CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206709Orig1s000
207223Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
INTEGRATED REVIEW

NDA Number	206,709 and 207,223
Link to EDR	\\CDSESUB1\evsprod\NDA206709\00000
Submission Date	12/20/2017
Submission Type	Priority (Rolling Submission)
Brand Name	DIACOMIT
Generic Name	Stiripentol (STP)
Dosage Form and Strength	Capsules (250 mg and 500 mg) and powder for oral suspension in (b) (4) in 250 and 500 mg
Route of Administration	Oral
Proposed Indication	For the (b) (4) treatment of (b) (4) (b) (4) seizures associated with Dravet syndrome in patients (b) (4).
Applicant	Biocodex
Associated IND	107979
OCP Review Team	Jagan Parepally, Angela Men, Xiaofeng Wang, Kevin Krudys
OCP Final Signatory	Ramana S. Uppoor, PhD. Deputy Director Division of Clinical Pharmacology I

Contents

1. EXECUTIVE SUMMARY

The applicant is seeking approval for stiripentol (STP), a pentenol derivative, as [redacted] (b) (4) treatment of [redacted] (b) (4) seizures associated with Dravet syndrome. To date, no treatment has been approved for Dravet syndrome in the United States. The proposed dosing regimen is 50 mg/kg daily. In two pivotal phase 3 trials (STICLO France and STICLO Italy), STP, as an add-on treatment to clobazam (CLB) and valproate (VPA), was significantly superior to placebo at the 50 mg/kg dose level, as judged by the primary efficacy endpoint, responder rate (a responder is defined as a patient with a ≥ 50% decrease in frequency of generalized tonic-clonic or clonic seizures). In both STICLO studies, the add-on treatment of STP resulted in increased exposures of CLB and its active metabolite, norclobazam (NCLB) due to a drug-drug interaction which may, in part, contribute to the observed efficacy.

This review focuses on evaluation of the contribution of STP independent of increased clobazam and norclobazam exposure on efficacy, and concludes that currently available data is insufficient to conclusively determine the independent pharmacodynamic efficacy contribution of STP. Nevertheless, the effectiveness of STP as an add-on treatment to CLB and VPA in Dravet Syndrome was well established in two pivotal STICLO studies.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology I and Pharmacometrics, have reviewed the information contained in NDA 206,709 and 207,223. The review team recommends approval of this NDA from a clinical pharmacology perspective. The key review issues with specific recommendations /comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Two pivotal trials in DS provide primary evidence of effectiveness of STP in conjunction with CLB and VPA. Currently available data appears insufficient to conclusively determine the independent pharmacodynamic contribution of STP to the observed efficacy.
General dosing instructions	The proposed dosing regimen is 50 mg/kg administered in 2 or 3 divided doses taken with food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Stiripentol is not recommended in patients with moderate and severe hepatic impairment and renal impairment. • Refer to Section 1.2 for PMRs for drug-drug interaction studies based on STP metabolism and its CYP inhibition/induction and its P-gp and BCRP inhibition potential.

Bridge between the "to-be-marketed" and clinical trial formulations	To-be-marketed formulations were used in clinical trials. The applicant has developed two dosage formulations of STP: Capsules of 250 mg and 500 mg and powder for oral suspension in (b) (4) 250 and 500 mg. A relative bioavailability was conducted comparing exposures of stiripentol following administration of 500 mg powder for oral suspension in (b) (4) formulation and 500 mg capsule after single oral administration. (b) (4) (b) (4). The mean values for AUC(0-t) and AUC(0-∞) were comparable for both formulations. However, the mean stiripentol Cmax was 23% higher after administration of the test (b) (4) in comparison to that obtained after dosing with the capsules. This change does not appear to be clinically significant (see section 3.3.5 for further details).

1.2 Post-Marketing Requirements

Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
Effect of hepatic impairment on PK of stiripentol and its metabolites	Stiripentol is primarily metabolized in liver.	A clinical study to evaluate the pharmacokinetics, safety, and tolerability of stiripentol in subjects with varying degrees of hepatic function.
Effect of strong CYP3A and CYP2C19 and UGT inducers on the pharmacokinetics of stiripentol	Stiripentol is primarily metabolized by CY3A4, CYP2C19 and glucuronidation.	A drug-drug interaction study to evaluate the effects of rifampin on the pharmacokinetics of stiripentol in healthy volunteers.
Effect of stiripentol on the pharmacokinetics of a CYP1A2 substrate	Stiripentol is an inhibitor and an inducer of CYP1A2.	A drug-drug interaction study to evaluate the potential effects of stiripentol on the pharmacokinetics of caffeine in healthy volunteers
Effect of stiripentol on the pharmacokinetics of CYP2B6 sensitive substrate	Stiripentol is an inhibitor and an inducer of CYP2B6.	A drug-drug interaction study to evaluate the potential effects of stiripentol on the pharmacokinetics of CYP2B6 sensitive substrate in healthy volunteers
Effect of stiripentol on the pharmacokinetics of CYP3A4 sensitive substrate	Stiripentol is an inhibitor and an inducer of CYP3A4.	A drug-drug interaction study to evaluate the potential effects of stiripentol on the pharmacokinetics of CYP3A4 sensitive substrate in healthy volunteers

Effect of stiripentol on the pharmacokinetics of CYP2C19 sensitive substrate	Stiripentol is an inhibitor of CYP2C19.	A drug-drug interaction study to evaluate the potential effects of stiripentol on the pharmacokinetics of a CYP2C19 sensitive substrate in healthy volunteers
Effect of stiripentol on the pharmacokinetics of P-gp sensitive substrate	Stiripentol is an inhibitor of P-gp.	A drug-drug interaction study to evaluate the potential effects of stiripentol on the pharmacokinetics of a P-gp sensitive substrate in healthy volunteers.
Effect of stiripentol on the pharmacokinetics of BCRP sensitive substrate	Stiripentol is an inhibitor of BCRP.	A drug-drug interaction study to evaluate the potential effects of stiripentol on the pharmacokinetics of a BCRP sensitive substrate in healthy volunteers.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Stiripentol is purported to act by potentiation of GABAergic neurotransmission and possibly of glutamatergic neurotransmission. Stiripentol acts postsynaptically as a direct allosteric modulator of the GABA-A receptor, and binds to the GABA receptor supramolecular complex at a site distinct from many commonly used anticonvulsant, sedative and anxiolytic drugs. The following is a summary of the clinical pharmacokinetics of stiripentol:

Absorption: Stiripentol is well absorbed by the oral route since the majority of an oral dose is excreted in urine. Stiripentol Tmax ranges from 1.25-2.96 hours under fed conditions. Absolute bioavailability is unknown. A dedicated food effect study on the bioavailability of STP was not conducted. In Phase 3 studies STP capsules were administered with meals, 2 or 3 times per day.

Distribution: Stiripentol binds extensively to circulating plasma proteins (about 99%). The apparent volume of distribution (Vss) ranges from 32 to 192 L, as body weight increases from 10 to 60 kg.

Metabolism: Stiripentol is extensively metabolized; 13 different metabolites having been found in urine. The main metabolic processes are oxidative cleavage of the methylenedioxy system and glucuronidation. In vitro studies indicate that CYP1A2, CYP2C19, CYP2C9, and CYP3A4 are the main liver cytochrome P450 isoenzymes involved in metabolism.

Elimination: The mean elimination half-life ranged from 4.5 to 13 hours, increasing with dose. Following oral administration of stiripentol, urinary metabolites accounted collectively for the majority (73%) of the dose; a further 13-24% was recovered in feces as unchanged drug.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant proposes an oral dosing regimen of 50 mg/kg administered in 2 or 3 divided doses taken with food. Two pivotal trials, Study BC.299 (STICLO France) and Study BC.385 (STICLO Italy), evaluated stiripentol at the proposed dose of 50 mg/kg daily in Dravet syndrome patients (N=59). The proposed dose is acceptable from clinical pharmacology perspective. This dose was found to be effective and appears to be safe.

2.2.2 Therapeutic individualization

Stiripentol is a substrate of several CYP enzymes including CYP1A2, CYP2C19 and CYP3A4. The metabolic stability of STP was evaluated in a CYP phenotyping assay and the results suggest that none of the single CYP has a major contribution to the metabolism. In addition, STP is glucuronidated, but the specific UGTs that are involved are not known. Oxidative metabolism accounts for approximately 75% of the total metabolism of STP. Since stiripentol is eliminated through several metabolic enzymatic pathways, drug-drug interactions due to CYP inhibition through single CYP pathway is unlikely.

CYP3A and CYP2C19 Inducers: Stiripentol is eliminated by metabolism involving several CYP enzymes, particularly CYP1A2, CYP2C19, and CYP3A4, and involving glucuronidation. The applicant did not submit studies evaluating induction-based interactions that may lead to decreases in stiripentol concentrations. Stiripentol concentrations may decrease when it is co-administered with potent inducers such as phenytoin, phenobarbital and carbamazepine. Concomitant use of strong inducers with stiripentol should be avoided or dose adjustments should be made.

Hepatic Impairment: There was no dedicated study of the pharmacokinetics and metabolism of STP in hepatically impaired patients in this submission. However, STP is metabolized primarily by the liver; administration to patients with moderate to severe liver impairment is not recommended.

Renal Impairment: There was no dedicated study of the pharmacokinetics and metabolism of STP in renally impaired patients in this submission. However, mass balance study indicates that majority of the dose (>73%) was recovered in urine in the form of 13 metabolites and 18% fecal recovery. Therefore, STP administration to patients with moderate to severe renal impairment is not recommended.

2.3 Outstanding Issues

We have issued 8 PMRs for clinical trials: (1) a hepatic impairment trial; (2) Effect of CYP and UGT induction on STP pharmacokinetics and (3) CYP inhibition/induction and transporter

interaction potential of STP. Refer to Section 1.2 above for details. In addition, the following comment should be conveyed to the applicant:

I. STP is an inducer of CYP1A2, CYP2B6 and CYP3A4/5. Per Agency's guidance, if the investigational drug induces CYP3A4/5, the applicant should evaluate the potential of the investigational drug to induce CYP2C. You should evaluate in vitro induction potential of STP followed by clinical drug-drug interaction studies, if warranted.

II. You should evaluate stiripentol's in vitro inhibition potential of UGTs followed by clinical drug-drug interaction studies, if warranted.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

- Treatment with Diacomit is not recommended in patients with moderate to severe hepatic and renal impairment.
- When Diacomit is co-administered with clobazam, dose reduction of clobazam should be considered based on safety and tolerability of CLB.
- Statements related to (b) (4) should be deleted. (b) (4) (b) (4).
- Statements related to (b) (4) should be deleted.
- Insignificant drug-drug interactions between STP and concomitant AEDs listed in section 7 should be moved to section 12.3.
- Effect of other drugs on Diacomit listed in section 7 should be moved to section 12.3.
- Labeling statements related to (b) (4) should be deleted.
- Statement related to (b) (4) (b) (4) should be deleted.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Stiripentol is approved by European Medicines Agency (EMA), by Health Canada, and by the Japanese health authority. The applicant has developed two dosage formulations of Diacomit: capsules of 250 mg and 500 mg, powder for oral suspension in (b) (4) 250 and 500 mg. It is proposed for the (b) (4) treatment of (b) (4) seizures associated with Dravet syndrome. No approved treatments are available for DS in the United Sates at this time. The approvals were based on responder rate (a responder was defined as a patient who experienced a $\geq$ 50% decrease in seizure frequency during the double-blind treatment period compared to baseline as a primary efficacy endpoint.) Treatment with stiripentol resulted in a responder rate of 68% and 71% in two pivotal trials.

3.2 General Pharmacological and Pharmacokinetic Characteristics

SUMMARY OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

<table>
<tr><th colspan="2">Pharmacology</th></tr>
<tr><td>Mechanism of Action</td><td>Stiripentol antiepileptic activity is thought to involve potentiation of the GABAergic and glutamatergic transmissions in the CNS. Stiripentol enhances the cortical glutamatergic transmission by increasing glutamate release from nerve terminals. The exact mechanism of action is not completely understood. In vitro, STP has been shown to directly enhance GABAA receptor-mediated transmission by acting both postsynaptically at a neuronal site coupled to the GABAA receptor and presynaptically to increase GABA release from nerve terminals.</td></tr>
<tr><td>Active Moieties</td><td>The only known active moieties in plasma are the two STP enantiomers. There are no known active metabolites circulating in plasma.</td></tr>
<tr><td>QT Prolongation</td><td>A QTc study using a supra-therapeutic dose of STP was not conducted. A PMR will be issued for the applicant to perform and submit the results of a thorough QT trial.</td></tr>
<tr><th colspan="2">General Information</th></tr>
<tr><td>Bioanalysis</td><td>Analytical methodology was based on high performance liquid chromatography (HPLC) and detected only STP (parent drug) in plasma .The 3 metabolites resulting from cleavage of the methylenedioxy ring (p-OH, m-OH and di-OH) could not be detected. The limit of sensitivity of this method was 1 µg/mL. A summary of the method validation reports is included as an appendix.</td></tr>
<tr><td>Healthy Volunteers vs Patients</td><td>The multiple-dosing of 3,000 mg in healthy adults yields concentrations similar to those obtained in pediatric Dravet patients treated with 50 mg/kg/day (cross study-comparison).</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen</td><td>In the pivotal trial STICLO France (BC.299), mean (± SD) age was 9.4 (± 4.0) years, mean (± SD) dose was 48.9 (±1.8) mg/kg/day and mean (± SD) minimum plasma concentration was 10.0 (± 3.6) mg/L. In STICLO Italy (BC.385), mean (± SD) age was 9.2 (± 3.6) years, mean (± SD) dose was 50.6 (±4.2) mg/kg/day and mean (± SD) minimum plasma concentration was 10.2 (± 2.98) mg/L.</td></tr>
<tr><td>Dose Proportionality</td><td>The pharmacokinetics of stiripentol were slightly non-linear. The median half-lives were 4.3 hours, 10.3 hours, and 11.9 hours following 500 mg, 1000 mg, and 2000 mg doses, respectively.</td></tr>
<tr><td>Variability</td><td>For single doses of 500 mg, 1,000 mg, and 2,000 mg, the STIUNI study (BC.337) the following table provides coefficients of variation for Cmax and AUC normalized with respect to dose.
<table>
<tr><th>Parameter</th><th>STP 500 mg</th><th>STP 1,000 mg</th><th>STP 2,000 mg</th></tr>
<tr><td>Cmax</td><td>44.9%</td><td>27.7%</td><td>34.9%</td></tr>
<tr><td>AUC</td><td>42.5%</td><td>33.3%</td><td>30.7%</td></tr>
</table>
</td></tr>
</table>

	For multiple dosing, inter-subject variability in Cmin values for healthy subjects were 20.3% and 27.2% on Days 12 and 13 sing at 1,500 mg given twice a day.
ADME	
Absorption	Stiripentol was administered as an oral capsule in most of the studies. The PK data was characterized by a two-compartment model with zero order absorption.
Tmax	The median Diacomit Tmax ranged from 2 to 3 hours.
Distribution	The apparent volume of distribution increased from 32 L to 192 L in children as body weight increased from 10 to 60 kg. High plasma protein binding was observed for stiripentol (about 99 %).
Elimination	
Mean Terminal Elimination half-life	The half-life of elimination ranges from 4.5 hours to 13 hours, increasing over dose range of 500 mg to 2000 mg.
Metabolism	
Primary metabolic pathway(s) [in vitro]	Metabolic pathway for stiripentol was not clearly elucidated. Stiripentol is a substrate of several CYP enzymes including CYP1A2, CYP2C19 and CYP3A4. The metabolic stability of STP was evaluated in a CYP phenotyping assay and the results suggest that none of the single CYP play a major contribution to the metabolism. In addition, STP is glucuronidated, but the specific UGTs that are involved are not known. The oxidative metabolism accounts for approximately 75% of the total metabolism of STP.
Inhibitor/Inducer (in vitro)	In vitro studies indicate that stiripentol inhibits CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2D6 and CYP3A4. Stiripentol induces CYP1A2, CYP2B6, and CYP3A4 in vitro at clinically relevant concentrations (see section 3.34 for further details).
Transporter Systems (in vitro)	Stiripentol is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. However, stiripentol is a significant inhibitor of P-gp and BCRP, with IC50 values of 92.1 and 2.34 μM, respectively. Stiripentol is not a significant inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 at the tested concentrations.
Excretion	Following a single oral dose of 1200 mg STP in a metabolic study (Moreland et al., 1986), 13 metabolites accounted for 73.3% and 97.8% of the dose, respectively in 2 subjects. A fecal excretion investigation was carried out in 3 subjects (2 males, 1 female) given a 1,200 mg dose with collections on Days 0, 1, 2, 3-4 (combined), and 5-7 (combined). A mean 18.1% of dose was recovered unchanged STP in feces.

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Although the exact mechanism of antiepileptic activity of STP is not clear, STP is purported to act by potentiation of GABAergic neurotransmission and possibly of glutamatergic neurotransmission in the CNS. At concentration levels likely achieved in the brain with therapeutic doses of STP, the drug has been shown *in vitro* to directly enhance GABA receptor medicated transmission by acting both postsynaptically and presynaptically. In addition, unlike any other AED, STP apparently enhances the cortical glutamatergic transmission by acting presynaptically to increase glutamate release from nerve terminals.

In clinical setting, the primary evidence of effectiveness for STP as add-on therapy in combination with CLB and VPA in patients with Dravet syndrome comes from two Phase 3 studies in patients with Dravet syndrome (STICLO France and STICLO Italy). In STICLO France, STP was found to be significantly superior to placebo with a responder rate (defined as proportion of patients with a ≥ 50% decrease in frequency of generalized tonic-clonic or clonic seizures) of 71.4% in the STP group versus 5.0% in the placebo group ($p < 0.0001$). In STICLO Italy, the responder rate was 66.7% in the STP group versus 9.1% in the placebo group ($p = 0.0098$).

In both STICLO studies, treatment with STP was associated with increased exposures of CLB and its active metabolite, NCLB, i.e. up to 2-fold increase in CLB exposure and up to 4-5-fold increase in NCLB exposure due to a drug-drug interaction. VPA exposures were not significantly altered with add-on STP treatment. Therefore, the review team investigated whether the increase in responder rate compared to placebo was due to independent effect of STP, to increased CLB and NCLB exposures when STP is co-administered, or both. Since all the subjects in both STICLO studies were on concomitant CLB and VPA treatment, direct comparison of the efficacy of STP in the presence or in the absence of CLB and VPA cannot be made.

A retrospective analysis of charts of Dravet Syndrome patients treated with STP conducted by the applicant did identify some patients treated with or without concomitant CLB. The results showed that the responder rates were similar between treatment groups with or without concomitant CLB treatment, i.e. 71% (5/7) in patients without concomitant CLB versus 73% (16/22) in patients with concomitant CLB. However, this analysis was not pre-specified and the data came from a medical care environment where a patient diary was not used and the seizure assessment was different from that in the clinical trial paradigm. Thus, comparison of responder rates in this retrospective chart analysis with responder rates in the clinical studies such as the STICLO studies might be misleading. Therefore, no conclusion regarding the efficacy contribution of STP and CLB/NCLB should be drawn based on this retrospective analysis. (please refer to Dr. Steven Dinsmore's review for details about this retrospective analysis).

A series of analyses including multivariate logistic regression analyses, exposure-response analyses, and evaluation of subjects with minimum CLB/NCLB exposure change were conducted by the applicant and the review team to further evaluate this issue. The analysis results were inconclusive, however, due to limitations in the data, i.e. the small sample size (N=33 on STP and N=31 on placebo) and the fact that all STP treated subjects in the STICLO studies received concomitant CLB (refer to Section 4 Appendix for analysis details). Therefore, we conclude that the currently available data is insufficient to partition the efficacy contribution of STP and CLB/NCLB. Nevertheless, the effectiveness of STP as an add-on treatment to CLB and VPA in Dravet Syndrome was well established in two pivotal STICLO studies.

3.3.2 Is the proposed general dosing regimen appropriate?

Yes, the proposed dosing regimen is appropriate for the general population.

The applicant proposes an oral dosing regimen of 50 mg/kg administered in 2 or 3 divided doses. Two pivotal trials, Study BC.299 (STICLO France) and Study BC.385 (STICLO Italy), evaluated stiripentol at the proposed dose of 50 mg/kg daily in Dravet syndrome patients (N=64). The effectiveness of the proposed dosing regimen was demonstrated in these two pivotal trials and the safety profile was acceptable.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Based on a population PK analysis, body weight was identified as a significant covariate for clearance (CL/F) and volume of distribution (V/F). Both CL/F and V/F increase as body weight increases, as shown in the table below. Since body weight-based dosing regimen, i.e. 50 mg/kg/day has been proposed, no further dose adjustment based on body weight is necessary. After adjusting for body weight, age and sex did not show significant effect on STP PK.

Body weight	CL/F (L/hr)	V/F (L)	T1/2 (hr)
10	2.60± 0.18	32.0± 3.8	8.5 ± 1.3
20	3.51± 0.24	63.9± 7.7	12.6 ± 1.9
30	4.19± 0.29	95.9± 11.5	15.9 ± 2.4
40	4.74± 0.33	127.8± 15.3	18.7 ± 2.8
50	5.22± 0.36	159.8± 19.2	21.2 ± 3.2
60	5.65± 0.40	191.8± 23.0	23.5 ± 3.5

Hepatic Impairment: There was no dedicated study of the pharmacokinetics and metabolism of STP in hepatically impaired patients in this submission. Stiripentol is metabolized primarily by the liver; administration to patients with moderate to severe liver impairment is not recommended. A PMR will be issued to the applicant to conduct a study in patients with hepatic impairment.

Renal Impairment: There was no dedicated study of the pharmacokinetics and metabolism of STP in renally impaired patients in this submission. However, mass balance study indicates that majority of the dose (>73%) was recovered in urine in the form of 13 metabolites and 18% fecal recovery. Therefore, STP administration to patients with moderate to severe renal impairment is not recommended. Considering the incidence of renal impairment in Dravet syndrome patients is rare, no dedicated PK study in patients with renal impairment is required.

Pharmacogenomics: Stiripentol is metabolized by CYP1A2, CYP2C19 and CYP3A4. In addition, STP is glucuronidated, but the specific UGTs that are involved are not known. Since STP is a substrate for several CYP isoforms, and a significant fraction of STP dose is glucuronidated, it is not expected to be subject to gene polymorphisms and associated ethnic differences.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No dedicated clinical drug-drug interaction studies were conducted for stiripentol. However, effects of stiripentol on concomitant administration with clobazam and valproate were evaluated from the pivotal clinical studies. The effects of other extrinsic factors such as herbal products, diet, smoking, and alcohol use on the dose or exposure / response for stiripentol were not assessed in a formal study. The in vitro drug interaction potential, clinical drug-drug interactions between STP, clobazam, valproate are further discussed in this section.

In Vitro DDI Potential

Stiripentol Metabolism: Metabolic pathway for stiripentol was not clearly elucidated. Stiripentol is a substrate of several CYP enzymes including CYP1A2, CYP2C19 and CYP3A4. The metabolic stability of STP was evaluated in a CYP phenotyping assay and the results suggest that none of the single CYP play a major contribution to the metabolism. In addition, STP is glucuronidated, but the specific UGTs that are involved are not known. The oxidative metabolism accounts for approximately 75% of the total metabolism of STP. According to the applicant, such interactions involving inhibition of CYPs or UGTs have not been reported.

Estimation of Percent (%) Contribution by Various CYPs to the Total Elimination of a STP Dose

CYP	% metabolized	% of metabolic clearance	% of dose
CYP1A2	75	27	20
CYP2C19	54	19.6	15
CYP3A4	50	18	14
CYP3A5	40	15	11
CYP2C9	29	11	8
CYP2D6	27	10	7.5

CYP Inhibition Potential

In vitro studies indicate that stiripentol inhibits CYP1A2, CYP2B6, CYP2C19, CYP2C8, and CYP3A. In vitro CYP inhibition potential was evaluated in human liver microsomes (HLM) using probe substrates for each CYP enzyme. Table below represents IC50 values calculated for each enzyme based on inhibition of activity.

Assay	IC50
CYP1A2 inhibition (HLM, phenacetin substrate)	6.6 µM
CYP2B6 inhibition (HLM, bupropion substrate)	14 µM
CYP2C19 inhibition (HLM, omeprazole substrate	9.2 µM
CYP2C8 inhibition (HLM, paclitaxel substrate)	6.8 µM

CYP2C9 inhibition (HLM, diclofenac substrate)	130 µM
CYP2D6 inhibition (HLM, dextromethorphan substrate)	N.C.
CYP3A inhibition (HLM, midazolam substrate)	13 µM
CYP3A inhibition (HLM, testosterone substrate)	21 µM

Current DDI guidance states that the initial assessment of the investigational drug as an reversible inhibitor of CYP enzymes should be based on the basic model R_1=1+ [Imax,u]/Ki. A R_1 value > 1.02 would trigger further investigation of the DDI potential by either using a mechanistic model or conducting a clinical DDI study. The STP IC_{50} values towards CYP450s isoenzymes and the calculated basic model ratio based on unbound STP C_{max} are presented in the table below (calculated by the reviewer):

CYP450 isoenzyme	**IC50 (µM)**	**Ki (µM)**	**R_1 value***
1A2	6.6	3.3	1.286
2B6	14	7	1.135
2C8	6.8	3.4	1.277
2C9	130	65	1.015
2C19	9.2	4.6	1.205
2D6	N.C	N.C	N.C
3A4	13	6.5	1.145

Source: IC_{50} data from report Eurofins 100029108.

*R_1=1+ [Imax,u]/Ki ; where [Imax,u] represents the mean unbound steady-state Cmax value for unbound drug following administration of the highest proposed clinical dose and Ki= IC_{50}/2. The maximum STP concentration was calculated using the largest body weight (60 kg) and the recommended dose of 50 mg/kg/day. STP concentration = 3,000 mg/day / 135.6 L/day = 22.1 mg/L. The corresponding Molar concentration is [Imax,u] = 0.01x22.1 x 1,000/234.295 = 0.943 µM (plasma protein-binding of STP is 99%).

The calculated R_1 values were above the threshold of 1.02 triggering further assessment of CYP450 inhibitory interaction for CYP1A2, CYP2B6, CYP2C8, CYP2C19 and CYP3A4. A PMR will be issued to the applicant to perform and submit DDI interaction studies evaluating STP as an inhibitor of CYP1A2, CYP2B6, CYP2C19, CYP2C8 and CYP3A4.

Transporter Interactions:

Stiripentol is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. However, stiripentol is a significant inhibitor of P-gp and BCRP, with IC50 values of 92.1 and 2.34 µM, respectively. Stiripentol is not a significant inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 at the tested concentrations.

Note: The Cmax unbound/ IC50 value (R=0.403) calculated indicates that STP is likely to cause drug-drug interactions with BCRP substrates. A PMR will be issued to the applicant to perform

and submit DDI interaction studies evaluating STP as an inhibitor of P-gp and BCRP.

Stiripentol induces CYP1A2, CYP2B6, and CYP3A4 in vitro at clinically relevant concentrations. A PMR will be issued to the applicant to perform and submit DDI interaction studies evaluating effect of STP on substrates of CYP1A2 (caffeine), CYP2B6, and CYP3A4 (see section 1.2).

Clinical Drug-Drug Interaction Evaluation

Clobazam (CLB):
The effects of STP on clobazam (CLB) and its active metabolite norclobazam (NCLB) were derived from the STICLO France study, a randomized, placebo-controlled, add-on clinical trial of STP in pediatric patients with Dravet syndrome. Following a baseline period, STP or placebo was added to VPA and CLB during the double-blind period. The effects of STP on CLB and NCLB were expressed by comparing their dose-normalized minimum concentrations (mg/L/mg/kg) between the two periods, in the group (N=20) receiving STP (49.3 mg/kg/day).

STP increased CLB concentration by approximately 2-fold. Whereas, NCLB concentration increased by 4 to 5-fold (Table 1). CLB is extensively metabolized in the liver via N-demethylation and hydroxylation, and has 2 major metabolites, N-CLB and 4'-hydroxyclobazam, the former of which is active. N-CLB is estimated to be one-fifth as potent as CLB. The main enzyme that facilitates the process of N-demethylation is CYP3A4, and to a lesser extent CYP2C19 and CYP2B6. N-CLB is metabolized via hydroxylation by CYP2C19, which is more dependent than CLB on CYP2C19 as indicated by in vitro data, the STP Ki for inhibition of NCLB metabolism is lower than the two Kis for inhibition of CLB.

Table 1: CLB and NCLB Concentrations and Dose-Normalized Concentrations in Placebo versus STP-Treated Patients

	Placebo	STP
Concentrations (mg/L)		
CLB	0.20	0.31
NCLB	0.95	4.32
Dose-Normalized Concentrations (mg/L/mg/kg)		
CLB	0.45	0.84
NCLB	2.1	11.6

Mean (95% CI) values of these ratios increased from 0.39 (0.33-0.45) to 0.84 (0.66-1.02) for CLB and from 3.6 (1.6-5.6) to 11.6 (10.3-12.9) for NCLB. Since concomitant stiripentol administration increases concentration of CLB by 2 fold and NCLB concentration increased by 4 to 5-fold, clobazam dosage should be reduced by atleast 2 fold when used concomitantly.

Valproic Acid (VPA)
In the STICLO France study (BC.299), STP at a mean dose of 48.8 mg/kg/day had no effect on VPA plasma concentrations.

The effect of STP on the kinetics and metabolism of VPA were also evaluated by Levy et al [1]. A group of eight healthy adult male subjects receiving 500 mg/day of VPA were administered 300, 600 and 1,200 mg/day of STP. These doses of STP achieved mean (SD) respective average plasma concentrations (Cav) of 0.12 (0.04), 0.45 (0.18) and 1.37 (0.24) mg/L. All 3 treatments

were associated with statistically significant (17-35%) decreases three primary metabolites formed by cytochrome(s) P450. Since the clinical relevance of relatively small decreases in VPA metabolite plasma levels is unknown, VPA dose adjustment when administered with STP is not necessary based on PK interaction.

Seven PMRs related to drug-drug interactions studies will be issued to the sponsor (see section 1.2). Examples of the most commonly used concomitant CYP enzymes substrates include following drugs. Midazolam and diazepam are known to cause respiratory depression at high blood levels. Drugs including warfarin, theophylline are narrow therapeutic index drugs, can cause seizures, bleeding at high blood concentrations.

CYP1A2: warfarin, theophylline, caffeine

CYP3A4: Midazolam, triazolam, quinidine

CYP2C19: Diazepam, clopidogrel

P-gp: Carbamazepine

BCRP: Methotrxate, prazosin, glyburide, cimetidine, sulfasalazine, and rosuvastatin

Food Effect

A dedicated food effect study on the bioavailability of STP was not conducted. In Phase 3 studies STP capsules were administered with meals, 2 or 3 times per day. The applicant claimed that stiripentol degrades rapidly in an acidic environment (e.g. exposure to gastric acid on an empty stomach). However, the stability of stiripentol (powder (b) (4) and capsule) assayed in simulated gastric fluid (acidic environment plus stomach lytic enzymes) demonstrated that stiripentol was stable for up to 6 hours. A dedicated food effect study is not needed as STP administration with food is supported by Phase 3 study dosing instructions and gastric stability studies. Administration with food is convenient in this population.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The to-be-marketed (TBM) formulations are same as clinical trial formulations. The sponsor has developed two dosage formulations of STP: Capsules of 250 mg and 500 mg containing povidone, sodium starch glycolate (b) (4), and magnesium stearate and powder for oral suspension in (b) (4) 250 and 500 mg containing povidone, sodium starch glycolate (b) (4), (b) (4) glucose (b) (4), erythrosine, titanium dioxide, aspartame, (b) (4) flavor, carmellose sodium, and hydroxyethylcellulose as inactive ingredients. A relative bioavailability was conducted comparing exposures of stiripentol following administration of 500 mg powder for oral suspension in (b) (4) formulation and 500 mg capsule after single oral administration in 24 healthy males. The (b) (4) formulation was not bioequivalent to the capsule formulation. The mean values for AUC(0-t) and AUC(0-∞) were comparable for both formulations. However, the mean stiripentol Cmax was 23% higher after administration of the test (b) (4) in comparison to that obtained after dosing with the capsules. The point estimate (1.23) and the 90 % confidence interval (1.10-1.37) was higher than the upper limit of the bioequivalence range (0.80-1.25) as shown in Table 2 below.

Table 2: The mean PK parameters of stiripentol are summarized in the following table.

STIRIPENTOL		C_{max} (µg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (h.µg/mL)	$AUC_{0-\infty}$ (h.µg/mL)	$AUC_{0-\infty}$ (h.µg/mL)
Treatment A (test (b) (4))	N	24	24	18	24	18	17
	Mean	7.32		14.38	32.97	38.00	37.36
	Geom. Mean	7.04		12.27	31.28	35.85	35.20
	CV%	29		53	34	34	35
	Median		3.50				
	[Min-Max]		1.50-4.00				
Treatment B (reference capsules)	N	24	24	21	24	21	17
	Mean	5.99		17.41	30.23	33.58	35.08
	Geom. Mean	5.72		13.75	28.54	31.55	32.93
	CV%	29		65	36	37	37
	Median		3.00				
	[Min-Max]		1.00-4.00				
90 % Confidence intervals		1.10-1.37	NS (1)		1.04-1.16		0.98-1.15
Point estimate		1.23			1.10		1.06

The maximum concentration, Cmax increase by 23% after administration of the test (b) (4) in comparison to that obtained after dosing with the capsules does not appear to be clinically significant. In this study, healthy volunteers did not have a differential tolerance between the treatments groups and the safety reports did not identify a difference based on formulation. Moreover, a large proportion of long term study patients were on (b) (4) without note of a differential effect. According to the clinical division, there does not appear to be a safety signal selectively due to the (b) (4) formulation. Two of the long-term studies, TAU-EAP and DIAVEY had a large proportion of patients on (b) (4), approximately 50% each. STP (b) (4) formulation is indicated for patients (b) (4). As part of the administration instructions the (b) (4) should be emptied in a glass of water and drunk immediately. Office of Pharmaceutical Quality (OPQ) is considering recommending alternative administration instructions to mix with food. The applicant was requested CMC data to support this change (refer to CMC review for further details).

4. Appendices

4.1 Summary of Bioanalytical Method Validation and Performance

Assay specificity
No major interference peaks were found for the compounds of interest in control blank plasma samples, run in the validation study.

Standard used in the validation procedure were assayed on three separate days.
Each curve contained standard at 1, 2.5, 5, 10, 20 µg/ml. Quality controls at low (2 µg/ml), Medium (8 µg/ml) and high (16 µg/ml) were assayed twice with each standard set. Each set also included a control zero and plasma blank. The limit of quantitation of stiripentol in extracted plasma sample was 1 µg/ml.

Precision
Precision of the assay over a range of 1 µg/ml to 20 µg/ml was demonstrated for a spiked plasma standard curve, assayed in triplicate in three separate days. The coefficients of variation at the lower (1 µg/ml) and upper (20 µg/ml) limits of quantitation are 15.8% and 1.22% respectively. The average coefficient of variation is 7.76%. The CV range for the 1 µg/ml standard was 4.2 to 8.80% while the CV range for the 20 µg/ml standard was 4.20 to 5.72%. Assayed values obtained are shown to be reproducible. The coefficient of variation for the low control is 10.9%, for the medium control is 6.51% while that of the high control is 6.71%.

Linearity
Linearity of the analytical method was demonstrated for spiked plasma standards assayed in triplicate on three separate days. The stiripentol standard curve was found to be linear from 1 µg/ml to 20 µg/ml

Recovery and dilution integrity for 100 times dilution factor of stiripentol from plasma was demonstrated at standard concentrations 1 µg/ml, 10 µg/ml and 20 µg/ml

STANDARD CURVE PARAMETERS

Standard curve	*(A) Y-Intercept*	*(B) Slope*	*(r) Correlation coefficient*
1	- 0.0093395	0.112	0.9999
2	- 0.0215157	0.119	0.9994
3	- 0.0151984	0.106	0.989
1	- 0.1159918	0.171	0.9970
2	- 0.07352629	0.157	0.9997
3	- 0.05131277	0.153	0.9985
1	- 0.0008180	0.144	0.9981
2	- 0.0675799	0.149	0.9994
3	- 0.1258961	0.157	0.9959

Stability
Results from the study stability of the controls are reported in table 7 for stiripentol. The coefficients of variation for the low control varies fron1 5. 03 to 14%, for the medium control varies from 1.96 to 11.1 %, for the high control varies from 3.13 to 7.35%. These results den1onstrate the stability of the samples on one, two or three cycles freezing/thawing.

Note: These assay validation and performance were done in 1994 with HPLC method. Several stability measures including short-term stability, long-term stability, hemolysis assessment usually included in the report were not conducted. However, the assay found to specific without major interference peaks were found for the compounds of interest in control blank plasma samples.

Assay Performance

Grieg trial (StudyBC.287)

- The range of the assay was 6.67 to 250 µg/mL and the between-day coefficient of variation for an 8 µg/mL standard was <10%.

STICLO trials (BC.299) STIUNI (BC.337) and Pons (BC.345)

- The validated linear range for the assay was from 1 µg/mL to 20 µg/mL.
- The limit of quantitation was 1 µg/mL.
- Within- and Between-Day Coefficients of Variation:

Concentration (µg/mL)	**Precision (%)**	
	Between-Day	**Within-Day**
2	10.9	7.37 ± 15.2
8	6.51	2.26 ± 6.83
16	6.71	5.36 ± 9.36

- STP-1 trial [BC.609]
  - LC/MS/MS method and validation described in more detail in [BC.609]
  - The validated linear range for the assay was from 250 to 25,000 ng/mL.
  - Within- and Between-Day Coefficients of Variation:

Concentration (µg/mL)	Precision (%)	
	Between-Day	Within-Day
750	5.1	2.1
4,000	2.9	1.5
20,000	3.8	1.4

- STIVAL trial [BC.481]
  - HPLC method and validation described in more detail in [BC.481]
  - The validated linear range for the assay was from 0.1 to 20 µg/mL.
  - Within- and Between-Day Coefficients of Variation:

Concentration (µg/mL)	Precision (%)	
	Between-Day	Within-Day
0.1	8.77	1± 9.11
0.3	4.03	1± 5.02
8	3.96	1± 3.22
16	3.51	1± 2.51

In addition, the R- and S-enantiomers in plasma were quantitated in one study described below.

- STIPOP trial [STP167]
  - Within- and Between-Day Coefficients of Variation:

Concentration (µg/mL)	Precision (%)	
	Between-Day	Within-Day
2	10.9	7.37 ± 15.2
8	6.51	2.26 ± 6.83
16	6.71	5.36 ± 9.36

- STP-1 trial [BC.609]
  - Within- and Between-Day Coefficients of Variation:

Concentration (µg/mL)	Precision (%)	
	Between-Day	Within-Day
750	5.1	2.1
4,000	2.9	1.5
20,000	3.8	1.4

4.2 Applicant's Population PK Analyses

Objective:

The objectives of this analysis were to evaluate the steady state population pharmacokinetic parameters of stiripentol in children with Dravet syndrome treated with stiripentol + valproate + clobazam and to evaluate the influence of age, weight, sex and co-medications on the pharmacokinetic parameters of stiripentol.

Data:

The database includes 35 children and 139 STP concentrations. There was no concentration below the lower limit of quantification of the method. Typically, the data of a patient were obtained during two consecutive days, after at least two weeks of treatment with STP, CLB and VPA.

Methods:

Different structural models including 1 or 2 compartments with first-order or saturable Michaelis-Mention elimination from the central compartment and a first-order or a zero-order absorption process were tested.

Interindividual variability was described by a multivariate lognormal distribution with mean vector and variance-covariance matrix to be estimated. Interoccasion variability in CL/F was also considered. Residual variability was described by a combined error model using both additive and proportional error. The population parameters were estimated by nonlinear regression on the mixed-effects model by a parametric maximum likelihood approach implemented in the software NONMEM VI with FOCEI.

A stepwise approach was used to build the covariate model with forward addition and backward elimination.

Visual predictive check (VPC) and bootstrap were used for model evaluation.

Results:

The analysis dataset consisted of 139 STP concentrations from 35 patients, out of which 18 were boys and 17 were girls. The age and body weight information are shown in Table 3.

Table 3. Demographic data

	N	Mean	SD	Median	Min	Max
Age (year)	35	7.95	4.96	7.3	1.0	17.6
Body weight (kg)	35	27.6	15.8	24.8	9.1	74.0

Source: Applicant's population PK report, appendix 16.1.10, Table 8.1.1-2

The results show that a one-compartment model with first order absorption and elimination rate best fitted the data. The typical value of STP apparent clearance and apparent volume of distribution were related to body weight through allometric scaling. Once body weight was included in the model, sex and age were not significantly related to STP clearance and volume of distribution. The final model parameter estimates are shown in Table 4.

Table 4. Final Model Parameter Estimates

	Fixed effects		Standard deviation of random effect[a]	
	Point estimate	SE (%)	Point estimate	SE (%)
CL/F = θ_1 x (BW/25) [6] (L/h)	θ_1 = 3.87	7.4	Interindividual: 0.157	137
	θ_6 = 0.433	31.9	Interoccasion: 0.322	63
V/F = θ_2 x (BW/25) (L)	θ_2 = 79.9	10.5	Interindividual: 0.231	84
Ka = θ_3 (h^{-1})	θ_3 = 2.08	40.1	Interindividual: 1.22	42
Residual error model[b]	θ_4 = 0.102	30.9		
SD(ε) = Pred x $\theta_4\theta_5$	θ_5 = 1.40	18.1		

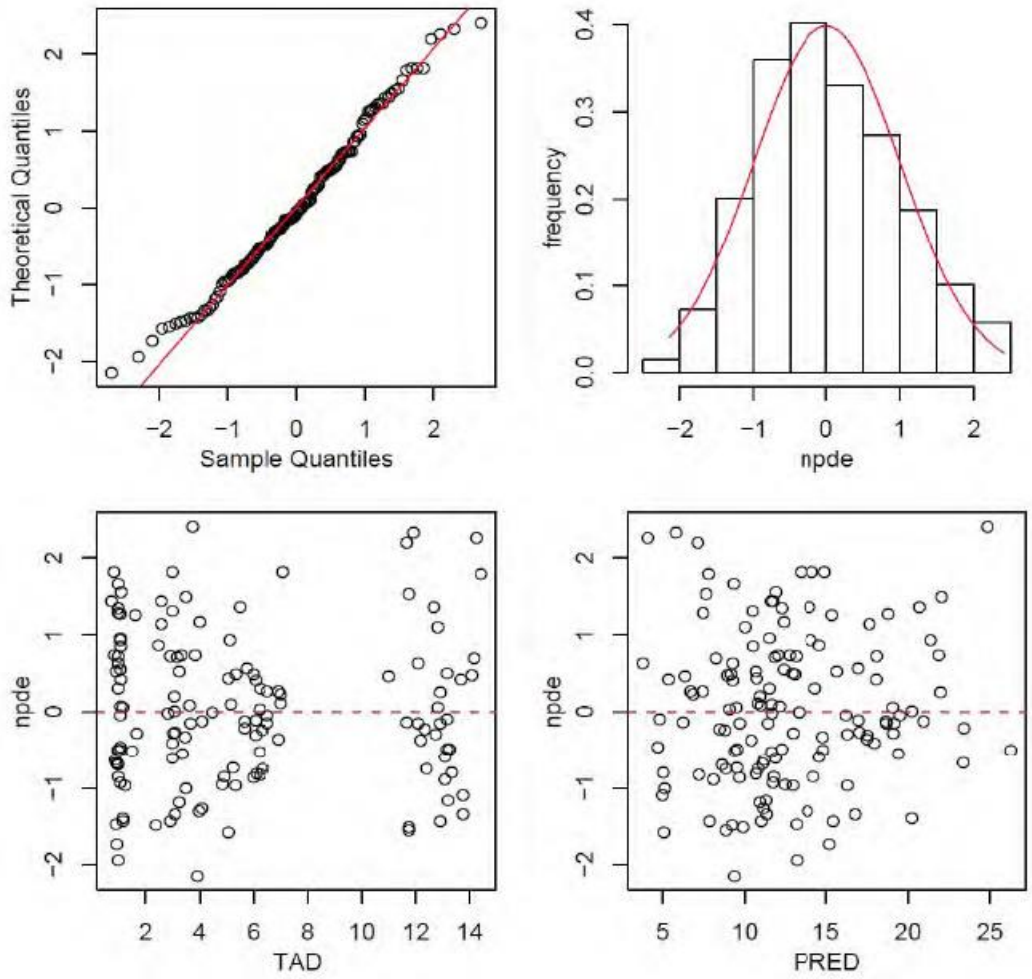
[a] The SD of random effect is approximately equal to the coefficient of variation of the parameter. For example, the interindividual variability of CL has a CV of 0.157, *i.e.* 15.7 %.

[b] Pred is the concentration predicted by the model. SD(ε) is the standard deviation of the residual error, *i.e.* the difference between the observed and the predicted concentration.

Source: Applicant's population PK report, appendix 16.1.10, Table 8.1.5-1

The normalized prediction distribution errors (NPDE) were used for model evaluation and the results show that the distribution of prediction errors is close to the expected normal distribution with zero mean (observed mean: 0.033) and unit variance (observed variance: 0.98), and it was random with respect to time after dose and predicted concentrations (Figure 1).

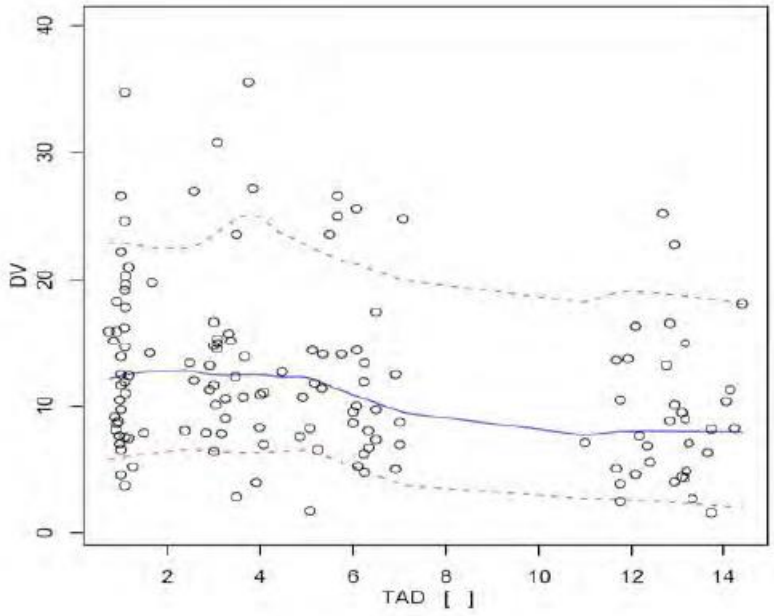
Figure 1. Distribution of NPDE for the final model



Source: Applicant's population PK report, appendix 16.1.10, Figure 8.1.3-1

Visual predictive check was conducted and the results are shown in Figure 2.

Figure 2. VPC for the final model



Visual Predictive Check of the final population model for STP, based on 500 replications.

The points are the observed concentrations versus time after dose. The solid line is the median of the replications. The dotted lines are 5th and 95th percentiles of the replications.

Source: Applicant's population PK report, appendix 16.1.10, Figure 8.1.3-3

Bootstrap analysis was conducted to assess the precision of parameter estimates and the results are shown in Table 5.

Table 5. Summary statistics of the bootstrap using the final model

Parameter	Mean	SD	SD (%)	Median	2.5th perc.	97.5th perc.
Typical CL/F	3.90	0.275	7	3.88	3.41	4.44
θ_2	77.9	11.6	15	75.8	60.8	102
θ_3	2.45	1.22	50	2.01	0.96	4.96
θ_4	0.087	0.051	59	0.098	0.01	0.17
θ_5	1.33	0.34	25	1.36	0.58	1.86
θ_6	0.454	0.13	29	0.456	0.23	0.72
SD(EtaCL) interindividual	0.132	0.095	72	0.152	0.045	0.259
SD(EtaCL) interoccasion	0.285	0.115	40	0.307	0.045	0.444
SD(EtaVd)	0.17	0.138	81	0.20	0.045	0.43
SD(EtaKa)	1.3	0.386	30	1.25	0.63	2.25

Source: Applicant's population PK report, appendix 16.1.10, Table 8.1.5-2

Reviewer's comments:
Overall, the population PK analysis for stiripentol when co-administered with clobazam and valproate is reasonable. Body weight, body surface area, age, sex, and CYP2C19 genotype were tested in the covariate modeling. Body weight was the only significant covariate retained in the final model affecting the apparent clearance and volume of distribution based on the data from 35 subjects.

4.3 Applicant's Analysis on the Effect of CLB and NCLB on Efficacy of STP

4.3.1 Covariate Analysis (Logistic Regression)

Objective:

The objective of this analysis was to address FDA's concern regarding the contribution of CLB/NCLB to efficacy as a result of the potent pharmacokinetic interactions with STP.

Data:

Data from studies STICLO France and STICLO Italy were used in this analysis. The number of patients enrolled and who received treatment in STICLO France was 41, out of which 21 received STP plus CLB and VPA and 20 received placebo plus CLB and VPA. The number of patients enrolled and who received treatment in study STICLO Italy was 23, out of which 12 received STP

plus CLB and VPA and 11 received placebo plus CLB and VPA.

Method:

To assess the contribution of CLB to the efficacy observed in subjects treated with STP, a covariate adjusted analysis was performed. This analysis was conducted using a logistic model where the dependent variable is the treatment response (i.e., reduction of ≥ 50% in total generalized clonic or tonic-clonic seizures), the independent variables being STP or placebo (i.e., treatment group), along with the change from baseline in the plasma concentrations of CLB and its metabolite (Norclobazam - NCLB) as covariates. The change from baseline in Cmin concentrations of CLB and NCLB are used as covariates or potential contributing factors in the analysis with the logistic model.

Results:

Logistic regression analyses with treatment group (STP or placebo) as independent variable and no adjustment for the change from baseline in the plasma concentration of CLB and NCLB were conducted and the results are shown in Table 6.

Table 6. Summary of Logistic Regression Analysis Results without Adjustment for Covariates

Study	P-value	Odds Ratio (STP *v.s.* Placebo) (95% CI)
STICLO – France and Italy (pooled)	<0.0001	34.50 (6.76 – 176.08)
STICLO – France	<0.0001	47.50 (5.15 – 438.49)
STICLO – Italy	0.0098	21.33 (1.81 – 251.26)

Note: an odds ratio close to 1 indicates the percent of subjects that achieved 50% or more decrease in total number of generalized clonic or tonic-clonic seizures are fairly equal between the two treatment groups. An odds ratio of >1 indicates more subjects achieved 50% or more decrease of generalized clonic or tonic-clonic seizures in the STP group compared to the placebo group. And an odds ratio of < 1 indicates fewer subjects achieved 50% or more decrease in total number of generalized tonic-clonic or clonic seizures in the STP group compared to the placebo group.

Source: Applicant's covariate analysis report, Table 5-1. 5-5

Logistic regression analyses with treatment group (STP or placebo) and change from baseline in the plasma concentration of CLB and NCLB as independent variables were conducted and the results are shown in Table 7.

Table 7. Summary of Logistic Regression Analysis Results with Adjustment for Covariates

Study	P-value			Odds Ratio (STP *v.s.* Placebo) (95% CI)
	Treatment Difference	Change from Baseline in CLB Conc.	Change from Baseline in NCLB Conc.	
STICLO – France and Italy (pooled)	0.0055	0.5038	0.6628	18.17 (2.34 - 141.04)
STICLO – France	0.0308	0.6152	0.2722	20.01 (1.32 - 303.33)
STICLO – Italy	0.0584	0.3496	0.6808	28.00 (0.89 - 883.02)

Source: Applicant's covariate analysis report, Table 5-4. 5-5

Reviewer's comments:
Based on the logistic regression analysis results, the applicant concluded that CLB and NCLB plasma concentrations are contributing to the responses; however, this contribution is insignificant compared to the contribution of the STP; and STP is the main efficacy contributor.

However, there are multiple limitations of the applicant's analyses.

- *All subjects were on concomitant CLB treatment; no information is available for STP treatment without concomitant CLB.*
- *Model assumptions of the logistic regression might be violated. Specifically, independent variables STP treatment and change from baseline in CLB and NCLB concentrations, are highly correlated. The interpretation of the odds ratio should be the ratio of the odds of being a responder in the STP arm versus that in the placebo arm, holding the other independent variables, i.e. change from baseline in CLB and NCLB concentrations, constant. Since there are no observed data for which STP or placebo treatment is independent of changes from baseline in CLB and NCLB concentrations due to the known PK interactions, the estimate of STP treatment effect on the responder rate while controlling for change from baseline in CLB and NCLB concentrations would be imprecise, and thus unreliable.*
- *Sensitivity analyses incorporating different independent variables such as steady state CLB and NCLB concentrations, centered steady state CLB and NCLB concentrations, and interaction terms between STP treatment and CLB and NCLB concentrations, conducted by the reviewer yielded inconsistent results compared to the applicant's.*

Due to the limitations, it's concluded that the applicant's covariate analysis is not robust and no conclusion regarding the efficacy contribution of STP and CLB/NCLB should be made based on this analysis.

4.3.2 Non-model based analysis

CLB dose change in responders and non-responders

The objective of this analysis was to assess the relationship between the response and the CLB dose change (increase or decrease) from baseline to post baseline using data form the STICLO and STP-1 Japan studies.

The proportion of patients whose CLB dose was changed/unchanged was compared between responders and non-responders in the STICLO studies. The results are shown in Table 8

Table 8. CLB dose changes in responders and in non-responders (STICLO studies)

CLB dose		NON-RESPONDER	RESPONDER	
(baseline to Wk 8)	CATEGORY	n (%)	n (%)	P-VALUE*
STP IN FRANCE	DECREASE	5 (83.33)	11 (78.57)	
	NO CHANGE	1 (16.67)	1 (7.14)	0.5353
	INCREASE		2 (14.29)	
STP IN ITALY	DECREASE	1 (25.00)	5 (71.43)	
	NO CHANGE	3 (75.00)	2 (25.00)	0.2405
	INCREASE		1 (14.29)	
PLACEBO	DECREASE	11 (37.93)		
	NO CHANGE	12 (41.38)	1 (50.00)	0.4715
	INCREASE	6 (20.69)	1 (50.00)	

**Chi-Square test*
Source: Applicant's covariate analysis report, Table 6-1

Data from the Japanese study was also used to evaluate the relationship between CLB dose change and treatment response. The results are shown in Table 9.

Table 9. CLB dose changes in responders and in non-responders (STP-1 Japan study)

CLB dose	NON-RESPONDER	RESPONDER	
(baseline to Wk 12)	n (%)	n (%)	P-VALUE*
DECREASE	4 (50.00)	4 (25.00)	
NO CHANGE	4 (50.00)	12 (75.00)	0. 2207
INCREASE	0	0	

**Chi-Square test*
Source: Applicant's covariate analysis report, Table 6-2

CLB and NCLB concentration change in responders and non-responders

The objective of this analysis was to assess the CLB and NCLB concentration change from baseline in responders and non-responders using the STICLO and STP-1 study data.

The CLB Cmin change from baseline to post baseline, i.e. week 8 in STICLO study and week 16 in the STP-1 study, was compared between responders and non-responders. The results are shown in Table 10 and Table 11.

Table 10. CLB Cmin change from baseline in responders and non-responders (STICLO

studies)

Treatment	Statistic	Non-responder	Responder	p-value*
STP IN FRANCE	n	6	14	
	mean (SD)	0.128 (0.106)	0.132 (0.138)	0.9484
	median	0.109	0.082	
	min	0.014	-0.026	
	max	0.301	0.384	
STP IN ITALY	n	4	7	
	mean (SD)	-0.045 (0.296)	0.053 (0.073)	0.5586
	median	-0.01	0.08	
	min	-0.396	-0.088	
	max	0.237	0.127	
PLACEBO IN FRANCE	n	16	1	
	mean (SD)	0.018 (0.035)	-.039 (0.000)	NA
	median	0.019	-0.039	
	min	-0.035	-0.039	
	max	0.094	-0.039	
PLACEBO IN ITALY	n	10	1	
	mean (SD)	-0.013 (0.091)	0.022 (0.000)	NA
	median	0.019	0.022	
	min	-0.222	0.022	
	max	0.097	0.022	

**T test*
Source: Applicant's covariate analysis report, Table 6-3

Table 11. CLB Cmin change from baseline in responders and non-responders (STP-1 Japan study)

Statistic	Non-Responder	Responder	P-Value *
N	8	12	
Mean (SD)	0.075(0.138)	0.080(0.082)	0.9211
Median	0.016	0.056	
Min	-.002	-.015	
Max	0.404	0.289	

**T test*
Source: Applicant's covariate analysis report, Table 6-4

The NCLB Cmin change from baseline to post baseline, i.e. week 8 in STICLO study and week

16 in the STP-1 study, was compared between responders and non-responders. The results are shown in Table 12 and Table 13.

Table 12. NCLB Cmin change from baseline in responders and non-responders (STICLO studies)

Treatment	Statistic	Non-responder	Responder	p-value*
STP IN FRANCE	n	6	14	
	MEAN (SD)	2.116 (2.862)	2.994 (1.068)	0.4949
	MEDIAN	2.806	2.919	
	MIN	-2.07	1.13	
	MAX	5.23	4.908	
STP IN ITALY	n	4	7	
	MEAN (SD)	3.582 (1.313)	3.180 (2.118)	0.7066
	MEDIAN	3.406	3.259	
	MIN	2.361	0.4	
	MAX	5.157	6.743	
PLACEBO IN FRANCE	n	16	1	
	MEAN (SD)	-.046 (0.207)	-0.088 (0.000)	NA
	MEDIAN	-0.001	-0.088	
	MIN	-0.53	-0.088	
	MAX	0.32	-0.088	
PLACEBO IN ITALY	n	10	1	
	MEAN (SD)	0.014 (0.170)	-0.056 (0.000)	NA
	MEDIAN	0.042	-0.056	
	MIN	-0.24	-0.056	
	MAX	0.24	-0.056	

**T test*
Source: Applicant's covariate analysis report, Table 6-5

Table 13. NCLB Cmin change from baseline in responders and non-responders (STP-1 Japan study)

Statistic	Non-Responder	Responder	P-Value *
N	8	12	
MEAN (SD)	0.744(1.507)	2.130(2.164)	0.1087
MEDIAN	0.767	1.978	
MIN	-1.80	-2.04	
MAX	3.192	6.471	

**T test*
Source: Applicant's covariate analysis report, Table 6-6

Reviewer's comments:
The applicant concluded that no statistically significant difference in CLB dose change and CLB/NCLB Cmin change from baseline was identified between responders and non-responders in the STICLO and STP-1 studies. However, these analyses were not sufficiently powered to detect any statistically significant difference due to the small sample size. Therefore, the results should be interpreted with caution.

4.4 Reviewer's Analyses to evaluate the contribution of stiripentol independent of increased clobazam and norclobazam exposure on efficacy

Given the limitations of the data and the concerns with the applicant's analysis, the reviewer approached the questions from multiple different directions to attempt to provide any additional insight into the potential independent effect of STP on efficacy. This includes:

- Exposure-response analysis of STP
- Evaluation of prior knowledge regarding exposure-response relationships of CLB/NCLB
- Subgroup analysis of individuals with minimal increases in CLB/NCLB levels

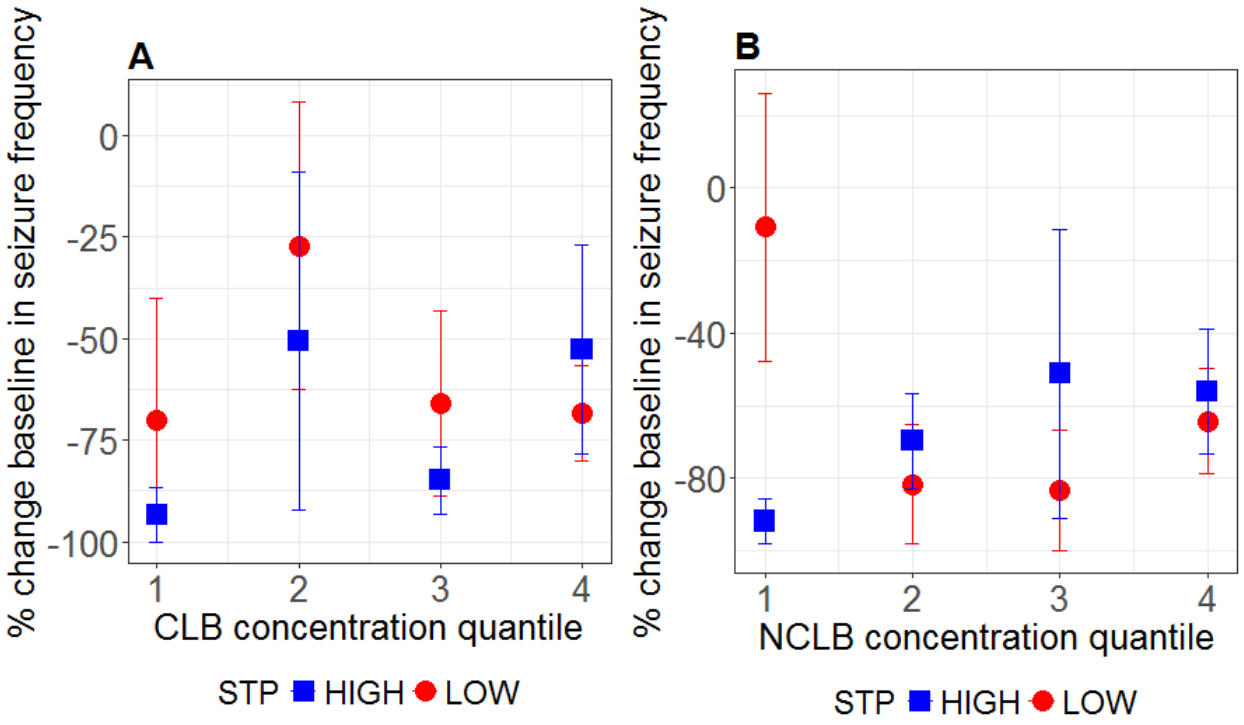
4.4.1 Exposure-Response Analysis of STP by Adjusting for CLB/NCLB Exposures

The primary objective of this review is to evaluate whether STP is contributing additional benefit, independent of increases in CLB and NCLB exposure, as an add-on treatment to CLB and VPA. Exploring the exposure-relationship between the efficacy endpoint, % change from baseline in seizure frequency, and STP exposure at fixed levels of CLB/NCLB exposure might be able to provide some insights into whether STP significantly adds benefit to the standard treatment with CLB and VPA.

To achieve this goal, all STP-treated subjects in the STICLO studies were evenly divided into four bins based on the CLB/NCLB exposure quantiles. CLB/NCLB exposure levels were considered sufficiently similar within each bin. Next, subjects within each bin are evenly divided into two subgroups based on the median of STP exposures within each bin, i.e. one with STP exposure above median STP exposure (high STP exposure subgroup) and the other with STP below the median level (low STP exposure subgroup). The mean % change from baseline in seizure frequency was computed for each subgroup within each bin (n=3/4). If the high STP exposure subgroup consistently provided better efficacy than the low STP exposure subgroup within each bin, we may be more likely to conclude STP provides additional benefit in conjunction with CLB/NCLB.

The analysis results are shown in Figure 3, suggesting no clear exposure-response relationship for STP. However, the lack of clear exposure-response relationship might be due to limited sample size, n=3/4 in each STP subgroup within each bin. Therefore, this E-R analysis for STP is considered inconclusive.

Figure 3. Comparison of % Change from Baseline in Seizure Frequency between High and Low STP Exposure Subgroups within Each Bin of CLB Exposure (A) or NCLB Exposure (B)



Note: Red and blue symbols represent mean % change from baseline in seizure frequency; error bars represent standard error.

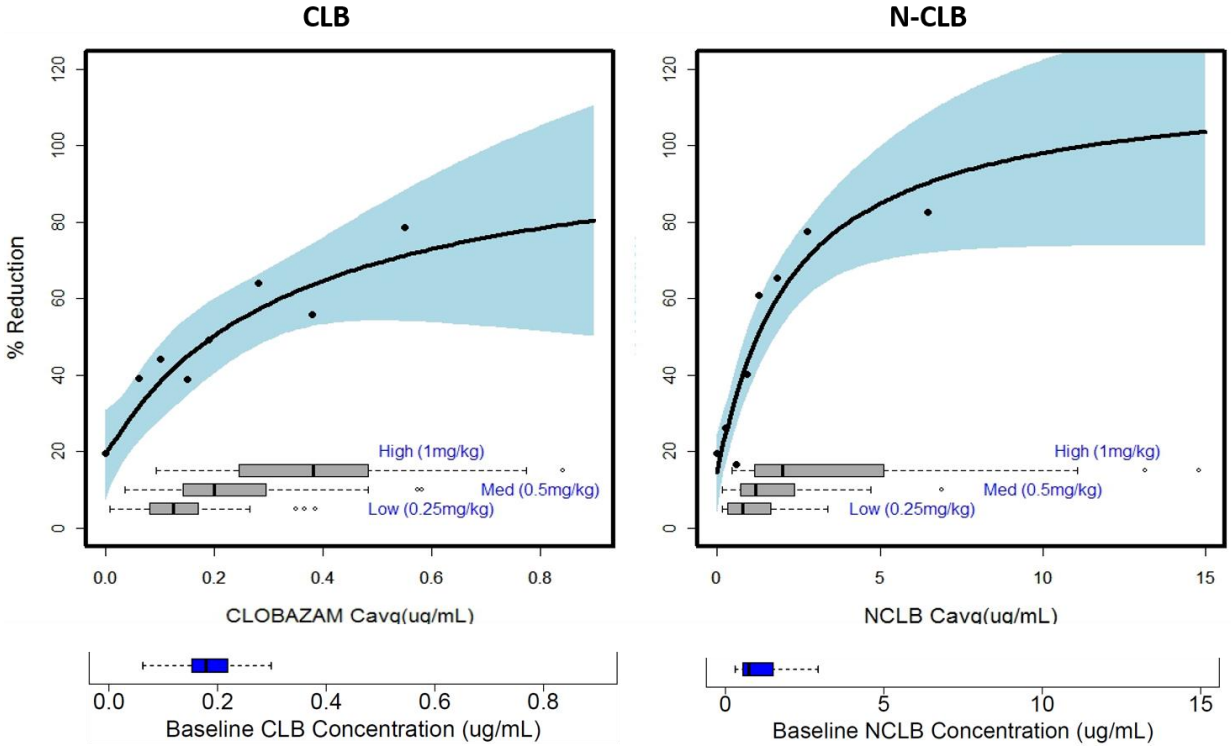
4.4.2 Evaluation of Exposure-Response (ER) Relationship of CLB/NCLB

The purpose of this exploratory analysis is to evaluate if baseline CLB/NCLB exposure levels in the STICLO studies are already at the plateau of the ER curves. If baseline CLB/NCLB exposure levels in the STICLO studies are already at the plateau of the ER curves for CLB/NCLB, additional efficacy benefit in the STP arms comparing to the placebo arms in the STICLO studies can be attributed to the add-on STP treatment.

Exposure-response relationships for CLB/NCLB concentrations versus percent reduction in seizure frequency in patients with Lennox Gastaut Syndrome (LGS) were used for this exploratory analysis due to lack of adequate data to establish the ER relationships of CLB/NCLB in patients with Dravet Syndrome. Baseline CLB and NCLB concentration levels in the STICLO studies were compared with the concentration ranges in the ER curves in LGS. The results show that the baseline CLB/NCLB concentration levels have not reached the plateau of the ER curves,

suggesting additional benefit due to increased CLB/NCLB cannot be ruled out (Figure 4).

Figure 4. ER Curves of CLB/NCLB in LGS with Baseline CLB/NCLB Exposures in the STICLO Studies



Note: the ER curves for CLB/NCLB in LGS are referenced from the pharmacometrics review for NDA 202067 by Dr. Joo-Yeon Lee; the blue horizontal boxplots at the bottom represent the distribution of baseline CLB/NCLB concentrations in the STICLO studies.

However, there are clear limitations in this analysis. The ER relationships of CLB/NCLB in the analysis were established in patients with LGS rather than Dravet Syndrome. Currently available data is insufficient to establish the ER relationships of CLB/NCLB in patients with Dravet Syndrome. The similarity of ER relationships of CLB/NCLB in Lennox-Gastaut Syndrome and Dravet Syndrome is unknown. Therefore, this analysis is considered exploratory and the results should be interpreted with caution.

4.4.3 Subgroup Analysis of Patients with Minimal Increase in CLB/NCLB Exposures from Baseline in the STP Treatment Arms of the STICLO Studies

The objective of this analysis was to identify a subgroup of STP-treated patients whose CLB/NCLB exposure did not increase significantly from baseline following add-on treatment of STP and to evaluate the efficacy response in this subgroup. Theoretically, some subjects, such as CYP2C19 poor metabolizers, would not experience significant increase in CLB/NCLB exposure from baseline following add-on of STP.

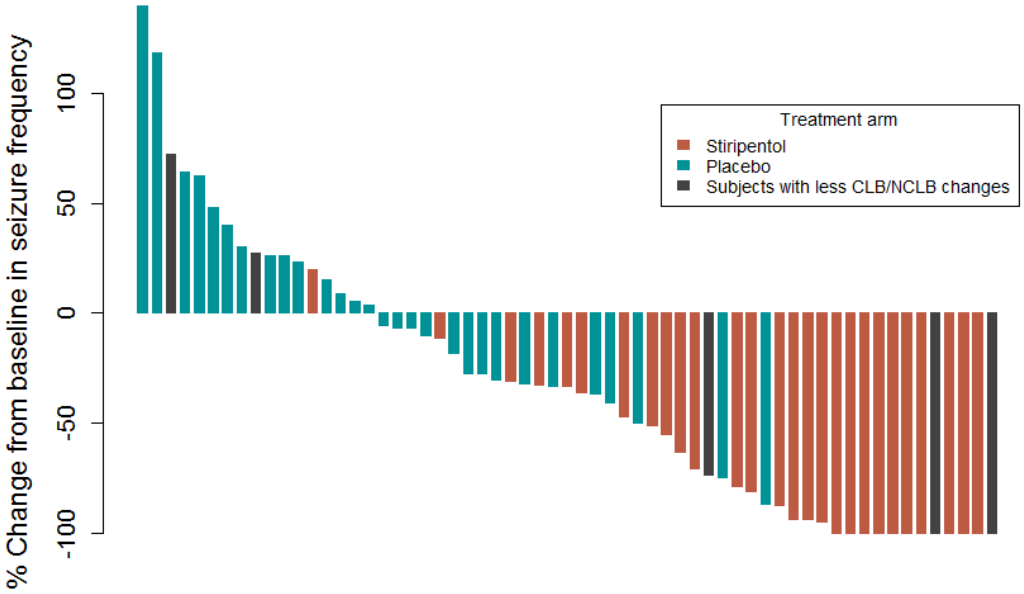
A total of 5 subjects were identified in this subgroup analysis based on the criteria that CLB exposure increased <50% and NCLB exposure increased <100% from baseline. The efficacy results of these 5 subjects are shown in Table 14. Figure 5 visualizes the efficacy results, i.e. % change from baseline in seizure frequency, by treatment groups and subgroup in the STICLO

studies. The results show no consistent trend in clinical response in the subgroup of patients with minimal increase from baseline in CLB/NCLB exposures, and therefore, are considered inconclusive.

Table 14. Efficacy Results of the 5 Selected Subjects

Subject ID	% change from baseline in CLB Conc.	% change from baseline in NCLB Conc.	% change from baseline in seizure frequency	Responder Status
FRANCE (b) (6)	25.3	-13.8	72.6	No
FRANCE	50.0	-30.8	27.6	No
FRANCE	11.8	62.4	-100	Yes
ITALY-	0.0	36.0	-73.6	Yes
ITALY-	-40.0	57.2	-100	Yes

Figure 5. Waterfall Plots for Efficacy Results in the STICLO Studies



Note: red bars represent patients in the STP arms of the STICLO studies; green bars represent patients in the placebo arm; black bars represent patients with <50% increase from baseline in CLB exposure and <100% increase from baseline in NCLB exposure.

4.5 Individual Study Summaries

Study BC481: **Bioavailability Study of Stiripentol after Single Oral Administration of Two 500 mg Stiripentol Formulations (Capsule and (b) (4))**

in 24 Healthy Male Volunteers

Objectives:

To determine the relative bioavailability of stiripentol contained in Diacomit® 500 mg, powder for oral suspension in (b) (4), compared to stiripentol contained in Diacomit® 500 mg, capsule after single oral administration of 2x500 mg of each formulation and to study the safety and tolerability of stiripentol.

Study Design	This study was an open label, cross-over, randomized, two single oral administrations study separated by at least a one-week wash-out period.
Study Population	Healthy Subjects (males) Age: 18-45 years BMI: 18 to 35 kg/m^2. 24 enrolled
Treatments	Test: Diacomit® 500 mg, powder for oral suspension (b) (4). Reference: Diacomit® 500 mg, capsule In this study the drug was given after a standard breakfast. Per Diacomit label, stiripentol must always be taken with food as it degrades rapidly in an acidic environment.
Sampling:	Blood samples (7 mL) were collected from all subjects at 0 (prior to dosing), and at 20 min, 30 min, 45 min, 1.0 h, 1.5 h, 2.0 h, 2.5 h, 3.0 h, 3.5 h, 4.0 h, 6.0 h, 8.0 h, 10.0 h, 12.0 h, 18.0 h, 24.0 h, 30.0 h and 36.0 hours post dosing.
Analysis	Plasma stiripentol concentrations were measured by a HPLC method involving a liquid/liquid extraction followed by reverse phase liquid chromatography with UV detection. The analytical procedure in plasma was shown to be linear from 0.100 to 20.0 µg/mL using 0.25 mL of sample. The lower limit of quantification (LLOQ) in human plasma was 0.10 µg/mL. No pre-study assay qualification was conducted prior to the analysis of the study samples. The assay was performed immediately before starting the analysis of the samples from this analytical study. Summary of control results are presented in the table below.

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (µg/mL)	0.3, 8.0 and 16.0 µg/mL	0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0 and 20 µg/mL
Between Batch Precision (%CV)	3.63 to 6.26	2.18 to 6.19
Between Batch Accuracy (%RE)	1.25% to 6.67%.	-1.3 to 2.0
Linearity	Weighted linear equation ($1/X^2$), mean r= 0.9994	
Linear Range (µg/mL)	0.1 to 20 µg/mL	

	Sensitivity (LLOQ, µg/mL) | 0.1 µg/mL
Pharmacokinetic Assessments	The pharmacokinetic parameters were calculated, using the WinNonlin. The following pharmacokinetic parameters were derived for each subject after each of the 2 treatments administered: Cmax, Tmax, tlag, Ke, AUC0-t, AUC0-inf and Frel.
Safety Assessments	Adverse events (AEs), standard laboratory assessments, vital signs, electrocardiograms and physical examination.
Statistical Methods	To assess the bioequivalence of the two formulations of stiripentol, an analysis of variance followed by the calculation of the 90 % confidence intervals for the ratio test/reference of Cmax and AUC were performed. Values of Cmax and AUC were a priori log-transformed. Bioequivalence was concluded if the corresponding 90 % confidence intervals for the ratio of the mean were included between 0.80 and 1.25 for AUC0-∞ (or AUCO-t) and Cmax.

RESULTS:

A total of 24 Caucasian male subjects between 20 and 43 years old participated to this study. Following table represents summary of demographic data.

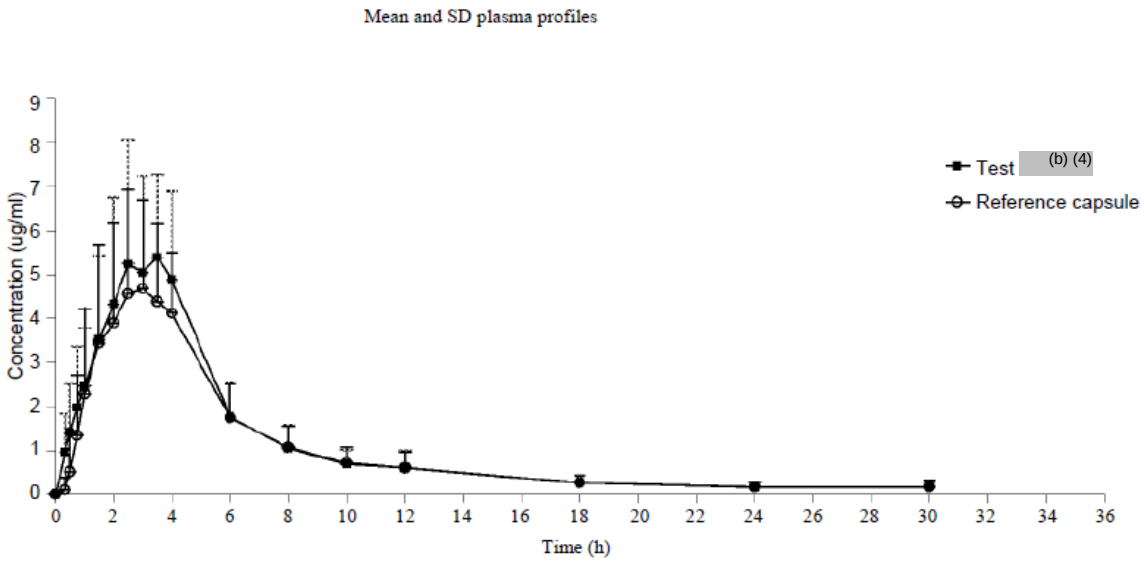
Summary of demographic data

Treatment sequences			A/B	B/A	Total
Gender	**Male**	N (%)	12 (100)	12 (100)	24 (100)
Age (year)		Mean (SD)	29.3 (6.2)	30.1 (9.4)	29.7 (7.8)
		Range	21 - 40	20 - 43	20 - 43
Weight (kg)		Mean (SD)	80.79 (12.09)	81.88 (10.32)	81.33 (11.00)
		Range	61.3 - 102.6	67.4 - 98.7	61.3 - 102.6
Height (cm)		Mean (SD)	182.3 (5.0)	179.1 (7.4)	180.7 (6.4)
		Range	174 - 192	167 - 193	167 - 193
Body Mass Index (kg/m^2)		Mean (SD)	24.33 (3.51)	25.48 (2.48)	24.90 (3.03)
		Range	19.3 - 29.3	22.0 - 29.2	19.3 - 29.3

PHARMACOKINETICS

Figure below represents PK profiles of stiripentol following administration of (b) (4) and capsule formulations.

Mean (SD) plasma concentration-time profiles of stiripentol



The mean PK parameters of stiripentol are summarized in the following table:

STIRIPENTOL		C_{max} (µg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (h.µg/mL)	$AUC_{0-\infty}$ (h.µg/mL)	$AUC_{0-\infty}$ (h.µg/mL)
Treatment A (test (b) (4))	N	24	24	18	24	18	17
	Mean	7.32		14.38	32.97	38.00	37.36
	Geom. Mean	7.04		12.27	31.28	35.85	35.20
	CV%	29		53	34	34	35
	Median		3.50				
	[Min-Max]		1.50-4.00				
Treatment B (reference capsules)	N	24	24	21	24	21	17
	Mean	5.99		17.41	30.23	33.58	35.08
	Geom. Mean	5.72		13.75	28.54	31.55	32.93
	CV%	29		65	36	37	37
	Median		3.00				
	[Min-Max]		1.00-4.00				
90 % Confidence intervals		1.10-1.37	NS (1)		1.04-1.16		0.98-1.15
Point estimate		1.23			1.10		1.06

- The mean stiripentol Cmax was 23 % higher after administration of the test (b) (4) in comparison to that obtained after dosing with the reference capsules. The point estimate (1.23) and the 90 % confidence interval (1.10-1.37 was higher than the upper limit of the bioequivalence range (0.80-1.25).
- The mean AUC0-t and AUC0-inf, were comparable between the two treatments with an average difference of 10 % and 6 %, respectively. The 90 % confidence intervals were within 0.80-1.25.
- The tmax was not statistically different between the two treatments.

CONCLUSIONS:

- The (b) (4) formulation was not bioequivalent to the reference Diacomit® capsule.
- The clinical relevance due to minor difference in stiripentol Cmax (23 % higher) after administration of the test (b) (4) in comparison with the reference capsules is unknown.
- The overall exposure (mean AUC0-t and AUC0-inf) was comparable between the two treatments following single dose administration.

Study BC337**: Study of pharmacokinetics, safety, tolerability of stiripentol (diacomit®) following single oral administration of 500 mg, 1000 mg, 2000 mg stiripentol to male healthy volunteers.**

Objectives:

- To determine the pharmacokinetic parameters of stiripentol following single oral dose administration of 500, 1000 and 2000 mg stiripentol.
- To verify the linearity of its pharmacokinetics, in particular within the dose range proposed for therapeutic purposes.

<table>
<tr><td>Study Design</td><td>This trial was an open-label study conducted on 12 healthy male volunteers. After screening of subjects, the study involved 3 periods of single dose administration separated by a time period of at least 6 days for each subject.</td></tr>
<tr><td>Study Population</td><td>Healthy subjects (male, Caucasian)
Age: 18-40 years
BMI: 18 to 28 kg/m^2.
12 Subjects enrolled</td></tr>
<tr><td>Dosage and Administration</td><td>The treatment was taken orally by the subject at approximately 8 a.m. within 10 minutes after a standardized breakfast (2 rolls). The drug was taken while standing or sitting with 150 mL water. Subjects were required not to lie down for at least two hours after dosing although semi-recumbent position was allowed. A mouth check was performed in order to verify that the drug was appropriately swallowed. The doses, administered in a random order, were as follows:
• 500 mg stiripentol
• 1000 mg stiripentol
• 2000 mg stiripentol</td></tr>
<tr><td>Sampling:</td><td>Blood samples for assay measurements of stiripentol were collected at the following times: Predose, 20 min, 30 min, 45 min, 60 min, 90 min, 2.0h, 3.0h, 4.0h, 6.0h, 8.0h, 10.0h, 12.0h, 18.0h, 24.0h and 30.0h after administration.</td></tr>
<tr><td>Analysis</td><td>STP plasma concentrations were analyzed by HPLC/UV. The minimum quantifiable concentration (MQC) was 0.1 mg/L. Summary of control results are presented in the table below.
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.4, 2, 8, and 16 mg/L</td><td>0.1, 0.25, 0.5, 1, 2.5, 5, 10, and 20, mg/L</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>4.46 to 12.8</td><td>1.17 to 7.74</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-12.2 to -2.29</td><td>-4.43 to 4.42</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.999</td></tr>
</table>
</td></tr>
</table>

	Linear Range (ng/mL): 0.1 to 20 mg/L Sensitivity (LLOQ, ng/mL): 0.1 mg/L
Pharmacokinetic Assessments	Pharmacokinetic parameters including Cmax, Tmax, t1/2, MRT, AUC0-t and AUC0-infwere evaluated. Calculation of pharmacokinetic parameters were based firstly on a non-compartmental model and secondly after using a compartmental approach. In the compartmental approach, the kinetics were analyzed based on a two-compartment model using a first order or zero-order process of absorption, with lag time to absorption. The variation according to the dose of each parameter (Cmax and AUC_{0-t}) was studied using repeated measures analysis of variance (following log transformation) with verification using the non-parametric FRIEDMAN's test. The dose-parameter relationship was then analyzed by using linear regression for all subjects and by calculating the PEARSON's correlation coefficient for each subject.
Safety Assessments	Adverse events (AEs), standard laboratory assessments, vital signs, ECG, blood pressure and pulse rate
Statistical Methods	Individual pharmacokinetic parameters were listed and mean, standard deviation, minimum value, maximum value, median and size of the data set were tabulated. Analysis of Cmax, AUC_{0-t}. AUC_{0-inf} was carried out by analysis of variance (ANOVA) on the logarithmically transformed data. Analysis of MRT and $t_{1/2}$ was carried out by ANOV A on natural data. The analysis of Tmax was based on the non-parametric Friedman test.

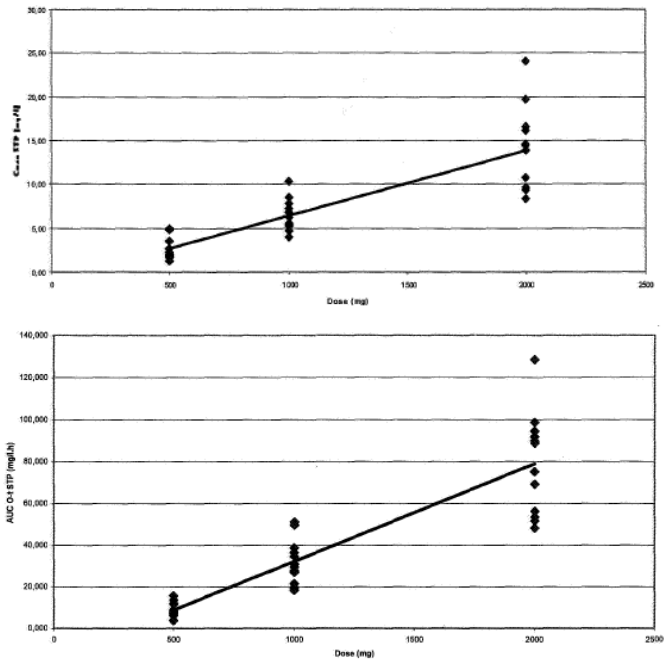
RESULTS:

The two-compartment model with zero-order absorption process satisfactorily described stiripentol's kinetics. Mean kinetic parameters (Cmax, lag time, T max, $T_{1/2}$, AUC_{0-inf}) obtained with this model are listed in table below.

Kinetic parameters: two compartment model zero-order absorption.

	500 mg dose (n=6)	1000 mg dose (n=12)	2000 mg dose (n=12)
Cmax STP (mg/l)			
Mean ± S.D.	3.1 ± 0.9	7.1±1.9	13.2±3.6
Median	2.8	7.2	12.6
Min-max	2.5 - 4.9	4.1-10.9	9.5-20.6
Lag time (h)			
Mean ± S.D.	0.87 ± 0.55	0.51 ± 0.46	0.48 ± 0.33
Median	0.69	0.42	0.37
Min-max	0.49 - 1.92	0 - 1.8	0.13 - 1.34
Tmax STP (h)			
Mean ± S.D.	2.7 ± 1.0	2.7±1.3	3.3±1.0
Median	2.9	2.5	3.4
Min-max	1.3 - 3.7	0.88-5.3	1.6-5.3
$T^{1/2}$ Beta (h)			
Mean ± S.D.	4.4 ± 2.1	10.1 ± 3.3	13.7 ± 6.2
Median	4.3	10.3	11.9
Min-max	2.3 - 7.3	5.4 - 15.4	7.5 - 29.3
AUC 0-inf (mg/l. h)			
Mean ± S.D.	9.9 ± 3.4	31.1 ± 10.9	87.7 ± 27.7
Median	10.3	31.5	88.0
Min-max	4.1-13.8	18.5 - 54.6	49.6 - 132

Analysis of the Cmax, and AUC_{0-t} parameters and the dose relationship using linear regression method



Following table represents Cmax and AUC normalized to 500 mg dose.

Mean (SD) Values of Cmax and AUC Normalized with Respect to the 500 mg Dose

Parameter	500 mg	1,000 mg	2,000 mg
Cmax (mg/L)	2.63 (1.18)	3.31 (0.916)	3.44 (1.20)
AUC (mg/Lxhr)	8.84 (3.76)	16.0 (5.33)	19.7 (6.05)

Statistical tests supported non-linearity, i.e., more than proportional increases in AUC. The ratio increased significantly with dose (Friedman's test, $p<0.05$).

CONCLUSIONS:

- Overall, the PK parameters were slightly non-linear. The median half-life changed from 10.3 hours to 11.9 hours following 1000 mg and 2000 mg doses respectively.
- The compartmental analysis showed that a twocompartment model with zero order absorption provided the best fit to the data.
- The absorption phase was responsible for the non-linearity observed, but the elimination phase was linear.

Study BC287**: Pharmacokinetic study comparing racemic stiripentol and stiripentol isomers after single oral administration of a dose equal to 1200 mg of each isomer, 1200 mg and 2400 mg of racemic stiripentol in 6 healthy volunteers.**

Objectives:

To define the pharmacokinetic profile of two stiripentol enantiomers and to study racemate metabolism at two different doses.

Study Design	This was a randomized, crossover pharmacokinetic study with single administration of 4 forms of stiripentol.
Study Population	Healthy subjects (males and females) Age: 18-40 years BMI: 18 to 35 kg/m^2. 6 patients enrolled and completed
Dose/Dosing Regimen/Study Duration	Treatment A: 4 capsules dosed at 300 mg of (+) stiripentol enantiomer. Treatment B: 4 capsules dosed at 300 mg of (-) stiripentol enantiomer. Treatment C: 4 capsules dosed at 300 mg of stiripentol in a racemic form. Treatment D: 8 capsules dosed at 300 mg of stiripentol in a racemic form. Treatments A, B, C and D were given in 4 periods of single administration separated by a 7 day wash-out period.
Sampling:	Blood samples: 0,15 min, 30 min , 45 min, 1, 1.30, 2, 3, 4, 6, 8, 10, 12 and 24 hours after administration. Urine collections: 0 (just before taking the drug) and the following intervals: 0-12/12-24h.
Analysis	Plasma samples were assayed by a chiral normal phase HPLC method resulting from a small modification of the method of Zhang et al. (1994). Detection of the analytes was conducted by a fluorescence detector. The excitation wavelength was set at 290 nm. Separation of urinary glucuronides was performed using the same conditions as used for plasma samples. Calibration standards in plasma and brain homogenate were prepared over a racemic stiripentol concentration range of 6.67-250 µg/ml and 7.8- 306.8 µg/g, respectively. The detection limit was 1 µg /ml in plasma and 2 µg g/ g in brain for each enantiomer. The inter-day coefficients of variation obtained by replicate assay of a set of spiked plasma (8 µg/ml) and brain homogenate (6.67 µg /g) samples were consistently < 10%.
Pharmacokinetic Assessments	The primary population pharmacokinetic parameters (clearance and volume) were estimated. Individual exposure parameters (AUC and Cmax) were estimated.
Statistical Methods	Subject characteristics: average and standard deviation. Side-effects: descriptive report.

Note: See following information request sent in the filing letter and sponsor's response.

2. We could not locate the detailed validation and analytical reports for the BC.287 (Greig) study. Please provide these reports or the location in your submission where they may be found.

Sponsor's Response:

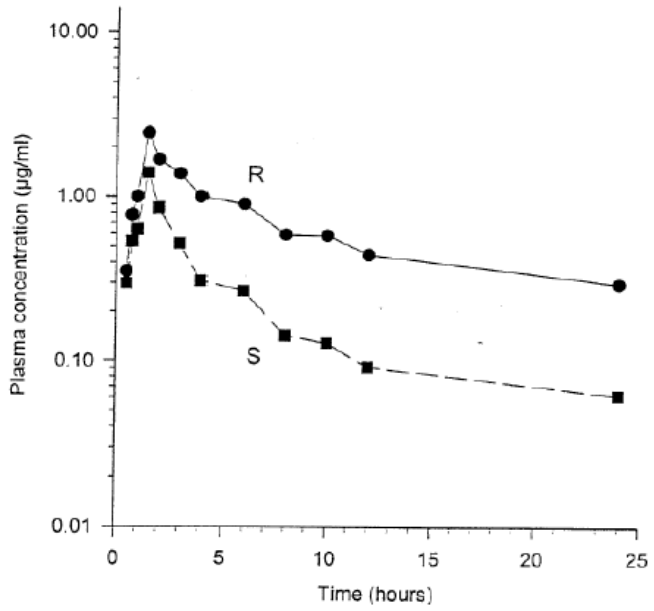
A description of the analytical method for the Greig study [5.3.3.1; BC.287] can be found in Section 2 of the Pharmacokinetic report for the study. Detailed validation and analytical reports are not available for this study.

Although the study was conducted according to GCP, Biocodex acknowledges that the study report (conducted in 1993) does not meet all FDA and ICH requirements for clinical study reports. A summary of results from the study and the full study report were included in the NDA for full disclosure. There are no clinical pharmacology claims in the labeling that rely on this Phase 1 study.

Reviewer's Comments: Without detailed analytical reports, the integrity of data obtained from this study cannot be assured. In Clinical Pharmacology aid submitted by the sponsor, this study is reported to be supportive of the label contrary to the statement in the sponsor's response above.

RESULTS:

Plasma concentration-time curve of STP enantiomers after a single oral dose of 1,200 mg of racemic drug



Administration of enantiomers: For the R and S enantiomers, mean (SD) Cmax values were 8.57 (4.27) and 5.74 (3.61) mg/L, respectively. The corresponding CL/F values were 25.54 (10.76) and 72.72 (42.62) L/hr. A larger apparent oral clearance for the S enantiomer was observed.

PK Parameters of STP Enantiomers and Racemic Drug in Six Subjects

Treatment	Cmax (mg/L)		T½ (hr)		AUC (mg·hr/L)	
	R	S	R	S	R	S
R-STP	8.57	0.60	8.66	3.46	52.05	0.29
S-STP	0.76	5.74	23.1	5.33	6.02	20.25
RS-STP 1,200	2.25	1.09	17.33	5.33	13.83	3.88
RS-STP 2,400	4.80	1.69	9.90	9.90	33.61	8.41

Following administration of the R enantiomer, measurement of plasma AUCs of the two enantiomers showed that the R/S AUC ratio was 180. The percent of dose excreted in urine was 4.84% as R-STP glucuronide and 1.42% as S-STP glucuronide. Some conversion from the R to the S enantiomer occurs, shown by trace amounts of the S enantiomer and the large AUC ratio of 180.

When the S enantiomer was administered, appreciable concentrations of the R enantiomer were present in plasma yielding an AUC S/R ratio of 3.1. The percent of dose excreted in urine as S-STP glucuronide was relatively large, 44 %, while no R-STP glucuronide was detected. The plasma data suggest that the S enantiomer is converted to the R enantiomer.

The urine data suggest that formation of glucuronide is much easier for the S enantiomer than for the R enantiomer. The S enantiomer has a much larger clearance than the R enantiomer.

Excretion of Glucuronides after Administration of STP Enantiomers and Racemic Drug to Six Subjects

Treatment	Time	% Dose		Total % Dose
		R	S	
R-STP	0-12 h	3.86 (2.25)	1.17 (0.88)	6.80 (3.38)
	12-24 h	0.98 (0.64)	0.25 (0.17)	
S-STP	0-12 h	-----	35.43 (7.69)	43.73
	12-24 h	-----	8.30 (4.69)	
RS-STP 1,200	0-12 h	0.88 (0.64)	10.19 (7.49)	15.14 (8.17)
	12-24 h	0.34 (0.18)	3.73 (1.74)	
RS-STP 2,400	0-12 h	0.87 (0.61)	7.53 (4.75)	12.84 (5.79)
	12-24 h	049 (0.34)	3.95 (2.37)	

The percent dose recovered in urine as combined (R-STP and S-STP) glucuronides was 23 to 28%. The S isomer accounted for 90-92% of the total (R-STP and S-STP) glucuronides that accounted for 23 to 28% of the dose.

CONCLUSIONS:
The data suggest that inter conversion of S enantiomer to the R enantiomer is significant when S enantiomer was administered. However, a minor conversion from R to S enantiomer was observed when R enantiomer was administered.

A larger apparent oral clearance for the S enantiomer was observed and the glucuronidation was enantioselective, favoring the S isomer, when recemate was administered.

Study BC345**: A study of the influence of stiripentol on the activity of cytochromes P-450, 1A2, 2D6 and 3A in healthy volunteers.**

Objectives:
The aim of this study was to study the effects of stiripentol on the activity of three hepatic P-450 cytochromes involved in the metabolism of very many medicinal products: CYP 1A2, 2D6 and 3A.

Study Design:
The effects of STP on in vivo cytochrome P450 (CYP) probes were evaluated in a group of 12 healthy subjects. The probes were administered on days -2, -1, and 13; STP was administered on days 1-14 according to the following regimen: 1,000 mg on day 1: 2,000 mg on day 2: 3,000 mg on days 3-13 and 1,500 mg on the morning of day 14; the two daily doses were given in the morning between 8 am and 9:30 am and in the evening between 8 pm and 9:30 pm. Blood samples to assess STP steady state were collected in the morning of days 12, 13 and 14, prior to the STP morning dose. Of these samples, those measured on days 12 and 13 are unaffected by intake of a probe.
The subjects received a dose caffeine citrate and dextromethorphan at D-1 and D14.

Note: The daily dosage of Diacomit is 50 mg/kg administered in 2 or 3 divided doses.

Determination of the effects of stiripentol on the activity of cytochrome 1A2 (CYP 1A2)

Stiripentol's effect on the activity of CYP1A2 was evaluated by caffeine test, or caffeine CO2 breath test. The radiolabelled caffeine test, or caffeine CO_2 breath test, consists of measuring exhaled radiolabelled 13C-CO_2 following the single oral administration of a test dose of caffeine specifically labelled with a stable isotope, carbon 13 (13C), in the methyl group at position N3. Following demethylation with CYP 1A2 in the liver, the radiolabelled methyl group in caffeine is partially eliminated in exhaled CO_2 in the form of 13C-CO_2.

Areas Under Curve (0–2 hours) of Changes in Atom Percent Excess (APE) Over Time

Subject no.	AUC (0–2h) D-1	AUC (0–2h) D14	Caffeine base at D-1 (mg)	Caffeine base at D14 (mg)	AUC (0-2h)/mg CAF base D-1	AUC (0-2h)/mg CAF base D14	(D14 – D-1)/D-1 x 100
(b) (6)	0.33	0.06225	325	324	0.00102	0.000192	-81.1
	1.335	0.27750	300	300	0.00445	0.000925	-79.2
	0.5685	0.06450	300	296	0.00189	0.000218	-88.5
	0.32925	0.00225	238	238	0.00139	0.000009	-99.3
	0.7183	0.05925	284	313	0.00253	0.000190	-92.5
	0.70425	0.07650	308	306	0.00229	0.000250	-89.1
	0.81	0.05215	220	220	0.00368	0.000237	-93.6
	0.8835	0.12525	213	213	0.00416	0.000589	-85.8
	0.9855	0.07125	325	325	0.00303	0.000219	-92.8
	0.5016	0.10575	263	263	0.00191	0.000403	-78.9
	0.44095	0.12065	275	275	0.00160	0.000439	-72.6
	0.7815	0.06975	275	275	0.00284	0.000254	-91.1
Mean	0.699	0.09059	277	279	0.00257	0.000327	-87.0
SEM	0.292	0.06744	38	39	0.00110	0.000238	7.7

Comparison of the areas under the curves (0-2 hours) showed a statistically significant decrease at D14 compared to D-1 (with $p<0.01$). The decrease was 87.0 ± 7.7% on average. This result showed a marked decrease in the elimination of 13C-CO_2 under the effect of stiripentol at the steady state with a mean plasma concentration of stiripentol of 12. 3 ±3.9 mg/l obtained after 14 days of treatment with a dose of 3 g per day.

The specific demethylation of radio labelled caffeine by cytochrome CYP 1A2 was, therefore, inhibited with stiripentol.

Determination of the effects of stiripentol on the activity of cytochrome 2D6 (CYP 2 D6)
Stiripentol's effect on the activity of CYP2D6 was evaluated by the determination of the urinary dextromethorphan/dextrorphan ratio, before and during treatment with stiripentol Dextromethorphan is a specific substrate of CYP 2D6, without any respiratory depressant effect at the 40 mg dose administered in this study.

URINARY CONCENTRATIONS OF DEXTROMETHORPHAN AND DEXTRORPHAN

Subject no.	DEM at D-1 (mg/l)	DEM at D13 (mg/l)	DOR at D-1 (mg/l)	DEM at D13 (mg/l)	DEM/DOR D-1	DEM/DOR D13
(b) (6)	0.165	0.740	8.86	11.2	0.0186	0.0661
	0.151	0.507	19.1	21	0.0079	0.0241
	0.141	1.63	37.0	19.0	0.0038	0.0858
	4.08	0.829	30.5	14.1	0.1338	0.0588
	0.170	0.448	14.0	20.0	0.0121	0.0224
	0.174	0.108	19.2	29.0	0.0091	0.0037
	0.065	0.316	15.3	15.1	0.0042	0.0209
	0.524	0.643	15.9	14.3	0.0330	0.0450
	0.108	0.388	15.4	17.7	0.0070	0.0219
	0.0930	0.264	24.6	28.4	0.0038	0.0093
	0.0790	0.604	12.3	11.8	0.0064	0.0512
	0.167	0.448	10.7	22.9	0.0156	0.0196
mean	0.49	0.58	18.6	18.7	0.0213	0.0357
SEM	1.14	0.39	8.3	5.9	0.0364	0.0252

Calculation of the dextromethorphan/dextrorphan ratio showed ratios:
– at D1, between 0.0038 and 0.1338 (0.0213 ± 0.0364),
– at D13 between 0.0037 and 0.0858 (0.0357 ± 0.0252).

A significant increase in the DEM/DOR ratio was observed ($p<0.05$). This increase was 67.6% on average with, for two subjects (nos. (b) (6)), a decrease of 56% and 59%, respectively.

Overall, stiripentol, at a concentration of 12.3 ± 3.9 mg/l, significantly increased in the dextromethorphan/ dextrorphan ratio showing inhibitory activity of CYP2D6.

Reviewer's Comment: For CYP2D6 study, two subjects showed decrease of 56% and 59% in the dextromethorphan/ dextrorphan ratio. On the contrary, the applicant claims no effect of stiripentol on CYP2D6 metabolism in summary reports.

In general the DDI data is usually presented as treatment ratios of geometric means and confidence intervals for the ratio. Several details including plasma concentrations profiles are not presented. Overall the study results appear unreliable. The applicant should repeat the study following Agency's DDI guidance.

Determination of the effects of stiripentol on the activity of cytochrome 3A (CYP 3A)
Stiripentol's effect on the activity of CYP3A was evaluated by the determination of the 6β-hydroxylation of endogenous cortisol into 6β-hydroxycortisol, a specific marker of CYP 3A activity.

The assays were performed at D1 using urinary volumes of 78.8 ± 42.6 ml collected at 9:20 am ± 16 min and then at D14 on urinary volumes of 78.8 ± 42.6 ml collected at 9:17 am ± 15 min. The 6β-hydroxycortisol/cortisol ratio was between 0.62 and 8.12 (4.10 ± 2.47) at D1 and between 2.28 and 9.87 (4.91 ± 2.34) at D14. Comparison of the 6βhydroxycortisol/cortisol ratio at D1 and D14 using the Wilcoxon nonparametric method did not demonstrate a statistically significant difference.

In this trial, a significant difference in the metabolic ratio was not demonstrated. 8 in 12 subjects ((b) (6)) showed an **increase in the metabolic ratio**. 6β-OH cortisol is a metabolite present in low concentrations in the urine of healthy subjects. Results obtained in this study are contrary to what was expected.

Reviewer's Comment: For CYP3A4 study no difference was seen for 6βhydroxycortisol/cortisol ratio at D1 and D14. On the contrary, the applicant claims no effect of stiripentol inhibits CYP3A4 metabolism in summary reports. Per Agency's DDI guidance CYP3A4 sensitive substrates include midazolam and triazolam.

The minimum concentrations of stiripentol at D12, D13 and D14 were evaluated to make sure the steady state plasma concentrations were reached. Following table represents Cmin concentrations.

STP Cmin Values (mg/L) on Days 12 and 13 in 12 Subjects

Subject	Day 12	Day 13
(b) (6)	10.5	12.1
	10.2	7.5
	10.1	11.9
	13.3	16.1
	10.2	10.2
	11.3	11.0
	16.4	15.0
	13.2	14.2
	10.6	8.8
	16.8	18.7
	14.5	15.0
	10.6	9.3
Mean	12.3	12.5
SD	2.5	3.4

This study showed the inhibitory effect of stiripentol on cytochromes 1A2 and 2D6. However, inhibitory effect of stiripentol on the activity of 3A4/5 was not demonstrated. Contrary claims were made by the applicant in summary reports submitted to the NDA based on literature studies.

CONCLUSIONS:

Overall the study results appear unreliable and contrary to in vitro findings due to reasons described in comments above.

[1] Levy RH, Rettenmeier AW, Anderson GD et.al., Effects of polytherapy with phenytoin, carbamazepine, and stiripentol on formation of 4-ene-valproate, a hepatotoxic metabolite of valproic acid. Clin Pharmacol Ther. 1990 Sep;48(3):225-35.

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