CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206709Orig1s000
207223Orig1s000

SUMMARY REVIEW

Summary Review

Date	August 20, 2018
From	Philip H. Sheridan, MD Eric Bastings, MD Robert Temple, MD
Subject	Summary Review
NDA/BLA # and Supplement#	NDA 206709 Capsule (250 mg or 500 mg); NDA 207223 Powder for Suspension (250 mg or 500 mg packet)
Applicant	Biocodex SA
Dates of Submission	December 20, 2017 (NDA 206709) January 19, 2018 (NDA 207223)
PDUFA Goal Dates	August 20, 2018 (NDA 206709) September 19, 2018 (NDA 207223)
Proprietary Name	Diacomit
Established or Proper Name	Stiripentol
Dosage Form(s)	Capsule, Powder for Suspension
Applicant Proposed Indication(s)/Population(s)	(b) (4) treatment of (b) (4) seizures associated with Dravet syndrome in patients (b) (4)
Applicant Proposed Dosing Regimen(s)	50 mg/kg/day administered in 2 or 3 divided doses
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam
Recommended Dosing Regimen(s) (if applicable)	50 mg/kg/day administered in 2 or 3 divided doses

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

This application provides data to support the effectiveness and safety of stiripentol (Diacomit) for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older taking clobazam. Stiripentol (STP) is a new molecular entity, and is structurally unrelated to other drugs approved for the treatment of seizures.

DS is a rare, severe, refractory epilepsy syndrome with onset in early childhood. DS is categorized as a developmental and epileptic encephalopathy, in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. DS is characterized by multiple seizure types that are generally refractory to the drugs typically used for the treatment of seizures. DS is associated with higher rates of mortality than those seen in the general epilepsy population, primarily because of a greater risk of status epilepticus and sudden unexpected death in epilepsy patients (SUDEP).

The applicant conducted two adequate and well-controlled trials in DS patients (STICLO France study and STICLO Italy study). A single STP dosage (50 mg/kg) was evaluated in these studies, administered in 2 or 3 divided doses, without initial upward titration. The primary endpoint in both studies was the percentage of patients who had at least a 50% reduction in their monthly seizure frequency from baseline. In the STICLO France study (n=41), 71% of patients on STP met the primary endpoint, compared to 5% on placebo ($p = 0.0003$). Similar results were observed in the STICLO Italy study (n=23): 67% of patients on STP had at least a 50% reduction in their monthly seizure frequency, compared to 9% of patients on placebo (nominal p value = 0.0006). A total of 43% and 25% of patients in the STICLO France and Italy trials, respectively, reported no generalized clonic or tonic-clonic seizure (i.e., 100 % reduction) for the duration of the study, which is remarkable, considering how refractory seizures typically are in patients with DS. No placebo-treated patients had such a response. Secondary endpoints supported the primary efficacy results in both studies.

The most commonly observed adverse reactions in controlled trials that occurred with a greater incidence in STP-treated patients than on placebo were in the following categories: central nervous system (e.g., somnolence and sedation), gastrointestinal (anorexia), and hematologic (e.g., neutropenia, thrombocytopenia). The risks associated with STP treatment are acceptable, particularly given the strength of the findings of clinical efficacy in DS, which is a serious, debilitating, and life-threatening disorder. Although the risk of neutropenia has the potential to be serious, it can be appropriately managed with inclusion of relevant language in labeling and education of prescribers regarding the need for periodic monitoring of white blood cell counts.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Dravet syndrome (DS) is a severe form of childhood epilepsy that is characterized by early onset of refractory seizures of multiple types, frequent episodes of status epilepticus, and developmental arrest or regression. Patients typically present prior to 2 years of age (although the diagnosis may not be recognized until about age 2 years) with a variety of disabling seizure types and developmental delay. Cognitive impairment is regularly seen and may be partly caused by the seizures. Although the diagnosis of DS is made by clinical criteria, most patients with DS (about 80%) have mutations in the SCN1A gene, but the individual mutations vary widely. Seizures in patients with DS are generally refractory to anticonvulsant drugs, and freedom from seizures almost never occurs. Many patients experience fewer seizures in late adolescence and adulthood. Sudden unexplained death in epilepsy (SUDEP) and status epilepticus are more common in patients with DS than in most other childhood epilepsy syndromes, and increased mortality in DS patients (compared to the general population) is, in part, related to these events.	DS is a severe epilepsy syndrome causes refractory seizures, cognitive impairment, and an increased risk of mortality related to seizures.
Current Treatment Options	In addition to the drugs commonly used off-label for the treatment of DS (clobazam, valproate, and topiramate), one drug (cannabidiol) was recently (June 2018) approved by FDA specifically for the treatment of seizures associated with DS.	There is only one other drug approved for the treatment of seizures associated with DS.
Benefit	Two adequate and well-controlled efficacy trials were conducted in DS patients: the STICLO France study and the STICLO Italy study. Both studies had the same design (multicenter, randomized, double-blind, placebo-controlled), and were conducted in refractory DS patients ages 3 to 18 years who were taking both clobazam and valproate and who maintained these drugs throughout the studies. Patients were required to have at least 4 generalized clonic or tonic-clonic seizures per month despite optimized therapy at the beginning of the trial. The stiripentol dosage in both studies was 50 mg/kg, administered in 2 or 3 divided doses, without initial upward titration.	This application has established that STP is effective for the treatment of seizures associated with DS for patients age 2 years and above treated with clobazam.

	In the STICLO France study (n=41), the percentage of patients who had at least a 50% reduction in their monthly seizure frequency from baseline rate (the primary endpoint) was 71% for stiripentol, compared to 5% on placebo (p = 0.0003). In the STICLO Italy study (n=23), the percentage of patients who had at least a 50% reduction in their monthly seizure frequency from baseline was 67% for stiripentol, compared to 9% on placebo (p value = 0.006; significance is nominal because the study was stopped prematurely). A total of 43% and 25% of patients in the France and Italy STICLO trials, respectively, reported no generalized clonic or tonic-clonic seizure for the duration of the study. No patients on placebo achieved this response. Secondary endpoints results (including percent reduction from baseline in monthly seizure frequency) were consistent with the primacy efficacy results in both studies. A significant rise in the levels of both clobazam (CLB) and its major metabolite, norclobazam (NCLB), was observed in both STICLO trials after STP was added in the active treatment arm (all patients in both studies were on background CLB treatment, which is commonly used off-label for the treatment of DS). Therefore, the review team considered whether the efficacy results observed in the STICLO studies reflected an independent effect of STP, the increased CLB and NCLB exposures when STP is co-administered, or both. Given the presence of continued seizures on standard doses of CLB, which was used at what was thought to be its fully effective dose, it was considered unlikely that a large fraction of the efficacy seen with STP could be attributed to increased CLB levels. Nevertheless, since the contribution to efficacy from the increase in CLB and NCLB levels could not be quantified, STP will be indicated for the treatment of seizures associated with DS in patients taking CLB.	
	Somnolence, decreased appetite and decreased weight, neutropenia and thrombocytopenia, and excess phenylalanine for patients with phenylketonuria were identified as safety issues of concern. The most commonly observed adverse effects in the two controlled trials were generally reversible, and mild to moderate in severity. The incidence of somnolence was 67% in STP-treated patients, compared to 23% in placebo-treated patients. The incidence of decreased appetite was 46% in STP-treated	The adverse effects of STP are acceptable. Although neutropenia and thrombocytopenia have the potential to be serious, these effects can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of neutropenia, and the requirement for periodic monitoring of complete blood counts (CBCs).

	patients, compared to 10% in placebo-treated patients. Decreased weight was observed in 27% of STP-treated patients, compared to in 6% of placebo-treated patients. The incidence of neutropenia was 13% in STP-treated patients, and neutropenia was not observed in any placebo-treated patient. Thrombocytopenia was observed in 12% of STP-treated patients, compared to 3% in placebo-treated patients. Although no patients with phenylketonuria (PKU) were included in the STICLO trials, the powder for oral suspension formulation is contraindicated in PKU patients because it contains phenylalanine.	The Warnings and Precautions section of labeling will describe the risks of somnolence, decreased appetite and decreased weight, neutropenia, and excess phenylalanine for patients with phenylketonuria. Class labeling warnings for suicidal behavior and for withdrawal of seizure medications should be included. The following postmarketing requirement (PMR) should be imposed: • A pregnancy outcomes study, using a different study design from the North American Antiepileptic Drug (NAAED) Pregnancy Registry, to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and SGA births in women exposed to stiripentol during pregnancy compared to an unexposed control population. • A thorough QT study. • PMRs to characterize drug-drug interactions that have yet to be investigated. • A PMR to characterize appropriate dosing in patients with hepatic impairment. • PMRs for nonclinical safety studies.

2. Background

This application provides data intended to support the effectiveness and safety of stiripentol (STP) for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older.

STP is an aromatic allylic alcohol. It is a new molecular entity and it is structurally unrelated to other drugs approved for the treatment of seizures. The precise mechanism by which stiripentol exerts its anticonvulsant effect in humans is unknown, but it is thought to act by potentiation of GABAergic neurotransmission and possibly of glutamatergic neurotransmission. Cannabidiol (CBD) is the only FDA-approved drug for the treatment of seizures associated with DS. CBD was approved in June 2018. Most DS patients are not expected to have complete seizure control on CBD.

DS (previously known as severe myoclonic epilepsy of infancy) is characterized by refractory epilepsy with multiple seizure types, febrile seizures, frequent episodes of status epilepticus, and developmental arrest or regression. Onset of DS is typically before 2 years of age, with an initial presentation of seizures and developmental delay. Most, but not all, patients with the clinical syndrome have a mutation in the SCN1A gene affecting the α-subunit of the voltage-gated sodium channel.

DS is rare disorder categorized as a developmental and epileptic encephalopathy in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. The multiple seizure types that are observed in DS are generally refractory to the drugs typically used for the treatment of seizures. DS is associated with higher rates of mortality than occur in the general epilepsy population, primarily related to a greater risk of status epilepticus and sudden unexpected death in epilepsy (SUDEP).

This application provides efficacy and safety data from two randomized, double-blind, placebo-controlled trials (discussed in section 7 of this review): the STICLO France study, and the STICLO Italy study.

In addition to the controlled safety data from these two trials, safety data were also provided from 18 other studies, listed in Table 2 of Section 8 of this review.

Stiripentol has been approved by European Medicines Agency (EMA), by Health Canada, and by the Japanese health authority. A detailed summary of the regulatory history of STP is provided in the clinical review of Dr. Steven Dinsmore.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson. Dr. Wilson's review lists the entire OPQ team that was involved with the review of this application. Refer to the OPQ review for details of the product quality assessment.

Stability and release testing were found to be acceptable. The specified impurity limits were found to be acceptable based on the qualification studies. The microbial quality of the active pharmaceutical ingredient (API) and drug product were found to be adequate. There were no outstanding issues identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable.

OPQ recommends approval.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Ed Fisher, with Dr. Lois Freed performing the secondary review. The main findings and conclusions from the nonclinical review are discussed below.

> STP is a pentanol derivative that is structurally different from other known antiepileptic drugs (AEDs). The mechanism of anticonvulsant action remains unclear. Several possible mechanisms of action have been proposed, including direct effects mediated through the gamma-aminobutyric acid (GABA) A receptor and indirect effects involving inhibition of cytochrome P450 activity (demonstrated for CYP1A2, CYP2C9, CYP2C19, and CYP3A4) leading to increased levels of concomitant CLB and its major metabolite NCLB. STP demonstrated independent anticonvulsant activity in several animal models.

As only a few of the nonclinical studies of STP were carried out by the applicant, most of this information comes from literature reports, and major limitations were observed in many of the studies. Based on the limitations of the nonclinical data, Dr. Fisher has concluded that the nonclinical studies do not support approval because of the failure to adequately characterize metabolism across species, the inadequate duration of the chronic non-rodent toxicity study, the excessive body weight effects in the rat carcinogenicity study, and an inadequate nonclinical safety assessment of the potential for STP to induce developmental toxicity during embryofetal, pre- and postnatal, and juvenile exposures.

Dr. Freed notes in her secondary review, however, that because of the severity of the indication and the age of the intended patient population, if the clinical team concludes that stiripentol is efficacious and addresses an unmet need and that the human safety data are adequate to support approval, the deficiencies in the nonclinical data may be addressed postmarketing. As these conditions are clearly met, additional studies to address the deficiencies identified by Dr. Fisher will be conducted as postmarketing requirements.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Jagan Parepally (clinical pharmacology reviewer), Dr. Angela Men (clinical pharmacology team lead), Dr. Xiaofeng Wang (pharmacometrics reviewer), and Dr. Kevin Krudys. (pharmacometrics team lead).

Refer to the OCP review for a more detailed discussion of these findings.

The following is a summary of the clinical pharmacology of STP and review issues based on the OCP review.

Formulations: The to-be-marketed (TBM) formulations are identical to clinical trial formulations. The applicant has developed two dosage formulations of STP: Capsules in strengths of 250 mg and 500 mg and powder for oral suspension in 250 mg and 500 mg (b) (4).

A relative bioavailability study 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. Although the mean values for AUC(0-t) and AUC(0-∞) were

comparable for both formulations, the mean stiripentol Cmax was 23% higher after administration of the test (b) (4) than after dosing with the capsules. The slight increase in Cmax is not clinically important, as there is a substantial variability in absorption between individual patients, and because the total amount absorbed (as reflected in the AUC) is the same for the (b) (4) and the capsule.

Active moieties: The only known active moieties in plasma are the two STP enantiomers. There are no known active metabolites circulating in plasma.

QT Prolongation: 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.

Absorption: STP is well absorbed by the oral route, as shown by the fact that most of an oral dose is excreted in the urine. Stiripentol Tmax ranges from 1.25-2.96 hours under fed conditions. Absolute bioavailability is unknown.

Food Effect: A dedicated food effect study on the bioavailability of STP was not conducted. In the 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), but 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. The Clinical Pharmacology reviewers concluded that a dedicated food effect study is not needed because STP administration with food is supported by the Phase 3 study dosing instructions and gastric stability studies. Administration with food is convenient in this population.

Distribution: STP 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: STP is extensively metabolized, with 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 of STP 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.

Drug-Drug Interactions: The interaction with concomitant clobazam and valproate (VPA) is discussed below under the heading "Independent Efficacy of STP versus Efficacy Dependent on Concomitant Clobazam and Valproate."

No dedicated clinical drug-drug interaction studies were conducted for STP. The effects of other extrinsic factors such as herbal products, diet, smoking, and alcohol use on the dose or exposure-response relationship for STP were not assessed in a formal study.

The following in vitro studies suggest the potential for drug-drug interactions:

- In vitro inhibitor/inducer studies indicate that STP inhibits CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2D6, and CYP3A4. Stiripentol induces CYP1A2, CYP2B6, and CYP3A4 in vitro at clinically relevant concentrations. PMRs will be issued calling for the characterization of these inhibition/induction effects in healthy volunteers.

- In vitro transporter system studies indicate that 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. PMRs will be issued to characterize the relevant transporter system effects in healthy volunteers.

Dosage: The proposed oral dosing regimen is 50 mg/kg administered in 2 or 3 divided doses taken with food. The two trials demonstrating effectiveness, STICLO France and STICLO Italy, evaluated STP using the same dosing in three divided doses.

Independent Efficacy of STP versus Efficacy Dependent on Concomitant Clobazam and Valproate:

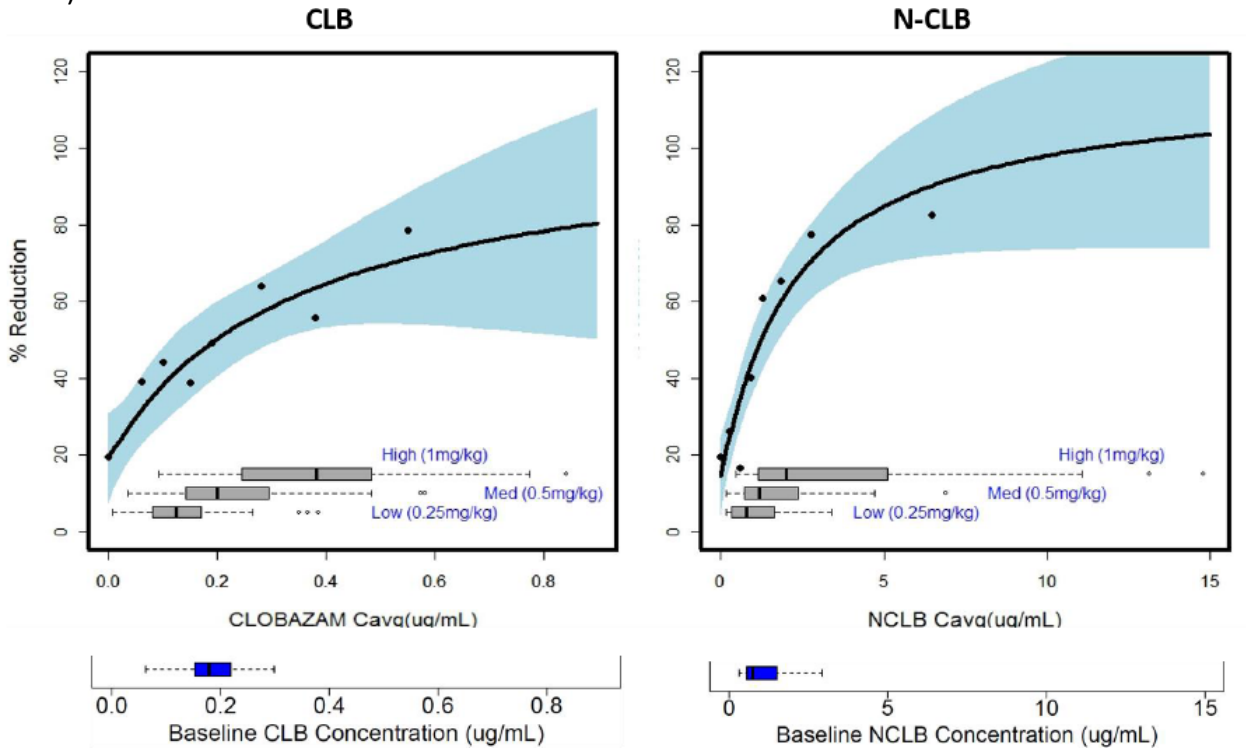
The evidence of effectiveness is based on studies of STP as add-on therapy to CLB and VPA in patients with DS (STICLO France and STICLO Italy). STP was not studied in the absence of CBD and VPA therapy.

In both STICLO studies, treatment with STP led to 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, reflecting inhibition of CLB metabolism by STP. VPA exposures were not significantly altered with add-on STP treatment. Therefore, the review team investigated whether the efficacy results observed in the STICLO studies were reflective of an independent effect of STP, to increased CLB and NCLB exposures when STP is co-administered, or both. Since all 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 could not be made.

A series of analyses including multivariate logistic regression analyses, exposure-response analyses (discussed below), and evaluation of subjects with minimum CLB/NCLB exposure change were conducted by the applicant and the clinical pharmacology review team to further evaluate this issue. The clinical pharmacology review team concluded that the available data are insufficient to fully partition the contribution to efficacy of STP and that of greater levels of CLB/NCLB, but there is evidence supporting an independent effect of STP, even if a contribution of increased blood levels of CLB cannot be ruled out.

A retrospective analysis of charts of DS patients treated with STP conducted by the applicant identified some patients treated with STP who did not receive concomitant CLB, who were compared to patients who also received CLB. The responder rates (rate of 50% reduction) were similar in both groups, i.e., 71% (5/7) in patients without concomitant CLB versus 73% (16/22) in patients with concomitant CLB. Although this data came from a medical care environment where patient diaries were not used, and seizure assessments were different from those in clinical trials, it appears clear that STP had an effect in patients not receiving CLB. The exposure-response of CLB for the treatment of Lennox-Gastaut Syndrome (LGS) was also examined. The following graphic, copied from the OCP review of NDA 202067 that supported FDA approval of CLB for the indication of LGS, depicts the exposure-response relationship for CLB and N-CLB in LGS.

Figure 1: Exposure-Response Curves of CLB and N-CLB in LGS with Baseline CLB/N-CLB Exposures from the OCP review of NDA 202067 (Onfi, Clobazam)



It appears that the blood levels of CLB and NCLB were close to the fully effective dose (the plateau of the concentration-response curve) of CLB, so that an increase in their blood levels would not be expected to have a major effect on efficacy. Although dose-response may be different in the LGS and in the DS populations, it appears very unlikely that the robust efficacy of STP that was observed in the STICLO trials could be substantially explained by the increase in CLB and N-CLB levels alone.

Need for Alternative Dosing Regimens in Special Populations:

Body Weight, Age, and Sex: Based on a population pharmacokinetic (PK) analysis, body weight was identified as a significant covariate for clearance (CL/F) and volume of distribution (V/F). Since a 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.

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 therefore not recommended. A PMR will be issued to the applicant to conduct a PK 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 was recovered in urine (>73%) in the form of 13 metabolites, with only 18% in feces. Therefore, STP administration to patients with moderate to severe renal impairment is not recommended. Considering the very low incidence of renal impairment in DS patients, a dedicated PK study in patients with renal impairment is not necessary.

Overall Clinical Pharmacology Recommendation: The OCP review team recommends approval from a clinical pharmacology perspective. Several PMRs are proposed. We concur.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Steven Dinsmore was the clinical reviewer for this application. Dr. Xiang Ling was the biometrics reviewer and Dr. Kun Jin was the biometrics team lead.

The applicant conducted two similar multicenter placebo-controlled, double-blind, randomized studies in which STP or placebo was added to CLB and VPA. To be enrolled in either study, patients were required to be over 3 years of age and less than 18 years; to have DS (Internal League Against Epilepsy [ILAE] classification of epilepsy, 1989); and to be inadequately controlled on clobazam and valproate, with at least 4 generalized clonic or tonic-clonic seizures per month despite optimized therapy. The other possible concomitant antiepileptic drugs were progabide (Gabrene) and rescue therapy with rectal diazepam.

Eligible patients were enrolled in a 1-month baseline period during which they continued to receive their optimized antiepileptic treatment. Following this 1-month baseline, patients were randomly allocated to receive either stiripentol (fixed dose of 50 mg/kg/day in divided doses with no dose titration) or placebo, each added to their treatment with clobazam and valproate. The duration of the double-blind treatment was 2 months. The frequency of generalized clonic or tonic-clonic seizures during the study was recorded daily by the patients and/or their caregivers, using a diary. Although patients with DS have several different types of seizures, only generalized clonic or tonic-clonic seizures were recorded, as other seizure types can be difficult to recognize as seizures by the patients and/or their caregivers.

The primary efficacy endpoint for both studies was the responder rate. A responder was defined as a patient who experienced a greater than 50% decrease in the frequency of generalized clonic or tonic-clonic seizures during month 2 of the double-blind treatment period (adjusted to 30 days) compared to baseline (i.e., during the placebo run-in).

A total of 41 patients were enrolled in the STICLO FRANCE study; 21 were randomized to receive stiripentol and 20 to placebo. A total of 23 patients were enrolled in the STICLO ITALY study; 12 were randomized to stiripentol, and 11 to placebo. In both studies, the age distribution, sex distribution, and age distribution by sex were similar for the STP-arm and the placebo-arm.

Across both studies, 6 patients on placebo versus 2 patients on stiripentol were withdrawn prematurely. In the 2 patients withdrawn from the stiripentol treatment group, one patient had an adverse reaction of status epilepticus, and one patient had

adverse reactions of drowsiness, balance impaired and sialorrhea. Results are shown in Table 1 (prepared by Dr. Ling) for both the 50% responder rate (primary endpoint) and the percent decrease in seizure frequency (secondary endpoint).

Table 1. Efficacy Results in the Intent-to-Treat Population in STICLO FRANCE and STICLO ITALY

	STICLO FRANCE N=41		**STICLO ITALY N=23**	
	DIACOMIT N=21	**Placebo N=20**	**DIACOMIT N=12**	**Placebo N=11**
Responder Analysis[a]				
No of responders/total (Responder Rate) [95% CI]	15/21 (71%) [52% – 91%]	1/20 (5%) [0.0% – 15%]	8/12 (67%) [40% – 93%]	1/11 (9.1%) [0.0%– 26%]
p-value [b]	<0.0001		0.0094[e]	
Percentage Change from Baseline in Seizure Frequency[c]				
n	20	16	11	9
Mean ± SD	-69% ± 42%	7.6% ± 38%	-74% ± 27%	-13% ± 62%
Median	-91%	7.4%	-81%	-27%
Min – Max	-100% – 28%	-75% – 65%	-100% – -33%	-87% – 140%
p-value [d]	0.0002		0.0056[e]	

[a] Responder is defined as a patient with a greater than 50% decrease in frequency of generalized tonic-clonic or clonic seizures
[b] Fisher Exact Test
[c] Frequency of generalized tonic-clonic or clonic seizures during month 2
[d] Wilcoxon Test with two-sided t-approximation
[e] Nominal p value, as Study 2 was stopped early
CI=confidence interval; SD=standard deviation.

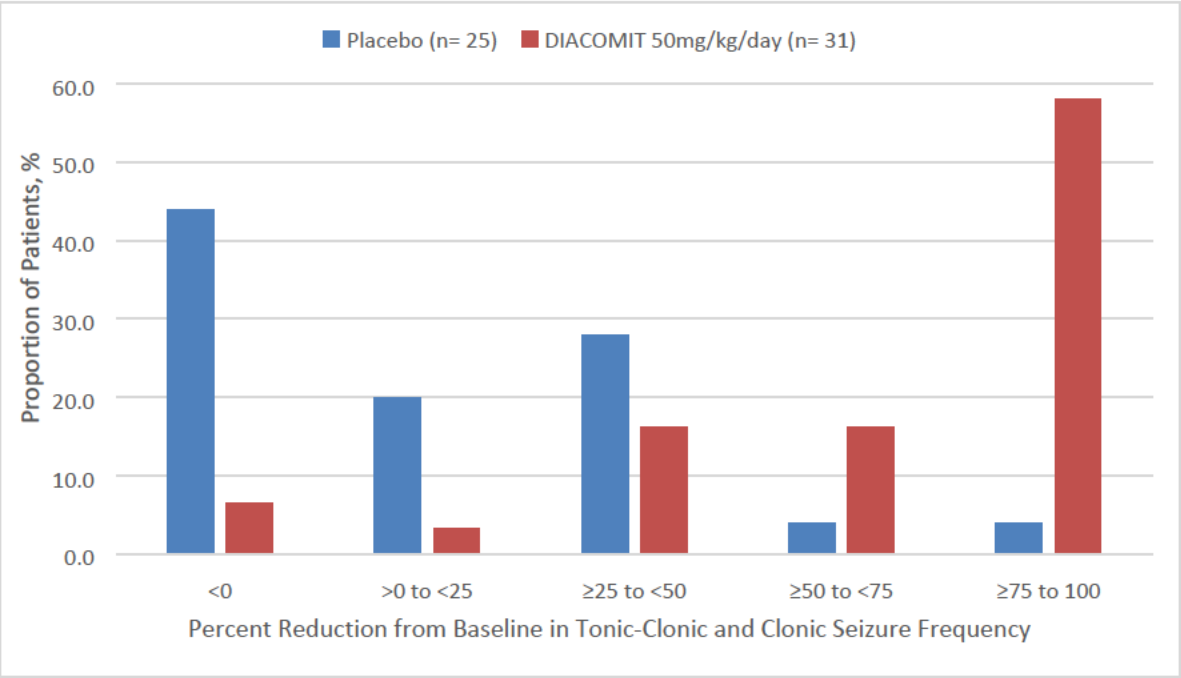
In both studies, the responder rate (primary efficacy endpoint) was greater for STP than for placebo. Of note, the p value generated for the primary efficacy analysis of the STICLO Italy study must be considered in light of the early stopping of that study. It is not known whether there were any interim analyses, although none is described. Overall, the STICLO Italy study can be used as an independent source of evidence of efficacy, considering the large effect size, the very low nominal p value (p=0.0094), and the circumstances under which the early stopping took place.

STP was also superior to placebo for the reduction in mean frequency of generalized clonic or tonic-clonic seizures (secondary efficacy endpoint). In the STICLO FRANCE study and the STICLO ITALY study, respectively 43% and 25% of patients receiving STP reported no generalized clonic or tonic-clonic seizure for the duration of the study.

The secondary endpoints had no prespecified adjustment for multiplicity. They included the reduction in mean seizure frequency (discussed above), the percentage of patients withdrawing from each treatment arm, and the time elapsed until the same number of seizures as that of the 1-month baseline period was experienced. All secondary endpoints were found to be in alignment with the primary efficacy outcome.

Figure 1 displays the percentage of patients by category of reduction from baseline in tonic-clonic and clonic seizure frequency (per 30 days) during the treatment period of STICLO FRANCE and STICLO ITALY (pooled), demonstrating substantial reductions (>50%) in the rates of seizures in about 76% of patients given STP, compared to <8% of patients given placebo.

Figure 1 Proportion of Patients by Category of Seizure Response for STP and Placebo in STICLO FRANCE and STICLO ITALY Pooled, Baseline to 2nd Month of Treatment (per 30 days)



Efficacy Conclusion:
The applicant has provided results from two randomized, double-blind, placebo-controlled trials conducted in patients with DS 3 to 18 years of age. The primary endpoints of both trials were responder rates (usually used in European epilepsy trials) rather than percent reduction in seizure frequency (usually used in American epilepsy trials), but there is a clear effect on seizure frequency as well (the first secondary endpoint). Both endpoints show large effects and, as noted above, over 70% of STP patients had reduction >50%, with over 50% of STP patients having >75% reduction. The studies clearly establish the efficacy of STP for the treatment of seizures associated with DS, with very large effect sizes, and consistent results across secondary endpoints.

As discussed in section 5 of this review, the relative contribution to efficacy of the increased levels of CLB and NCLB with STP treatment remains incompletely defined, and all data were from subjects on concomitant clobazam. Therefore, STP will be indicated for the treatment of seizures in DS in patients treated with clobazam.

Although the applicant proposed extrapolating (b) (4), the two controlled trials enrolled only patients between the ages of 3 years and 18 years. It is reasonable, however, to extrapolate the efficacy of clobazam from patients 3 years and older down to age 2 years. Age 2 years corresponds to the age at which the diagnosis of DS is likely to be made clinically.

8. Clinical - Safety

Dr. Steven Dinsmore performed the safety review.

The primary safety analysis was conducted using the controlled safety database derived from the 20 clinical studies shown in Table 2.

Dr. Dinsmore categorizes these studies as category 1 through category 5 as follows:

- The two STICLO trials have parallel adjunctive (each added to CLB and valproate) placebo and STP treatment arms, allowing a controlled comparison of adverse effects, and are considered Category 1 studies.
- Non-pivotal studies of only DS patients where .xpt datasets for independent analysis are provided are labeled Category 2.
- Long-term open-label studies with both DS and non-DS patients are considered Category 3.
- Exploratory, early efficacy studies in non-DS patients are Category 4.
- The biopharmaceutic and pharmacokinetic studies in healthy volunteers are evaluable only via text study reports and the Integrated Summary of Safety (ISS). These are identified in the study key as Category 5.

Table 2: Safety Studies (copied from Dr. Dinsmore's clinical review)

STUDY iIDENTIFIER (Sponsor Study Number) (Name) (xx* year)	CATEGORY	OBJECTIVE	DESIGN	MedDRA Version	POPULATION (n)	DURATION
Biopharmaceutic and Pharmacokinetic Studies in Healthy Volunteers-						
BC.481 *STIVAL (2007)*	5	Bioavailability (BA)	Open-label (OL)-Crossover	10.1	Healthy= 24	Single dose
BC.287 *Greig (1993)*	5	Pharmacokinetic (PK)	OL-Crossover	Not provided	Healthy= 6	Single dose
BC.337 *STIUNI (2002)*	5	PK	OL-Crossover	Not provided	Healthy= 12	Single dose
BC.345 *Pons (1995)*	5	PK	OL	Not provided	Healthy= 13	14 days
Biopharmaceutic and Pharmacokinetic Studies in Dravet Syndrome Patients						
STP167 STIPOP (LP 2008)	2	PK	OL	19.0	DS = 35	From other studies
Double-Blind, Placebo-Controlled Pivotal Studies in Dravet Syndrome Patients						
BC.299 *(LP 1998)* *STICLO France*	1	Efficacy and Safety (DS only)	Double-blind (DB)	19.0	DS= 42	2 months

BC.385 (LP 2000) STICLO Italy	1	Efficacy and Safety (DS only)	DB	19.0	DS= 23	2 months
Non-Pivotal Studies in Dravet Syndrome Patients						
BC.609 *(LP 2012)* *STP-1*	2	Efficacy and Safety (DS only)	OL	19.0	DS= 33	16 weeks, (>52 weeks)
BC.458 *TAU-EAP (LP 2007)* *(ATU de COHORTE)*	2	Efficacy and Safety (DS only)	OL	19.0	DS= 272 (210)	Years
Non-Pivotal Studies in Dravet Syndrome and Non-Dravet Syndrome Patients						
BC.288 *STEV (LP 1997)*	3	Efficacy and safety (multiple seizure type)	Single-blind (SB)	19.0	DS= 25 Non-DS= 202	12 weeks
BC.387 *STILON (LP 2001)*	3	OL Safety extension of STICAR, LENNOX, WOW, STEV, STISERV, STICLO		19.0	Non-DS= 110 DS= 45	Years
BC.627 *DIAVEY (SR 2012)*	3	Long-Term Safety – postmarketing	OL	19.0	DS=153 non DS=77	Up to several years
BC.274 (SR1994) *Lennox- Gastaut*	4	Efficacy (LGS)	SB	Not provided	Non-DS= 24	2 month
BC.246 *STICAR (LP 1990)*	4	Efficacy, add on to CBZ	DB	Not provided	Non-DS= 62	2 month
BC.484 *STISEVR (LP 2000)*	4	Efficacy, add on to CBZ	SB-OL	Not provided	Non-DS= 32	3 month
BC.276 *WOW (LP 1991)*	4	Efficacy, add on to CBZ	OL	Not provided	Non-DS= 64	70 days
BC.244 *Martinez-Lage (SR 1986)*	4	Efficacy	OL	Not provided	Non-DS= 31	16 week
BC.109 *Courjon (SR 1976)*	4	Efficacy	OL	Not provided	Non-DS 135	1 month to more than 6 months
BC.243 *Loiseau (SR 1984)*	4	Efficacy	OL	Not Provided	Non-DS = 44	16 weeks
*LP = Last Patient complete date, SR = Study report date						

The methodology to analyze safety data across the entire NDA package of 20 clinical studies is not uniform because of differences in safety data format available across the panel of studies. From among the category 1, 2, or 3 studies (see Table 2), patients have data entries in SAS (.xpt) transport files available and independent counts of deaths, serious adverse events (SAEs), discontinuations, and

common adverse events as well as an examination of relationships between variables were possible. A safety signal analysis could be performed to examine overall frequency of events as well as considering events by age, duration of treatment, seizure worsening, event-term splitting, and a close inspection of significant adverse events was conducted. In the remaining categories (4 and 5), conclusions are based on ISS and study report presentation.

Overall Patient Exposure:

Table 3: (Applicant's Table 3-12, ISS p65) Overall Exposure to STP by Treatment Duration in Trials that Enrolled Dravet Syndrome Patients

		STICLO Studies							TOTAL Unique Patients	
	STEV			**STILON**	**STIPOP**	**STP-1**	**TAU-EAP**	**DIAVEY**		
		France	Italy							
STP Exposure	N=24	N=21	N=12	N=45	N=35	N=30	N=210	N=152	N=438	
N	23	21	12	45	35	30	210	152	437	
Duration (years)										
Mean ± SD	0.24 ± 0.07	0.19 ± 0.04	0.18 ± 0.04	2.92 ± 0.94	0.01 ± 0.03	0.95 ± 0.29	2.47 ± 1.49	1.84 ± 1.13	2.21 ± 1.84	
Median	0	0	0	3	0	1	3	2	2	
Min – Max	0.10 – 0.30	0.10 – 0.20	0.10 – 0.20	0.00 – 4.20	0.00 – 0.10	0.00 – 1.10	0.00 – 4.30	0.10 – 4.30	0.00 – 8.50	
	n	n	n	n	n	n	n	n	n	%
< 3 months	12	21	12	2	35	1	13	11	58	13.2
3 to < 6 months	11	0	0	0	0	3	14	3	22	5
6 months to < 1 years	0	0	0	0	0	2	22	25	47	10.7
1 to < 2 Years	0	0	0	4	0	24	35	49	105	24
2 to < 3 Years	0	0	0	12	0	0	25	32	57	13
3 to < 4 Years	0	0	0	26	0	0	45	26	68	15.5
4 to < 5 Years	0	0	0	1	0	0	56	6	54	12.3
>= 5 Years	0	0	0	0	0	0	0	0	26	5.9
Missing	1	0	0	0	0	0	0	0	1	0.2

Dr Dinsmore notes, "Although Dravet syndrome is a rare disease, the STP exposure exceeds the recommended threshold for 3 months and 1 year identified in ICH E1 guideline. Exposure by dose also demonstrates that an adequate number of patients (353) have been exposed in the range of proposed dosing. Data from long-term extension studies of patients with Dravet syndrome and

other seizure types also identify additional STP dosages and durations of exposure. Taken in total, the safety database is adequate. We agree that the safety database is acceptable.

Safety Results:

Deaths:

There were no deaths in the two double-blind, placebo-controlled STICLO trials (category 1 studies).

In the category 2, 3, and 4 studies, there were a total of 21 deaths that occurred from among a total of 1409 DS and non-DS patients. There were no deaths in the small controlled trials. Examination of Death and SUDEP in the TAU-EAP, DIAVEY and STILON long-term studies, where patient level duration of treatment was available, reveals an incidence of Death (per) / 1000 patient years that is lower in the DS cohort of the DIAVEY and STILON studies than in the non-DS cohort. The SUDEP rate is similar in DIAVEY for both the DS and non-DS cohort while in STILON it is higher in the non-DS cohort. The overall incidence of death and SUDEP in the DS cohort treated with STP is commensurate with the observed high mortality rate of DS.

The incidence rate of SUDEP in TAU-EAP, DIAVEY and STILON, although high, is in the range seen in candidates for epilepsy surgery, identified as 9 events per 1000 patient years. The incidence of death and SUDEP observed across the clinical studies does not appear to be more than the incidence expected for DS.

We agree with Dr. Dinsmore's conclusion that the incidences of death and SUDEP observed across the clinical studies in this application are consistent with the expected rates in patient with DS.

Serious and Significant Adverse Events:

Controlled trials (category 1)

In the two double-blind, placebo-controlled STICLO trials (the category 1 studies), there were 8 serious adverse events (SAEs) reported in five patients; all 8 SAEs occurred in the STICLO France trial. Three patients (9.7%) with 5 SAEs were in the placebo treatment cohort, while two (6.1%) patients with 3 SAEs were in the STP treatment arm. Of the 5 SAEs in the placebo arm, 3 were

related to seizure exacerbation, and are more properly considered treatment failures than adverse effects. Similarly, of the 3 SAEs in the STP treatment arm, 2 were related to seizure exacerbation and are also more properly considered treatment failures than adverse effects. Within all 64 patients in the two randomized controlled STICLO studies, the incidence of seizure exacerbation and status epilepticus was the same in the placebo and STP treatment arms. One SAE in the STP treatment arm was an urticarial rash that resolved with dechallenge, but did not recur after rechallenge with STP. We agree with Dr. Dinsmore's conclusion that there is no clear difference in SAEs between the STP arm and the placebo arm in the two controlled (category 1) trials.

Uncontrolled trials (category 2 and 3)

From the uncontrolled category 2 (DS patients only) and category 3 (DS and non-DS patients) trials, Dr. Dinsmore separated the DS and non-DS patients. For the DS patients, the top three preferred terms associated with serious adverse events in the non-pivotal (non-STICLO) DS patient cohort were "seizure", "decreased appetite" and "status epilepticus", in 3.4%, 2.2%, and 1.6% of patients, respectively. For the non-DS patients, the most frequent preferred terms associated with serious adverse events in the non-DS cohort were "seizure" and "status epilepticus", at 5.3% and 2.7%, respectively. The terms "thrombocytopenia" and "cachexia" occur with a frequency of 0.81% (4 reports) and 0.4% (2 reports), respectively. The preferred terms "seizure" and "status epilepticus" were frequent and consistent across diagnoses (DS and Non-DS), age groups, and duration of treatment. We agree with Dr. Dinsmore's conclusion that these events are best explained by the high frequency of seizures and status epilepticus that occur in the underlying disease process rather than as adverse events attributable to STP.

Discontinuations Due to Adverse Events:

Controlled trials (category 1)

In the two double-blind, placebo-controlled STICLO trials (the category 1 studies), there were 6 discontinuations in the placebo treatment arm and 2 in STP treatment arm. Four of the discontinuations in the placebo arm were due to "lack of efficacy", with none in the STP arm due to "lack of efficacy". Each treatment arm had 1 discontinuation for "status epilepticus", and there was 1 discontinuation in each arm for a CNS-related adverse effect containing the terms "drowsiness".

We agree with Dr. Dinsmore that there were no features in the profile of discontinuations in the two controlled studies that undermine the study integrity. There were a higher proportion of discontinuations due to lack of efficacy in the placebo group compared to the STP treatment group, which reflects the positive treatment effect of STP.

Treatment-Emergent Adverse Events (TEAEs) of All Severities:

Controlled trials (category 1)

The most common adverse reactions, occurring in at least 10% of STP-treated patients and more frequently than on placebo included somnolence (67%), decreased appetite (45%), agitation (27%), ataxia (27%), weight decreased (27%), hypotonia (24%), nausea (15%), tremor (15%), dysarthria (12%), and insomnia (12%).

Table 4 lists the adverse reactions that occurred in 5% or more of STP-treated patients and at a rate greater than in patients on placebo in the 2 randomized, double-blind, placebo-controlled, clinical trials in patients with DS.

There were no instances of "neutropenia", "thrombocytopenia" or "cachexia." Although the frequency of somnolence was high in the STP treatment group, there was 1 discontinuation each in the placebo and STP arms that included "somnolence" as an adverse event term, as well as 1 SAE for "somnolence" in the placebo arm, and none in the STP arm.

Table 4. Adverse Reactions in 5% or More of STP-Treated Patients and More Frequent than on Placebo in Patients with Dravet Syndrome (STICLO FRANCE and STICLO ITALY)

	STICLO FRANCE/ITALY– Pooled Total	
Adverse Reactions	**STP (50mg/kg/day) N=33 %**	**Placebo N=31 %**
Gastrointestinal disorders		
Nausea	15	3
Vomiting	9	0
Salivary hypersecretion	6	0
General disorders and administration site conditions		
Fatigue	9	3
Pyrexia	6	3

Infections and infestations		
Bronchitis	6	0
Nasopharyngitis	6	0
Investigations		
Weight decreased	27	6
Weight increased	6	3
Metabolism and nutrition disorders		
Decreased appetite	46	10
Nervous system disorders		
Somnolence	67	23
Ataxia	27	23
Hypotonia	18	13
Tremor	15	10
Dysarthria	12	0
Psychiatric disorders		
Agitation	27	16
Insomnia	12	7
Aggression	9	0

Uncontrolled trials (category 2 and 3)

The frequency of overall adverse events in these studies is shown in Table 5.

Table 5 Category 2 and 3 Studies, DS Patients, Percent with Adverse Event (Copied from Dr. Dinsmore review)

STUDYID	Unique Patients with AE	n in study	% with AE
TAU-EAP	55	210	26
DIAVEY	91	152	60
STEV	22	24	92
STILON	32	45	71
STP1	29	30	97
STIPOP	2	35	6

The ten most frequent events preferred terms for each study, TAU-EAP, DIAVEY, STILON, STP-1, and STIPOP shown in Table 6 from Dr. Dinsmore's review.

Table 6 Top 10 Adverse Events (preferred terms) from Individual Category 2 and 3 Studies

Preferred terms				
TAU-EAP	**DIAVEY**	**STILON**	**STP 1**	**STIPOP**
Decreased appetite	Gamma-glutamyltransferase increased	Seizure	Somnolence	Nasopharyngitis
Somnolence	Aspartate aminotransferase increased	Decreased appetite	Nasopharyngitis	Pyrexia
Agitation	Decreased appetite	Epilepsy	Decreased appetite	
Sleep disorder	Fatigue	Rhinitis	Ataxia	
Thrombocytopenia	Neutropenia	Ear infection	Upper respiratory tract inflammation	
Death	Somnolence	Pyrexia	Diarrhea	
Hypotonia	Aggression	Weight decreased	Gamma-glutamyltransferase increased	
Insomnia	Alanine aminotransferase increased	Abnormal behavior	Hordeolum	
Seizure	Ataxia	Aggression	Influenza	
Status epilepticus	Thrombocytopenia	Ataxia	Tremor	

These studies differ in duration and the frequency of patient contact, both of which can affect detection of adverse events. The STILON, TAU-EAP and DIAVEY studies were all approximately 4.3 years in duration. A factor that can influence the frequency of adverse events is whether patients had past exposure to STP. Most TAU-EAP and STILON patients entered the study on ongoing STP treatment, while in the DIAVEY study, all patients had STP newly prescribed at study entry.

Examination of the pooled DS and non-DS Category 2-3 studies reveals the highest frequency of adverse events occurred in the System Organ Class group (SOC) "Nervous system disorders", where 32.5% had an event in this SOC. Within this SOC, the 2 most frequent preferred terms were "somnolence" and "ataxia". The second highest frequency of adverse events occurred in the SOC "metabolism and nutritional disorders", where 19% of patients had an event in this SOC. Within this SOC, the 2 most frequent

preferred terms were “decreased appetite” and “cachexia”. The third highest frequency of adverse events was in the SOC “investigations”. Within this SOC, the most common preferred terms were “GGT increased” and “AST increased”.

On examination of preferred terms event frequency in the total pool of category 1-3, DS and non-DS patients, those with frequency greater than 5% were “decreased appetite”, “somnolence”, “gamma-glutamyltransferase increased”, “ataxia”, “aspartate aminotransferase increased” and “seizure”. The frequency of each preferred term was 17.6%, 13.6%, 8.0%, 6.88%, 6.24% and 6.24%, respectively. When the frequency of these adverse events in the DS patient cohort was compared to the non-DS syndrome cohort, the frequency was higher in the DS cohort in all cases, except for seizures. This may reflect the younger mean age of the DS cohort, where there may be greater susceptibility to gastrointestinal and central nervous system adverse effects. The lower rate of seizure in the DS cohort may reflect a better response to STP treatment.

Overall, examination of the frequency of TEAE by SOC and preferred term reveals the most prominent signal is observed for occurrence of decreased appetite and central nervous system adverse effects of somnolence and ataxia, as was seen in the controlled trials in DS (see Table 4). There was also a high frequency of events under the preferred terms gamma-glutamyltransferase increased and aspartate aminotransferase increased (although not for other indices suggestive of hepatic toxicity); from among these two preferred terms, there were 4 SAEs and one discontinuation.

Laboratory Findings:

Examination of adverse events and clinical chemistry laboratory values reveals no evidence of a hepatotoxicity signal.

Examination of hematology parameters reveals a trend toward hematopoiesis depression, identified by a decline in hemoglobin, erythrocytes (without evidence of hemolysis or blood loss), and leukocytes, in analyses of the STICLO studies.

There is a more notable depression of neutrophils. In the controlled trials, there was a higher frequency of decline in neutrophils, with a larger magnitude of decline in STP than placebo. Among the DS patients in non-STICLO studies, there was a consistent trend of decreasing neutrophil counts associated with STP treatment. The STP-1 study reveals a declining trend in neutrophil counts in a notable proportion of patients. Thirty-eight (38%) of patients with baseline neutrophil values within reference range had a decline to absolute neutrophil count (ANC) < 1000.

Examination of the total category 2 and 3, DS and non-DS patient adverse event (AE) pool reveals 30 instances of either

"neutropenia" or "neutrophil count decreased" in 25 patients. From among these, there was a single discontinuation in STP-treated patients. There is some reassurance that adaptation develops, since all but a single patient remained on STP treatment. However, in the STP-1 study, there were SAEs in the SOC "infections and infestations" associated with several patients who had low neutrophil counts, suggesting that the decline in neutrophil count could have had physiologic consequences.

The magnitude and frequency of decline from baseline for thrombocytes in the STP-1 study was not as large as seen for neutrophils. There were 4 SAEs in the open-label study data for thrombocytopenia, with a nadir near 40,000 /mm^3 in one patient who had a baseline of 183,000 /mm^3. In two reports, there was a rebound (positive dechallenge) with either discontinuation or dose reduction, and in a third where STP was not discontinued, the narrative indicates the patient remained on study drug for years after the event. These data indicate a risk of thrombocytopenia, but this may be monitored, and is reversible.

QT interval:

This was inadequately assessed by the applicant. To satisfy the need for a complete clinical electrocardiographic evaluation for the effects of STP on the QT interval, a TQT study must be performed as a PMR.

Vital Signs:

There were no clinically significant differences in heart rate, blood pressure, or body temperature between the STP-arm and placebo-arms of the two controlled STICLO studies. A decrease in weight was commonly seen in the STP arm as discussed above.

Safety Conclusion:

We agree with Dr. Dinsmore that the risks associated with STP are acceptable, given the demonstrated benefit of improved seizure control for the DS patient population. Although the risks of neutropenia and thrombocytopenia have the potential to be serious, they can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of a neutropenia/thrombocytopenia, and periodic hematologic monitoring. The adverse events of somnolence, decreased appetite and decreased weight, and neutropenia and thrombocytopenia, will be addressed under **Warnings and Precautions** in the prescribing information (PI).

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the safety profile of stiripentol is acceptable for the proposed indication.

10. Pediatrics

The studies in DS were conducted in a pediatric population down to three years of age. Issues specific to the pediatric population are discussed within the review. Because the product has orphan designation for DS, the Pediatric Research Equity Act (PREA) is not triggered.

11. Other Relevant Regulatory Issues

- No Good Clinical Practice (GCP) issues were identified in Dr. Dinsmore's clinical review.
- Dr. Dinsmore concludes in his clinical review that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.
- OSI Review: Two sites of the STICLO France study and two sites of the STICLO Italy study were inspected, and no issues were identified.
- The Controlled Substance Staff (Reviewer James M. Tolliver, Ph.D. and Team Leader Silvia N. Calderon), concluded on the basis on nonclinical, clinical, and postmarketing data included in the application, that stiripentol did not meet the criteria to be scheduled under the Controlled Substance Act (CSA).

12. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Division of Risk Management (DRISK) reviewer for this application is Dr. Charlotte Jones. Dr. Jones concludes that a risk evaluation and mitigation strategy (REMS) is not necessary for STP.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following studies are recommended as PMRs:

3462-1	Studies to characterize the in vivo metabolic profile of orally administered stiripentol in the species and strains used in the pivotal developmental toxicity and carcinogenicity studies.
3462-2	Bridging toxicokinetic studies to document steady-state plasma exposures to stiripentol and any major human metabolites under the conditions used in the pivotal developmental toxicity and carcinogenicity studies.
3462-3	An embryofetal development study of stiripentol in rat.
3462-4	An embryofetal development study of stiripentol in rabbit.
3462-5	A pre- and postnatal development study of stiripentol in rat.

3462-6	A juvenile animal toxicology study of stiripentol in one species, with selection of species based on interspecies comparison of in vivo metabolic profiles.
3462-7	Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Diacomit (stiripentol) during pregnancy compared to an unexposed control population.
3462-8	Conduct a thorough QT trial for Diacomit as per the ICH E14 guidelines.
3462-9	Conduct a clinical pharmacokinetic trial to determine an appropriate dose of Diacomit (stiripentol) to minimize toxicity in patients with varying degrees of hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."
3462-10	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of rifampin, a CYP3A, CYP2C19, and UGT inducer, on the single dose pharmacokinetics of Diacomit (stiripentol) in healthy volunteers to assess the magnitude of decreased drug exposure. You should also evaluate metabolite concentrations, if any of the identified metabolites is less polar than the parent drug (stiripentol) and has an AUC ≥25% of the AUC of stiripentol. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry."
3462-11	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of caffeine (a sensitive CYP1A2 substrate) in healthy volunteers to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry."
3462-12	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol), on the single dose pharmacokinetics of a CYP2B6 sensitive substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry."

3462-13	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of CYP3A4 sensitive substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry."
3462-14	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of a CYP2C19 sensitive substrate in healthy volunteers to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry."
3462-15	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of a P-gp sensitive substrate in healthy volunteers to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry."
3462-16	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of Diacomit (stiripentol) on the single dose pharmacokinetics of a BCRP sensitive substrate in healthy volunteers to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry."

The timetables for draft protocol submission, final protocol submission, study completion, and final report submission for each for the PMRs are specified in the action letter.

14. Recommended Comments to the Applicant

See action letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
08/20/2018

ERIC P BASTINGS
08/20/2018
I concur.

ROBERT TEMPLE
08/20/2018