavourable effects

The product is applied for according to an Article 10(3) hybrid application. Hybrid applications can rely on the results of preclinical tests and clinical trials of an approved reference medicinal product. The chosen EU reference product is Fenamide, 50 mg, tablet that was first authorized in 1960 and has been marketed by Farmigea S.p.A. on the Italian market until October 2014. In the context of this legal basis, where data from the reference medicinal product are relied on a bridge should be established between the applied product and the reference product taking into account the extent of reliance of the data contained in the dossier of the reference medicinal product in the context of the therapeutic indication applied for..

No nonclinical studies have been provided with this application. The applicant refers to the reference product Fenamide. Essentially no bibliographic documentation on the nonclinical safety has been provided. The absence of nonclinical data on genotoxicity, carcinogenic potential and reproductive and developmental toxicity is a major deficiency.

In case the applicant wishes to refer to data from the reference product Fenamide in terms of pharmacokinetic as well as safety aspects, the applicant needs to address the relative bioavailability between the two products. At present, the applicant has not addressed whether the formulation of the test product, Ekesivy, is expected to result in the same plasma exposure as the reference product, Fenamide. This is essential to be able to claim that data from Fenamide are relevant for the current drug formulation. Moreover, data on many pharmacokinetic aspects of diclofenamide, which are also relevant for drug safety e.g. absorption, distribution, elimination (via metabolism and urinary excretion), interaction potential as a perpetrator and victim (via CYP enzymes and transporting proteins), pharmacokinetics in special patient populations (such as hepatic and renal impairment) are at present very limited or not available.

Relatively few AE in the extension phase of the HYP-HOP study were reported. In the study only 36% of the patients were treatment naïve, which enhances the likelihood of including patients which are known to tolerate the treatment. Furthermore, history of worsening symptoms with the use of CAI´s was an exclusion criterion. Narratives of SAEs and AEs are missing, furthermore the applicant´s presentation of laboratory values requires further clarification.

Since DCP is used off label the characteristic and otherwise quite rare side effects like paraesthesia may have jeopardised the blinding.

Exclusion criteria were extensive and patients with coincidental renal, hepatic, restrictive or obstructive lung disease, active thyroid disease and heart disease were not included. Furthermore, history of life-threatening episodes of respiratory muscle weakness or cardiac arrhythmias during attacks were also exclusion criteria just like a variety of concomitant medications. No studies in special populations (children, elderly, pregnant or lactating women or patient with decreased renal function) or direct studies of drug interactions have been performed.

Long term safety data are missing. Of special interest is the effects of chronic metabolic acidosis.

Many different mutations are responsible for HYP and HOP and other forms of periodic paralysis. There may be associations between ion channels in skeletal muscle and ion channels in cardiac muscle. Andersen Tawil syndrome is a rare genetic disorder characterised by periodic paralysis, life threatening ventricular arrhythmias and a variety of facial features. The knowledge about associations between different mutations, different types of periodic paralysis, different ion channels, effects in skeletal muscle and/or other organs (e.g. cardiac muscles) is incomplete. The applicant excluded Andersen Tawil syndrome and also HOP patients with known mutation in the α subunit of sodium channel (despite that genetic testing was not mandatory?) likely to avoid potential side effects known in these mutations.

To summarize the proposed indication/ target population is broader than the studied population which is a safety concern. The applicant's presentation of the data is difficult to interpret, and missing data further limits the conclusions that can be drawn.

5.6. Effects Table

Table 32: Effects Table for Ekesivy for the treatment of periodic paralysis (data cut-off: unknown)

Effect	Short Description	Unit	DCP	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects (Pivotal Study HYP-HOP)						
HYP Weekly attack rate[1]	Self-reported attack rate over final 8 weeks (Weeks 2-9) of the double-blind period. Missing diaries = no attack	Median (IQR)	0.9 (0.4, 1.5)	4.8 (0.5, 7.1)	Treatment effect Δ: -4.1 (95% CI: NA, 0.9) **P = 0.08** Uncertain. Small sample size. MO related to blinding, acute worsening criteria, SAP, missing data handling, study population characteristics	
HYP Weekly attack rate[2]	As above but days with missing diaries removed from calculations	Median (IQR)	3.9 (1.0, 6.9)	7.3 (6.2,14.0)	-3.8 (95% CI: NA, 3.3) **P = 0.11** Uncertain, as above.	

Effect	Short Description	Unit	DCP	Placebo	Uncertainties/ Strength of evidence	References
HOP Weekly attack rate[1]	See above.	Median (IQR)	0.3 (0.1, 1.6)	2.4 (0.5, NA)	-2.2 (95% CI: NA, 3.3) **P = 0.02** Uncertain, as above.	
HOP Weekly attack rate[2]	See above.	Median (IQR)	0.7 (0.2, 3.3)	4.4 (0.8, NA)	-3.9 (95% CI: -7.4, -0.6) **P = 0.02** Uncertain, as above.	
Unfavourable Effects						
Paraesthesia						
HYP-HOP (n=65 patients)	Self- reported AE	Nr of reports	17	4	Small sample size, self-reported, inconsistency in the presentations of AEs	
Cognitive disorder						
HYP-HOP (n=65 patients)	Self- reported AE	Nr of reports	5	2	Small sample size. Self-reported. Reactions may be reported under different terms but represent the same phenomenon, inconsistency in the presentations of AEs	
Hypokalemia						
Healthy volunteer (n=36 subjects)	Laboratory finding, s-potassium	Ten (28%) healthy volunteers had at least one s-potassium value in the range 2.5-3.4 mmol/L (reference 3.6-5.2 mmol/L)			Evidence for mechanism of action (DCP increases the renal potassium excretion)	
HYP- HOP (n=65 patients)	Laboratory finding, s-potassium	There were decreases in potassium in only HYP subjects at 9 weeks (in 8% of subjects) and at 61 weeks (in 20 % of subjects).			Inconsistency in the presentation of laboratory findings. The assessment of strength of evidence is dependent on further clarification of data by the applicant.	
Metabolic acidosis						
HYP- HOP (n=65 patients)	Laboratory finding, s-potassium	At 9 weeks bicarbonate levels in the DCP subjects were reduced in 46% of HYP subjects and in 41% of HOP subjects who were normal at baseline (no effect in the placebo treated subjects). At 61weeks, 27% of HYP subjects and 6% of HOP subjects who were normal at baseline had low bicarbonate levels.			Evidence for mechanism of action (DCP increases renal bicarbonate excretion)	

Abbreviations: HYP: hyperkalemic periodic paralysis; HOP: hypokalemic periodic paralysis.
Notes: 1=missing diary entries interpreted as no attack*; 2=missing diary entries not counted*
**In both cases, patients who reached a criterion of acute worsening were assigned an artificially high attack rate.*

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

A multidisciplinary major objection is raised requesting further information and justification for the bridge to the reference product.

The development of the dissolution method has not been described and further data is requested. The discriminatory power of the dissolution method should be shown.

Essential nonclinical and pharmacokinetic documentation for the applied product and the reference product are missing, and this would need to be addressed.

Concerning the clinical data, some of the data in the pivotal HYP-HOP study suggests that treatment with DCP may have an effect in the treatment of patients with primary periodic paralysis. The primary endpoint of the trial, attack rate, was reduced following treatment with DCP, relative to placebo. The same was the case for some of the secondary endpoints, including severity weighted attack rate and attack duration. Statistical significance was largely restricted to the HOP subjects, but it is recognized that the number of HYP patients included was low. HOP subjects also reported improvements in functional physical parameters. Reduction in rate, severity and duration of attack as well as improvements in QoL could be considered as potential outcome measures for a patient population for which no approved treatment options exist, assuming that the clinical relevance of the reported improvements would be adequately justified.

However, the current major deficiencies in the conduct and analysis of the study and data presentation and the resulting uncertainties preclude a full appreciation of the importance of these potentially favourable effects.

In addition, the studied population does not reflect the much broader proposed target population which is a concern from an efficacy as well as a safety point of view.

The AEs reported in the current studies (paraesthesia, dysgeusia, hypokalemia, metabolic acidosis, rash and nephrolithiasis) are known effects of the class of CAIs. No unexpected events or safety signals were reported. However, extensive exclusion criteria were implemented in a relatively small safety database which limits the ability to generalize. Long-term safety data are missing, which is a concern for understanding risks e.g. chronic metabolic acidosis. In addition, and importantly, the presentation of the safety data in the dossier was generally poor.

5.7.2. Balance of benefits and risks

Major issues have been identified concerning the link to the reference product both from a pharmaceutical and a PK perspective, and there is a lack of essential nonclinical and pharmacokinetic documentation.

In addition, major issues have been identified in relation to the quality of the submitted clinical study documentation which raises uncertainties regarding the conduct and data analysis of the pivotal HYP-HOP study. In addition, the proposed indication is insufficiently supported. Accordingly, the balance of benefits and risks is considered to be negative at this stage.

5.7.3. Additional considerations on the benefit-risk balance

The proposed indication, *treatment of periodic paralysis*, is substantially broader than the population studied, which consisted of 2 subgroups of (adult) patients with primary periodic paralysis and not the full disease spectrum. In addition, extensive exclusion criteria were implemented and there is no data in special populations. Patients with secondary periodic paralysis (e.g. due to diuretics) have not been studied, nor patients with e.g. Andersen-Tawil syndrome. Also, the data in HYP patients were very limited.

It is not clear whether the efficacy and safety results observed for adult HOP patients can be extrapolated to other patient groups. A thorough justification, both from an efficacy and safety point of view, would be necessary to further assess this. Alternatively, a more suitable revised indication should be proposed.

5.8. Conclusions

The overall B/R of Ekesivy is negative.