CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206709Orig1s000
207223Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206709 Capsules, 207223 powder for oral suspension
Priority or Standard	Priority
Submit Date(s)	12/20/17
Received Date(s)	12/20/17
PDUFA Goal Date	8/20/18
Division/Office	DNP/OND 1
Reviewer Name(s)	Steven Dinsmore DO
Review Completion Date	5/29/18
Established Name	Stiripentol
(Proposed) Trade Name	DIACOMIT
Applicant	Biocodex SA
Formulation(s)	Capsule / powder for oral suspension
Dosing Regimen	50mg/kg administered in 2 or 3 divided doses
Applicant Proposed Indication(s)/Population(s)	indicated for (b) (4) treatment of (b) (4) (b) (4) seizures associated with Dravet syndrome.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	DIACOMIT is indicated for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older taking clobazam.

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Glossary

AC	*advisory committee*
AE	*adverse event*
AED	Antiepilepsy Drug
AST	*Aspartate aminotransferase increased*
BPCA	*Best Pharmaceuticals for Children Act*
BRF	*Benefit Risk Framework*
CDTL	*Cross-Discipline Team Leader*
CFR	*Code of Federal Regulations*
CLB	clobazam
CMC	*chemistry, manufacturing, and controls*
CRF	*case report form*
CRO	*contract research organization*
CRT	*clinical review template*
CSR	*clinical study report*
CSS	*Controlled Substance Staff*
DB	*double blind*
DDI	*Drug-drug interaction*
DMC	*data monitoring committee*
DS	Dravet Syndrome
ECG	*electrocardiogram*
eCTD	*electronic common technical document*
EOS	end of study
ETASU	*elements to assure safe use*
FDA	*Food and Drug Administration*
GCP	*good clinical practice*
GGT	*Gamma-glutamyltransferase*
ICH	*International Conference on Harmonization*
IND	*Investigational New Drug*
ISE	*integrated summary of effectiveness*
ISS	*integrated summary of safety*
ITT	*intent to treat*
MedDRA	*Medical Dictionary for Regulatory Activities*
mITT	*modified intent to treat*
NCI-CTCAE	*National Cancer Institute-Common Terminology Criteria for Adverse Event*
NCLB	N-desmethylclobazam
NDA	*new drug application*

NME	*new molecular entity*
Non-DS	non-Dravet syndrome patients
OORR	*Out of Reference Range*
OSI	*Office of Scientific Investigation*
PD	*pharmacodynamics*
PI	*prescribing information*
PK	*pharmacokinetics*
PMC	*postmarketing commitment*
PMR	*postmarketing requirement*
PP	*per protocol*
PPI	*patient package insert*
PREA	*Pediatric Research Equity Act*
REMS	*risk evaluation and mitigation strategy*
SAE	*serious adverse event*
SAP	*statistical analysis plan*
SOC	MedDRA “System Organ Class” category
SOC	*standard of care*
STP	stiripentol
TEAE	*treatment emergent adverse event*
VPA	valproic acid

1

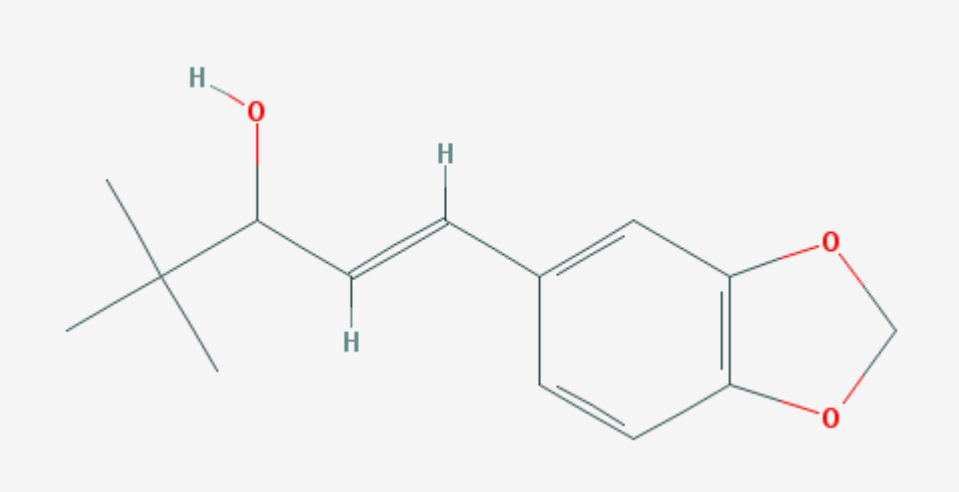
1 Executive Summary

1.1. Product Introduction

Stiripentol is an aromatic allylic alcohol.

Chemical Name: 4,4-dimethyl-1-[3,4{methylenedioxy}-phenyl]-1-penten-3-ol
Molecular Formula: $C_{14}H_{18}O_3$
Molecular weight: 234.295 g/mol

Figure 1 Stiripentol Structure, PubChem



Stiripentol (Diacomit, proprietary name) is a derivative of α -ethylene alcohol and was chosen from a series of compounds for further studies owing to its favorable effects upon the CNS.[1] [2] Its chemical structure is structurally unrelated and completely different from other currently marked antiepileptic agents. STP was found to positively modulate all recombinant $GABA_A$ receptors tested, but had its greatest effect when the receptor contained an alpha-3 subunit. Unlike the benzodiazepines, STP did not require presence of a gamma-subunit and was a strong

[1] Astoin J, Marivain A, Riveron A, Crucifix M, Lapotre M, Torrens Y. 1978. CENTRAL NERVOUS-SYSTEM AGENTS - NEW ALPHA-ETHYLENIC ALCOHOLS. European Journal of Medicinal Chemistry 13:41-47.
[2] Czuczwar SJ, Trojnar MK, Gergont A, Kroczka S, Kacinski M. 2008. Stiripentol - characteristic of a new antiepileptic drug. Expert Opinion on Drug Discovery 3:453-460. http://dx.doi.org/10.1517/17460441.3.4.453

modulator of delta-containing receptors. This mechanism is similar to that of benzodiazepine-site agonists, but the STP site is clearly distinct from other well-known $GABA_A$ receptor modulators. The activity of STP is not blocked by antagonists of the benzodiazepine or neurosteroid sites.[3]

The product has two formulations a capsule form and a powder for suspension. These have been submitted under separate NDA numbers. The capsule is submitted under NDA 206709 and the powder under NDA 207223. NDA206709 was under rolling review with PDUFA goal date (action date) of 8/20/18 while NDA 207223 was submitted on 9/5/17 with a PDUFA goal date (action date) of 9/19/18. There was no new nonclinical or clinical data in the NDA 207223 submission.

Proposed Indication: "DIACOMIT is indicated for (b) (4) treatment of (b) (4) (b) (4) seizures associated with Dravet syndrome in patients (b) (4) (b) (4)"

Proposed Dosing: " (b) (4) dosage of DIACOMIT is 50 mg/kg administered in 2 or 3 divided doses. (b) (4) (b) (4)

Recommended Indication: "DIACOMIT is indicated for treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older taking clobazam"

Recommended Dosing Information: " (b) (4) dosage of DIACOMIT is 50 mg/kg daily administered (b) (4) in 2 or 3 divided doses (b) (4) (b) (4)

"DIACOMIT capsules must be swallowed whole with a glass of water during a meal. Capsules should not be broken or opened."

1.2. Conclusions on the Substantial Evidence of Effectiveness

The sponsor has provided substantial evidence of the effectiveness of stiripentol for the treatment of seizures associated with Dravet syndrome.

The Evidence of stiripentol effectiveness is based on the STICLO France and Italy studies. Both

[3] 1. Fisher JL. The effects of stiripentol on GABA(A) receptors. Epilepsia 2011;52:76-78. 10.1111/epi.12303

studies have the same multicenter, randomized, double-blind, placebo-controlled design with inclusion criteria that requires inclusion of refractory Dravet syndrome patients on clobazam and sodium valproate. Stiripentol dose in these studies was 50mg/kg without upward titration. STICLO France, a study of 41 patients and STICLO Italy, a study of 23 patients with Dravet syndrome were pivotal studies to demonstrate efficacy. In the STICLO France study the responder rate for STP treatment arm was 71.4% compared to 5% in the PBO arm. In the STICLO Italy study the responder rate in the STP treatment arm was 67% compared to 9% in the PBO arm. Both studies had a significant treatment to placebo difference. Examination of all secondary endpoints also identified STP treatment benefit.

Dravet syndrome is an epilepsy generally refractory to currently available antiepilepsy drugs. On the background of this refractory to treatment characteristic the observed reduction in seizure frequency and associated 50% responder rate in the stiripentol treated patients is a compelling therapeutic advance for Dravet syndrome.

Development of STP for use as an antiepilepsy drug was supported by a non-clinical signal for an anticonvulsant effect. In early clinical studies, the therapeutic benefit was modest. In a study of patients with a mix of epilepsy disorders where the study endpoint was 50% responder rate, the response rate in Dravet patients was high (80%); by contrast, response rate was low (25-30%) in the remaining non-Dravet patients. In addition, 30% of Dravet patients were found to be seizure-free on Day 28, see section 6.2.1 STEV Study. Data that further supports the possibility of a selective Dravet syndrome benefit is the much higher STP response rate in SCN1A mutation positive patients compared to mutation negative patients seen among the STP treated patients in the STICLO studies with known SCN1A status, see Table 21. However, in support of an STP treatment effect that is independent of concomitantly administered VPA and CLB there are only 7 patients retrospectively identified in a medical chart review study, see Laux Retrospective Chart Review. This small group did reveal a greater than 50% reduction in seizure frequency in 5 (71%) of the patients. Overall, a benefit of STP is consistent across data from the pivotal study to the examination of seizure frequency in the open label STP-1 and STEV studies as well as the observed high retention of DS patients in long term premarketing safety studies and one European post marketing safety study, see Additional Study Data on STP.

As noted in the prior paragraph, the common standard of care for treatment of seizures associated with DS is use of sodium valproate and clobazam. The available Dravet syndrome population for clinical studies very frequently have ongoing treatment with VPA and CLB. Stiripentol inhibits metabolism of clobazam and active metabolite norclobazam. It is established that STP increases exposure to clobazam by 2 to 2.5 fold and the active metabolite norclobazam by 4 to 5 fold. The increase in VPA exposure is 11% and unlikely to influence seizure frequency. This characteristic of the study population results in difficulty differentiating an independent STP treatment effect from the potential therapeutic augmentation of clobazam exposure. Several strategies were used by the Clinical Pharmacology team to identify STP standalone

efficacy. No approach was successful as discussed in section 4.2.3, Stiripentol – Clobazam Interaction. The consequential conclusion is the efficacy of STP cannot be separated from sum of STP and the ongoing concomitant antiepilepsy therapies. It is most biologically plausible that there is a CLB contribution to the treatment effect of STP due to the interaction with CLB metabolism with notable elevation of CLB and NCLB levels. Because of this biologic plausibility the STP indication for use should include concomitant treatment with CLB.

Although patients in the pivotal studies were enrolled at age 3 years and above there is no evidence of a sharp change in response to STP below age 3 years. Patients in the STEV and DIAVEY studies between the ages of 2 and < 3 were examined and the data revealed the majority of these patients who were newly treated with STP in an open label had a decline in seizure frequency. Examination of the patient cohort between age 3 and <6 years in the STICLO studies reveals a responder rate of 71% in the STP treatment cohort and 0 in the PBO cohort. In addition, there were 163 DS patients <3 years of age contributing to safety data in the long term open label studies. These observations support an indication for that treatment of DS patients age 2 years and older where age 2 years is the generally recognized age of DS diagnosis.

In summary, the pivotal and supporting studies that provide key evidentiary support have small sample sizes. This is commensurate with the limited population of patients with this rare disease. The robust benefit when considered in the context of the marked refractory nature of the seizures in Dravet syndrome is conclusive evidence that stiripentol is effective for treatment of seizures in this disease. The findings from data across open label studies and long-term safety studies are also in alignment with the STP treatment benefit seen in the evidentiary studies.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dravet syndrome is a rare but severe condition with seizure frequency and intensity that is refractory to current therapy, especially in the 1 to 5 year old age range. The severity of seizure in Dravet syndrome results in impaired activities of daily living, developmental delay and is life threatening due to the occurrence of status epilepticus and SUDEP. Several studies reveal a death rate of 16% to 17%. Permanent disability develops following onset due to the severity of the seizure disorder and / or the underlying sodium channel lesion. There is currently no approved drug treatment and available interventions produce incomplete seizure control.

In this submission two small pivotal studies of the same design identified robust results with a large STP treatment to PBO seizure frequency gradient that was statistically significant. In these studies, STP was administered to patients who were refractory to ongoing treatment with clobazam and valproic acid. Due to inhibition of clobazam metabolism there were large increases in exposure to clobazam and an active metabolite, norclobazam. A benefit of STP alone could not be isolated from the effect of STP acting in concert with clobazam and valproic acid. Examination of secondary endpoints also identified STP treatment benefit. Additional supportive data is present from two open label add on studies with a design that compared baseline to treatment seizure frequency. Long term open label extension studies also show results that are in alignment with an STP treatment benefit.

The reduction in seizure frequency identified in this body of evidence may reduce the frequency of life disruptive, threatening seizures and the associated mortality of severe seizure events. Seizure reduction is associated with an increase in quality of life and a decrease of the threat that is present with each event. There is potential for a reduction in the deleterious neurocognitive effects seen in Dravet syndrome.

Risks identified in the clinical safety data include somnolence, decreased appetite and weight loss, even cachexia. There was also an indication of depression of neutrophil and platelet counts.

Somnolence is observable and decreased appetite with weight loss may be observed and measured. When necessary an intervention of STP discontinuation can take place. The clinical laboratory finding of declining neutrophil or platelet count with neutropenia or thrombocytopenia can be monitored. If monitored values reveal a threat, STP treatment can be discontinued. The clinical features of the safety dataset indicate that reversibility is expected on discontinuation. Blood counts (CBC) should be obtained at baseline and every six months to monitor for decline in neutrophil and platelet counts.

Conclusion: The benefit risk analysis reveals that the benefit of STP treatment for this severe condition more than balances the safety risks that have been identified. The risks are monitorable and expected to be reversible with discontinuation of stiripentol.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Dravet syndrome is a rare epilepsy syndrome characterized by onset in the 1st year of life followed by development of multiple seizure types, worsening to approximately age 5 years with delayed cognitive development and worsening seizures, generally resistant to antiepileptic drugs. After age 5, seizure severity tends to decrease, mental development may improve but cognitive impairment persists. • There is a high likelihood of recurrent prolonged seizures • There is significant risk of sudden unexplained death • Estimates are that approximately 2000 patients affected in the U.S. but may increase as precision in clinical and genetic diagnosis advance.	This is a severe "epileptic encephalopathy" with threat to life from sudden death and permanent change in cognitive and behavioral function based on the current state of knowledge of Dravet syndrome.
Current Treatment Options	• There is a single recently approved therapy for DS not yet available on the market. Cannabidiol (CBD) was approved for treatment of DS on 6/25/18 and is currently in the scheduling review process. • Non-approved but medical standard of practice drug therapies include valproic acid, clobazam, topiramate, and bromide	The responder rate analysis endpoint can be compared where this was the primary outcome measure for STP and a secondary endpoint for CBD. The result of this outcome measure is more robust for STP than CBD. CBD is not yet market available at the time of this writing thus treatment for the severe seizures of Dravet syndrome continues to represent an unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Two clinical studies identified clear benefit of stiripentol treatment when added at a dose of 50mg/kg (without titration) in 2 or 3 divided doses to ongoing valproic acid and clobazam treatment over valproic acid and clobazam alone. • A 71% responder rate was observed in the stiripentol treatment arm and a 5% responder rate in the placebo arm • The benefit was obtained in a disease known to be refractory to antiepilepsy drug treatment • Patient entering the study, before starting stiripentol, had continued seizures while on their established background therapy of valproic acid and clobazam	Stiripentol is an important addition to treatment options expected to provide benefit over existing, unapproved standard of care therapies, when used together with clobazam and valproic acid. Dravet is a refractory epilepsy syndrome with no approved antiepilepsy drug therapies.
Risk	• Neutropenia ○ In controlled studies at end of study there were 6 (18%) patients in the STP arm and 1 (3%)in PBO arm with neutrophil count < 1500 ○ Consistent trend of declining neutrophil count across studies ○ In one open label study of 24 patients new to STP treatment thirty-eight (38%) of patients with baseline neutrophil values within reference range had a decline to ANC < 1000 ▪ Frequent infection related adverse events in this study, though uncertain relationship ○ A Single patient had SAE & discontinuation due to decline to < 1000 neutrophils /mm^3 at 40 days of STP treatment • Thrombocytopenia ○ There were 4 SAEs in the open label study data for thrombocytopenia with a nadir near 40,000 /mm^3. There are	Neutropenia is a risk supported by consistency of decline across studies. The decline tends to plateau. Most patients with a decline remaining on treatment. This risk may be monitored. Dechallenge data is not available (only 1 discontinuation) but the observation of plateau of values and frequency of patients remaining on treatment is evidence that monitoring for severe instances is adequate Thrombocytopenia is a risk supported by the frequency of serious adverse events in open label studies. This risk is reversible and may be monitored, dechallenge data shows

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	two reports with reversal after STP discontinuation ○ trend of platelet count decline inconsistent across studies • Somnolence ○ Most frequent adverse event in STP arm of controlled studies ○ 67% of patients in STP treatment, 23% of patients in PBO treatment ○ 1 SAE each containing term "somnolence" in STICLO PBO and STP arms ○ 2nd most common adverse event term in all studies (DS, non-DS patients) • Decreased appetite ○ 2nd most frequent term in the STP treatment arm of controlled studies ○ 46% of patients in STP treatment arm, 10% of patients in PBO treatment arm ○ Most frequent adverse event term in all studies (DS, non-DS patients) ○ Decreased appetite in 11 (1.8%) patients all study (625 unique patients) ○ Cachexia in 3 (0.5%) patients all studies (625 unique patients) • Weight Decreased ○ 3rd most frequency adverse event term in the STP treatment arm of controlled studies ○ 27% of patients in STP treatment, 6.5% of patients in PBO treatment ○ Weight decreased AE in 29 (5%) patients from all studies with	reversibility. Somnolence, an effect of central nervous system depression seen frequently in antiepilepsy drug treatment is reversible upon discontinuation of treatment. Dechallenge data from one patient in open label study had resolution of somnolence. This adverse reaction may be monitored. Depression of appetite and weight loss may be severe and require discontinuation of treatment. Dechallenge data from two reports shows reversibility of this adverse effect. This may be monitored.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	1 SAE	
Risk Management	• Proposed labeling; The safety data do not indicate need for a special risk evaluation and mitigation strategy. Some modification of proposed labeling will be required in response to the observation of effect on neutrophils and platelets. • A thorough QT study has not been performed and should be completed post marketing.	Addition of risk of neutropenia should be added to section 5, Warnings and precautions. Instruction for blood count at baseline and every six months thereafter. The observation of thrombocytopenia should be added as an identified Hematologic Abnormality in Section 6.1 PMR should be added for a thorough QT study

2 Therapeutic Context

2.1. Analysis of Condition[4]

Dravet syndrome (DS; severe myoclonic epilepsy of infancy, is an epileptic and genetic encephalopathy that is characterized by onset in the first year of life, with prolonged generalized or hemiclonic seizures often associated with fever, followed by the development of multiple seizure types generally resistant to antiepileptic drugs, and slowing of neurodevelopment. Long-term prognosis for both seizure control and neurodevelopmental outcome is poor. Patients may continue to have an average of more than 4 tonic–clonic seizures per month, despite being treated with a combination of an average of 3 drugs.[5] Dravet syndrome is considered an epileptic syndrome highly refractory to treatment in addition to an ''epileptic encephalopathy,'' defined as a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. However, it is not proven that the cognitive decline observed in the first stages of the disease is the consequence of the epilepsy.

Dravet syndrome is rare but its actual frequency is not well known. An investigator in the U.S. estimates an incidence of 1/37000 in children ≤ 7 years old in three Texas health regions in 1990.[6] This incidence is applied to available population statistics from the 2010 census. Age group breakouts from this data presented for age < 5 years and the total age group < 18 years were 20201362 and 74181467 people respectively.[7] If the Texas incidence data of 1/37666 in the ≤ 7-year group is applied to the total U.S. population less than age 5 then 536 patients with Dravet syndrome may be estimated to be present in this US age group. If the Texas 1/31666 (≤ age 7) is applied to the total US population under age 18 then 1969 patients with Dravet syndrome may be estimated to be present in the age – population cohort. This rough calculation is performed to provide a tangible characterization of the magnitude of the Dravet population. Slightly different figures (1/20,000 or 30,000) were reported by in France (1992).[8] Even if the recognition of the syndrome increases based on refined clinical criteria and more

[4] 2. Ceulemans B. Overall management of patients with Dravet syndrome. Developmental Medicine and Child Neurology 2011;53:19-23.
[5] Prager C, Cross JH. 2017. Management of Dravet syndrome and emerging therapy options. Expert Opinion on Orphan Drugs 5:219-227.
[6] Hurst DL. Epidemiology of Severe Myoclonic Epilepsy of Infancy. Epilepsia, 31(4): 397-400, 1990.
[7] Age and Sex Composition: 2010. 2010 Census Briefs, Issued May 2011.
https://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf
[8] Yakoub M, et al. Early Diagnosis of Severe Myoclonic Epilepsy in Infancy. Bain Dev 1992; 14: 299-303.

precise knowledge of SCN1A mutation frequency the Dravet syndrome remains rare.[9] The Dravet Syndrome Foundation currently posts that "Previously known as Severe Myoclonic Epilepsy of Infancy (SMEI), it affects 1:15,700 individuals, 80% of whom have a mutation in their SCN1A gene"[10].

Three stages can be distinguished: (1) the febrile or diagnostic stage in the first year; (2) the worsening (preferred to ''catastrophic'') stage between 1 and 5 years: period with frequent seizures and statuses, behavioral deterioration, and neurologic signs; and (3) the stabilization stage after 5 years: convulsive seizures decrease and occur mainly in sleep, myoclonic and absence seizures can disappear, focal seizures persist or decrease; mental development and behavior tend to improve but cognitive impairment persists, although of variable degree.[11] The clinical profile characterized by greater epilepsy severity observed up to age five years is also reported in a recent review of Dravet syndrome.[12] Between age 1 and 4 years, episodes of status epilepticus with fever, as well as episodes of non-convulsive status epilepticus, are frequent.[13]

A greater degree of cognitive and behavioral impairment has been linked to both higher frequency of convulsive and non-convulsive seizures.[14] The rate of sudden unexpected death in epilepsy is high in Dravet syndrome patients. Several studies reveal a frequency of 16% to 17%, likely greater in the younger cohort. In their 1992 review, Dravet et al. noted that 16% among 63 patients died at a mean age of 11 years.[15] In a discussion of mortality in Dravet syndrome several series are cited, the first noted that 6 of their 37 patients died before age 18 and in a second there were 12 deaths among 84 patients, at a mean age of 65 months.[16]

A feature of DS is its strong association with de novo mutations in a particular gene. Approximately 80% of patients with DS carry mutations in SCN1A, encoding the type I voltage gated sodium channel (Nav1.1) alpha subunit. The Nav1.1 channel protein belongs to a larger family of nine sodium channel proteins that are also associated with, and are modulated by,

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[9] {Dravet, 2011 #11} Dravet, C. The Core Dravet Syndrome Phenotype. Epilepsia, 52(Suppl. 2):3–9, 2011. doi: 10.1111/j.1528-1167.2011.02994.x
[10] https://www.dravetfoundation.org/what-is-dravet-syndrome/
[11] Dravet C. The core Dravet syndrome phenotype. Epilepsia, 52 (suppl2):3-9, 2011. doi: 10.1111/j.1528-1167.2011.02994.x
[12] Wirrell EC. Treatment of Dravet Syndrome. Canadian Journal of Neurological Sciences 2016;43:S13-S18.
[13] Bender AC, et al. SCN1A mutations in Dravet syndrome: Impact of interneuron dysfunction on neural networks and cognitive outcome. Epilepsy & Behavior 23 (2012) 177–186. doi:10.1016/j.yebeh.2011.11.022
[14] Wirrell EC. Treatment of Dravet Syndrome. Canadian Journal of Neurological Sciences 2016;43:S13-S18
[15] Dravet C, et al. Severe myoclonic epilepsy in infants. Chapter 8. Epileptic Syndrome in infancy, childhood and adolescence. (2nd edition) J. Roger, M. Bureau, Ch. Dravet, F.E. Dreifuss, A Perret and P. Wolf. 1992 John Libbey & Company Ltd. pp. 75-88.
[16] Genton P, et. al. Dravet Syndrome: The long term outcome. (Epilepsia, 52(Suppl. 2):44–49, 2011. doi: 10.1111/j.1528-1167.2011.03001.x

smaller beta subunits. These voltage-gated sodium channels are important for the excitability of cells such as neurons and myocytes, and in the brain they are critical for the initiation and propagation of action potentials in neurons.

Mutation in the SCN1A has been shown to play role in the phenotype in at least 85% of Dravet syndrome. To date, more than 500 mutations of SCN1A have been associated with Dravet syndrome. Voltage gated sodium channels play an important role in neuronal excitability. Mutations cause either a gain or a loss of function. Although most cases arise de novo, familial cases with missense mutation have also been reported.[17]. It has been proposed that the term Dravet syndrome be reserved for SCN1A mutation carriers only.[18]

In summary, Dravet syndrome is a rare but severe condition with seizure frequency and intensity that is refractory to current therapy, especially in the 1 to 5 year old age range. The seizure severity results in impaired activities of daily living and is life threatening due to the occurrence of status epilepticus and SUDEP. Permanent disability develops following Dravet onset due to the severity of the seizure disorder and / or the underlying sodium channel lesion. There is currently no approved drug treatment and available interventions produce incomplete seizure control.

2.2. Analysis of Current Treatment Options

There is a single recently approved therapy for DS not yet available on the market. Cannabidiol (CBD) was approved for treatment of DS on 6/25/18 and is currently in the scheduling review process. Overall, there have been few evidence-based studies to evaluate the best therapies for DS, and recommendations for most first- and second-line therapies are based predominantly on expert opinion and a limited number of small, mostly retrospective, open-label studies. First-line management typically involves either valproic acid and/or clobazam.

Complete control of seizures is rarely achieved and most children will have recurrent seizures despite optimal drug treatment. Second line agents when seizures persist are topiramate and the ketogenic diet. Additional later therapeutic options are levetiracetam, bromides or vagal nerve stimulation. [19]

[17] Gursoy S, Ercal D. Diagnostic Approach to Genetic Causes of Early-Onset Epileptic Encephalopathy. Journal of Child Neurology 2016, Vol. 31(4) 523-532. DOI: 10.1177/0883073815599262
[18] Lemke JR, Syrbe S. Epileptic Encephalopathies in Childhood: The Role of Genetic Testing. Semin Neurol 2015;35:310–322
[19] 3. Wirrell EC. Treatment of Dravet Syndrome. Canadian Journal of Neurological Sciences 2016;43:S13-S18.

Table 1 Antiepilepsy Drug Treatment for Dravet Syndrome[20]

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved treatments					
Cannabidiol (CBD)	Dravet Syndrome, Lennox-Gastaut Syndrome	2018 (not yet market available) *	Oral Solution, Dose 10mg/kg/day to 20mg/kg/day	In DS, Primary Endpoint Median Change in Seizure frequency Baseline to Treatment PBO = -13%, CBD -39%. Secondary Endpoint, ≥50% Responder Analysis PBO = 27% , CBD= 43%	Transaminase elevations identified in 13% of cannabidiol patients compared to 1% of PBO patients. Somnolence and sedation noted in 32% of cannabidiol compared to 11% of PBO patients.
Other Treatments, 1st Line					
Clobazam	adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older	2011	Begin 5mg/day, titrate up to 20mg/day	limited amount of data on the efficacy of clobazam in DS, single retrospective study	behavioral disinhibition, sedation, ataxia and increased salivation.
Valproic acid	Monotherapy and adjunctive therapy of complex partial seizures; sole and adjunctive therapy of simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures	1978	Start at 10 to 15 mg/kg/day, increasing at 1 week intervals by 5 to 10 mg/kg/week until seizure control or limiting side effects	There is minimal literature on its use in DS (level 4), and in retrospective studies14,15 responder rates (>50% reduction in seizure frequency) were 22.2-48%.	potential for several severe adverse effects, including hepatotoxicity (particularly with underlying mitochondrial disease), hyperammonemia, pancreatitis and thrombocytopenia. Additionally, other adverse effects may include decreased or increased appetite, tremor (at higher doses), hair loss and sedation.
Other Treatments, 2nd and 3rd line options					
Topiramate	initial monotherapy in patients ≥2 years	1996	For monotherapy use in adults	Observational, open label and a retrospective study	Adverse effects include somnolence, decreased

[20] 4. Prager C, Cross JH. Management of Dravet syndrome and emerging therapy options. Expert Opinion on Orphan Drugs 2017;5:219-227.

	of age with partial onset or primary generalized tonic-clonic seizures (1.1); adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and for patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome		and pediatric patients 10 years of age and older starting at 400 mg/day in two divided doses.	have shown responder rates of 35 – 78%.	appetite, slowing of verbal processing, metabolic acidosis and nephrolithiasis.
Levetiracetam	Partial onset seizures in patients one month of age and older with epilepsy , myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.	1999	Starting at 7mg/kg twice daily in children 1 Month to < 6 Months up to 500mg twice daily in adults	Reported to have a responder rate of 64% in a single open label prospective study.[21]	behavioral disinhibition
Bromides	19th century treatment for epilepsy, not available for prescription in North America	N/A		The responder rates for generalized clonic or tonic clonic seizures were 71% and 94% in SCN1A-positive and SCN1A-negative patients,	side effects of bromides are typically minor and include rash, somnolence and decreased appetite. Comment: bromide is not widely used in view of the lack of availability and monitoring required.

[21] 5. Striano P, Coppola A, Pezzella M, et al. An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. Neurology 2007;69:250-254.

				respectively	
* cannabidiol was approved 6/25/18 but will not have DEA scheduling until September 2018 thereafter will be available on the market					

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

STP was granted orphan designation for the treatment of Dravet syndrome by the Food and Drug Administration (FDA) (orphan designation number 08-2661) on October 30, 2008

Stiripentol is a new molecular entity not marketed in the US thus without regulatory actions.

3.2. Summary of Presubmission/Submission Regulatory Activity

Stiripentol has been developed by BIOCODEX outside the US. All the studies in this application were not performed under an IND.

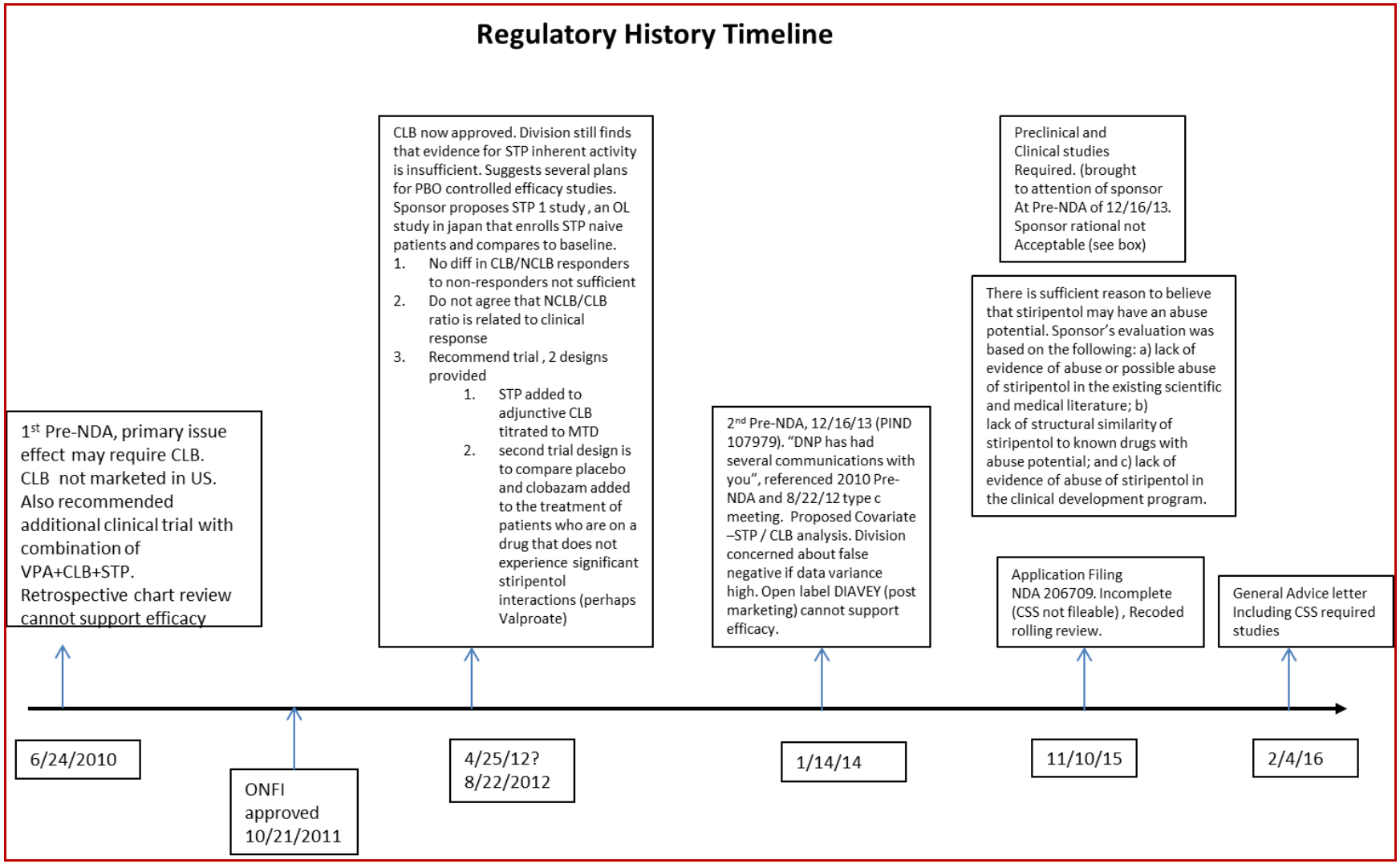
On June 24, 2010 a Pre-NDA meeting was held. The primary conclusions of this meeting were that "Two major clinical issues were identified in the pre-meeting responses; the uncertainty as to the contribution of STP in STILCO trials on-face efficacy given the increase in clobazam and norclobazam levels and the lack of availability of clobazam in the U.S. market".

The uncertainty of STP's role in the efficacy seen in the STILCO trials is not a trivial issue and likely would require additional, new clinical data as FDA does not believe the data from clinical practice can be used in a determinative manner to establish efficacy." "FDA strongly encouraged the conduct of a placebo-controlled clinical trial."

There are preliminary comments from a Type C meeting in August 2012. The discussion in this meeting acknowledges that clobazam was approved in the U.S. therefore eliminating the issue of co-administration with STP. The Division continued to recommend an adequately controlled trial.

A Pre-NDA meeting was held December 16, 2013. The meeting package included a proposal for a covariate analysis to assess the contribution of clobazam and norclobazam to the efficacy of stiripentol, inclusion of study STP-1 a 30 patient open-label Japanese study and an update on a European post marketing survey as supportive evidence of STP efficacy. The division response included concerns that a covariate analysis is likely to result in a false negative result if the variance of the data is too high. The division also noted that uncontrolled open-label data provided by the DIAVEY study cannot support the determination of efficacy.

Figure 2 Timeline of Regulatory Events



3.3. Foreign Regulatory Actions and Marketing History

STP was granted orphan designation for the treatment of Dravet syndrome by the European Medicines Agency (EMA) on December 5, 2001.

STP (Diacomit®) has been approved for use added on to valproate (VPA) and clobazam (CLB) as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with Dravet syndrome by the EMA (conditional authorization on January 4, 2007 followed by full marketing authorization on January 8, 2014), the Japanese Health Authority (September 28, 2012), and by Health Canada (December 21, 2012). In the EU, Canada, and Japan, the indication, daily recommended dose of STP, contraindication, warnings, and precautions are the same.

By January 1, 2003, all clinical trials in Dravet syndrome patients in the EU had been completed. Only one long-term open-label clinical trial (STILON) was still ongoing. In January 2003, the STILON study was closed and a Temporary Use Authorization Extended Access Program (TAU-EAP) went into effect in France. Dravet syndrome patients in France could continue or start treatment with STP under the TAU-EAP until the program was closed on March 31, 2007, 3 months after STP had been granted conditional approval by the EMA (January 4, 2007). A total of 210 Dravet syndrome patients received STP under the TAU-EAP; of these, 34 (16%) had previously been treated with STP.

During the interval of conditional marketing approval an EU-wide phase 4 clinical trial was required in Dravet and non-Dravet patients who had not previously been treated with STP. This study, entitled DIAVEY was completed in May 2012. As noted above, STP received full marketing authorization on January 8, 2014.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

There was a total of 64 evaluable patients from 20 sites in both STICLO studies. From STICLO France there were 41 evaluable patients from 14 sites and from STICLO Italy there were 23 evaluable patients from 6 sites. Examination of these sites did not reveal notable differences or marked outliers in protocol deviations, discontinuations, screen failures, adverse event recording, or financial conflict of interest reporting (none were reported). Sites for audit were

subsequently selected based on contribution to efficacy outcome and magnitude of patient enrollment.

Four sites were selected, two from STICLO France and two from STICLO Italy. All four clinical investigator inspections have been classified as No Action Indicated (NAI) and the sponsor inspection has also been classified NAI, see Table 2.

Table 2 OSI Study Audit Sites and Results

Site #, Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
Site #01 Catherine Chiron, M.D., Ph.D. Inserm U1129 et Centre de Référence Epilepsies Rares Hôpital Necker-Enfants Malades Service de Neuropédiatrie 149, rue de Sèvres 75743 Paris Cedex 15 France	STICLO France Subjects: 15	9/5/2016 to 9/9/2016	NAI
Site #11 Jean-Claude Netter, M.D. Service de Pédiatrie-Néonatalogie CH Intercommunal de Tarbes-Vic en Bigorre Boulevard de Lattre de Tassigny 65013 Tarbes France	STICLO France Subjects: 4	9/12/2016 to 9/14/2016	NAI
Site #01 Anna Rita Ferrari, M.D. Instituto di Neuropsichiatria Infantile Università di Pisa – IRCCS Tella Maris Via dei Giacinti, 2 56018 Calambrone (Pisa) Italy	STICLO Italy Subjects:4	9/12/16 to 9/14/2016	NAI
Site #02 Francesca Darra, M.D. Cattedra di Neuropsichiatria Infantile Policlinico GB Rossi – Borgo Roma piazzale L.A. Scuro 10 37134 Verona Italy	STICLO Italy Subjects: 3	9/19/2016 to 9/21/2016	NAI

4.2. Product Quality

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4.3. Nonclinical Pharmacology/Toxicology

Deficiencies are identified in the nonclinical review that will be addressed as post marketing requirements, see the PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION.

Concentration Response of PTZ Threshold

There is evidence for an independent anticonvulsant effect in animal models. In the mouse and rat, stiripentol antagonized convulsions and lethality induced by pentylenetetrazol (PTZ) or bicuculline, but showed only limited activity against strychnine-induced convulsions. Stiripentol also showed activity against maximal electroshock (MES)-induced convulsions in the mouse and rat.

Figure 3 concentration /response relationship for elevation of the PTZ threshold dose for induction of clonic convulsions in mice

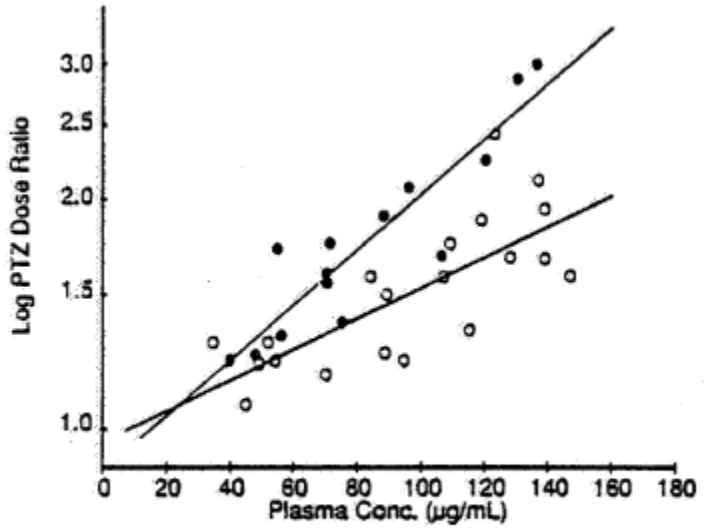


Fig. 1. Relationship of anticonvulsant effect, expressed as $\log_{10}$ PTZ threshold dose ratio, to plasma drug concentration after acute intraperitoneal (●) and subacute oral (○) treatment with stiripentol.

4.1. Clinical Microbiology

N/A

4.2. Clinical Pharmacology

4.2.1. **Mechanism of Action**

Discussion of Proposed Mechanism of Action from Sponsor eCTD, Module 2, Introduction 2.2 section 2.2.3, page 7.

The mechanism of antiepileptic activity of STP is thought to involve potentiation of the GABAergic and glutamatergic transmissions in the CNS. In concentrations likely achieved in the brain with therapeutic doses of STP the drug has been shown to directly enhance GABA-A receptor mediated transmission by acting both postsynaptically to significantly prolong IPSC decay and presynaptically to enhance GABA release. Postsynaptically, STP is a positive allosteric modulator of the GABA-A receptor and acts at a neuronal site different from those of other allosteric modulators, such as barbiturates and benzodiazepines. The in vitro activity of STP at this site is potentiated by benzodiazepines such as diazepam or CLB. This in vitro result is in keeping with the in vivo animal pharmacology results showing a more than additive protection against metrazol-induced seizures when STP is coadministered with a benzodiazepine. The benzodiazepine-site antagonist flumazenil has no effect on the STP-induced increase in IPSC, confirming that STP acts at a site which is distinct from the benzodiazepine receptor. Consistent with these results, in vivo pharmacology has shown that flumazenil doses not affect STP-associated sedation. STP was also shown to act presynaptically to enhance glutamate release from nerve terminals, a property that distinguishes it from barbiturates and benzodiazepines.

The sodium-channel gene SCN1A mutation associated with Dravet syndrome **causes loss of function with haploinsufficiency of SCN1A**. These channels are found on cortical glutamatergic pyramidal neurons that synapse with GABAergic neurons. As a result of the SCN1A haploinsufficiency, **glutamate transmission in the cortex is decreased with consequent decrease in GABAergic transmission**. Thus, Dravet syndrome involves both hypo-glutamatergic and hypo-GABAergic neurotransmissions. The decrease in cortical glutamatergic transmission distinguishes Dravet syndrome from other epilepsies. Most epilepsies are thought to involve hyperactivity of the glutamatergic system and hypoactivity of the GABAergic system. Not surprisingly, drugs that decrease glutamatergic transmission either by blocking the sodium channel (such as CBZ) or by inhibiting glutamate release (such as lamotrigine) and that are effective against a wide range of seizures have been reported to worsen seizures in Dravet syndrome patients. It is possible that the increase in glutamatergic transmission induced by STP also explains why the drug was found not to be effective in a number of seizure types and syndromes and **may explain the selective efficacy of STP in Dravet syndrome patients**; the drug's dual activation of both GABAergic and glutamatergic transmissions uniquely compensates for the underlying neurotransmitter deficits that characterize Dravet syndrome. See references in section Appendix 12.1 Mechanism of Action.

4.2.2. Pharmacodynamics

QT Effect

The sponsor has not performed a formal TQT study. At initial NDA submission, study STP-1 contained ECG data but was not a formal TQT study. A query was sent to the sponsor on 1/19/17 concerning their intent on performing a TQT study. The response of 2/13/17 stated: "The Sponsor believes that the ECG data in the "Report on the results of Electrocardiogram analysis" for Study STP-1 [5.3.5.2; BC.609; Appendix 16.2.7, ECG Analysis] by (b) (4) (b) (4), is adequate to serve as an alternative to a "Thorough QT/QTc Study".

Subsequently this study was reviewed in a TQT consult to the IRT team. This study had several deficiencies that make it unacceptable to substitute for a formal TQT study. ECGs were not obtained at tested at substantial multiples of the anticipated maximum therapeutic exposure and ECG was obtained only at C_{trough} rather than C_{max}. The data that is available from STP-1 do not reveal changes that suggesting a safety signal for QT prolongation. The results are shown in section 7.4.9, STP-1 ECG Study Results, however, due to the deficiencies noted, the consulting Division found the ECG data provided in study STP-1 cannot substitute for a TQT study. The QT-IRT response to DNP states : "We recommend that the sponsor conducts a TQT study as per the ICH E14 guidelines."

4.2.3. Pharmacokinetics

Formulations

The product has two formulations, as noted in Product Introduction, a capsule form and a powder for suspension. These have been submitted under separate NDA numbers. The capsule is submitted under NDA 206709 and the powder under NDA 207223. NDA206709.

The OCP team notes the following in their review:

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 3 below.

Table 3 Mean PK Parameters of STP Capsules and Powder Formulation from STIVAL Relative Bioavailability Study

STIRIPENTOL		Cmax (µg/mL)	tmax (h)	tl/2 (h)	AUC0-t (h.µg/mL)	AUC0-∞ (h.µg/mL)	AUC0-∞ (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. 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, see section 7.6 "patients using (b) (4) formulation".

Food Effect

In their review the OCP reports "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.[22] 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."

The clinical reviewer examined the "Method of administration" section of the EMA label. This section indicates STP should not be taken with mild or dairy products (yogurt, soft cream cheese, etc.), carbonated drinks, fruit juice or food and drinks that contain caffeine or theophylline.

There is no support for the dairy product avoidance recommendation identified in the NDA 206709 submission. The avoidance of theophylline or caffeine is likely derived from the known STP inhibition of CYP 1A2 that is the CYP for N-demethylation of theophylline. At the time of this writing there is ongoing exchange with the OCP team on this labeling issue.

Stiripentol – Clobazam Interaction

In vitro, stiripentol inhibited CYPs lA2, 2C9, 2C19, 2D6, and 3A4, with inhibition constant values at or slightly higher than therapeutic (total) concentrations of stiripentol.[23] STP exhibited a larger inhibitory effect on NCLB (4-5-fold increase) than CLB (2-fold). [24]

Although there is currently no approved treatment for Dravet Syndrome, clobazam and valproate sodium are recognized as standard therapy[25]. As stated in the discussion of

[22] Study RAP-15-052 "Evaluation of Stiripentol and DIACOMIT 250mg in Simulated Gastric Fluid pH 1.2" Report date 12/03/2015, submitted 3/14/2018, seq 0043, SD 44.
[23] 6. Tran A, Rey E, Pons G, et al. Influence of stiripentol on cytochrome P450-mediated metabolic pathways in humans: In vitro and in vivo comparison and calculation of in vivo inhibition constants. Clinical Pharmacology & Therapeutics 1997;62:490-504.
[24] eCTD, Section2: Summary of Clinical Pharmacology Studies, P38
[25] Wallace A, et al. Pharmacotherapy for Dravet Syndrome. Paediatric drugs. , 2016, Vol.18(3), p.197-208

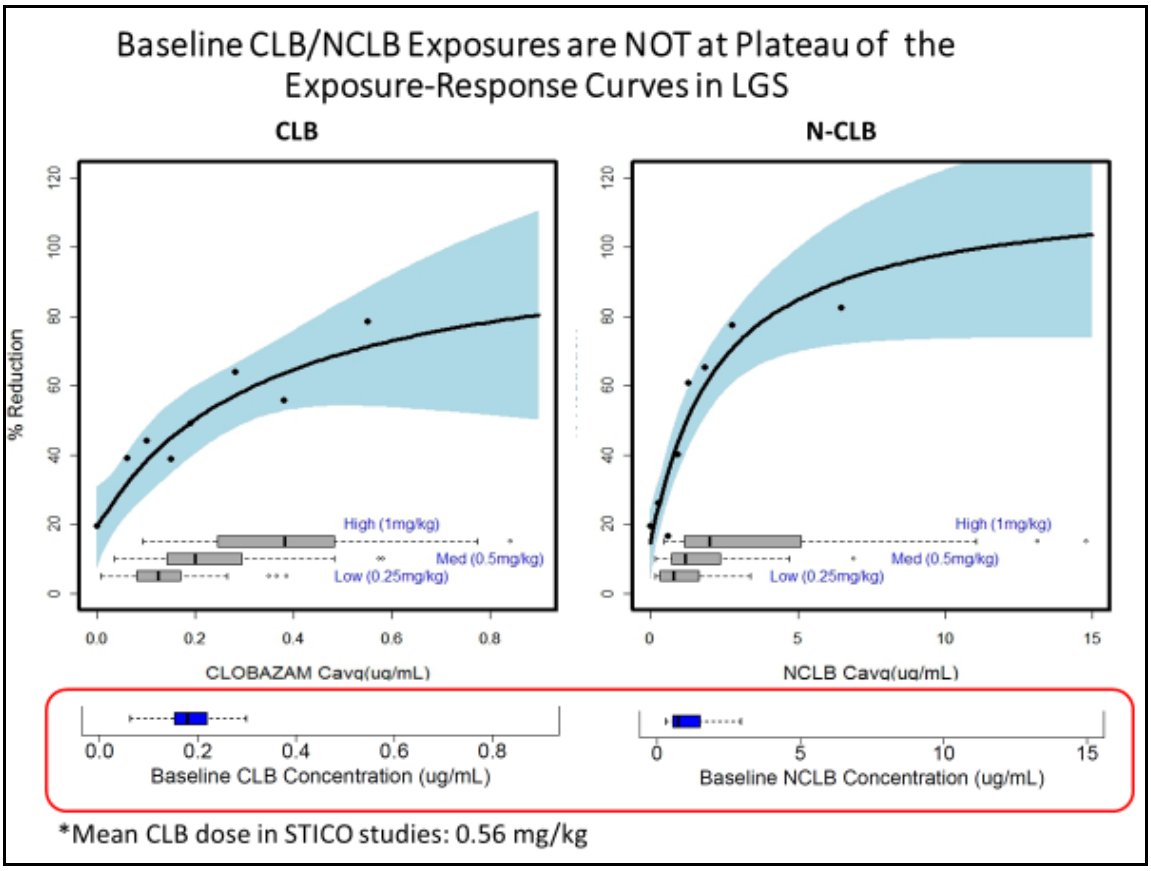
concomitant medications, clobazam and sodium valproate were obligatory concomitant therapy for all patients in the STICLO studies.

CLB is primarily metabolized by CYP3A4 to form an active metabolite, norclobazam (NCLB) while NCLB is extensively metabolized by CYP2C19. Stiripentol interacts with this metabolism as a potent inhibitor of CYP2C19 and a less potent inhibitor of CYP3A4. This drug-drug interaction results in an approximate 2 fold increase in CLB exposure and a 4 to 5 fold increase in NCLB exposure over baseline. This consistent drug – drug interaction results in a question whether STP has intrinsic antiepilepsy effect to account for the responder rate in the STP arm of the STICLO studies or is the seizure reduction due to elevation of CLB and NCLB concentration.

Due to the interaction of STP with CYP2C19 and CYP3A4 an overarching challenge in the analysis of STP efficacy has been the higher CLB and NCLB exposure that occurs in the STP treatment arm compared to the PBO arm.

The first method to attempt differentiation of CLB/NCLB effect from STP effect in the STICLO studies was to identify a CLB/NCLB exposure response relationship. If the baseline levels at entry to the STP treatment period are at the plateau of exposure-response, then additional reduction in seizure frequency may be attributed to STP. A study of clobazam for the treatment of Lennox-Gastaut syndrome (LGS) was identification as a source of an exposure response relationship between CLB/NCLB and reduction in seizure frequency. The relationship seen in the LGS study was compared to the baseline CLB and NCLB concentration seen at baseline in the STICLO studies. This analysis, Figure 4, reveals that STICLO study baseline CLB and NCLB concentrations are at the low end of the concentration response curve extracted from the LGS study.

Figure 4 Comparison of STICLO Baseline CLB and NCLB Concentration to Exposure Response Model of LGS Study[26]

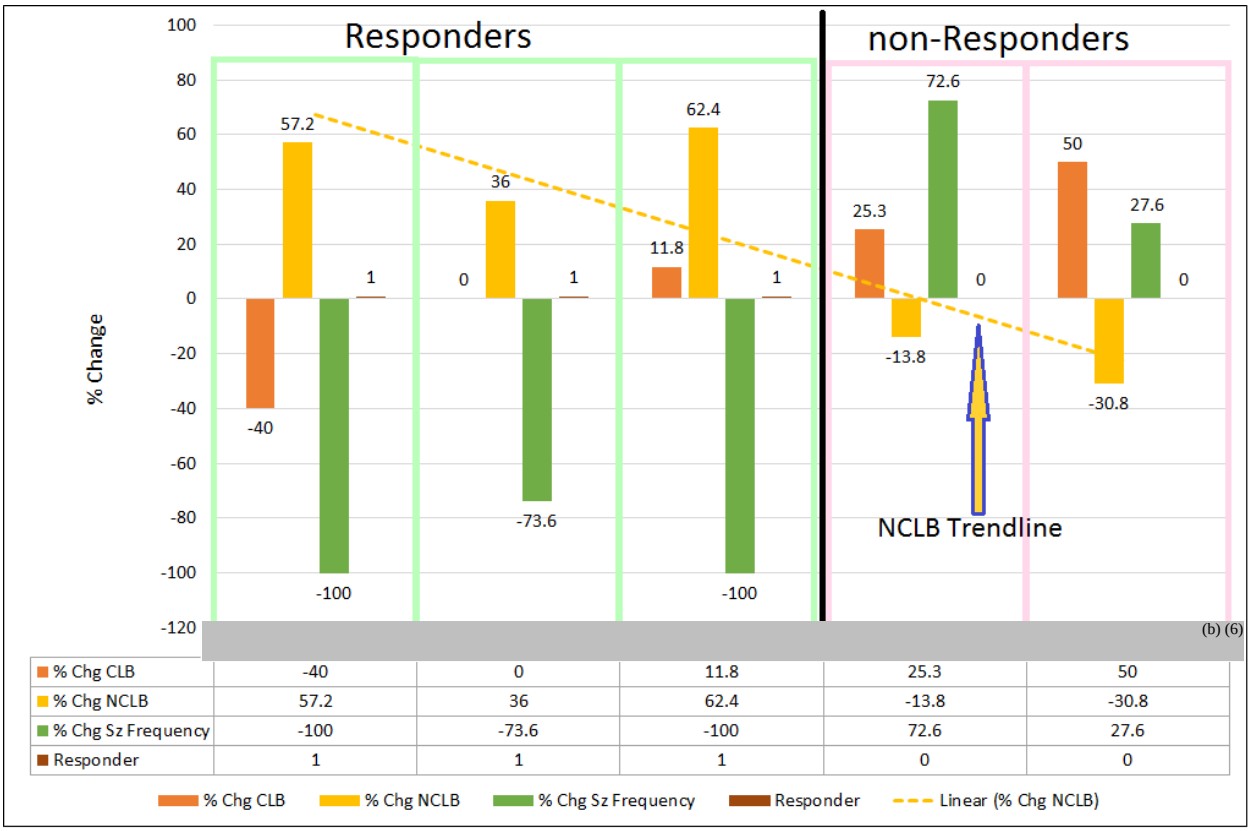


A second method performed to attempt CLB/NCLB – STP effect differentiation was examination of the CLB/NCLB change in concentration among all STP treatment patients in the STICLO studies. This examination was done to search for a subset of patients with minimum baseline to treatment change in CLB/NCLB concentration. If this subset retains a reduction in seizure frequency comparable to STP treatment patients with larger, more typical, increases in CLB/NCLB concentration it may be considered a point of support for an independent STP treatment effect. The STP treatment arm was examined for patients who had a percent change in CLB <50% and NCLB <100% change from baseline. Five (5) patients were identified in this search. From among this cohort there were 3 responders and 2 non-responders. Ideally to support an independent treatment effect the responders would have very small change from baseline for both CLB and NCLB. The observed pattern revealed responders tended to have very small change in CLB ranging from -40% to + 11% where the mean STP treatment arm change

[26] New Drug Rounds, 3/10/2017, OCP Review Team

from baseline was 57%. The range of NCLB exposures among responders revealed a low end increase ranging from 36% to 62% where the mean NCLB change over baseline observed in the STP treatment arm was 476%. There were 2 non-responders who had an increase in CLB of 25% and 50% respectively with a decline from baseline in NCLB of -31% and -14% respectively, Figure 5. The OCP team concluded there was no evident trend in clinical response that was traceable to the magnitude of CLB and NCLB exposure in this group of 3 responders and 2 non-responders.

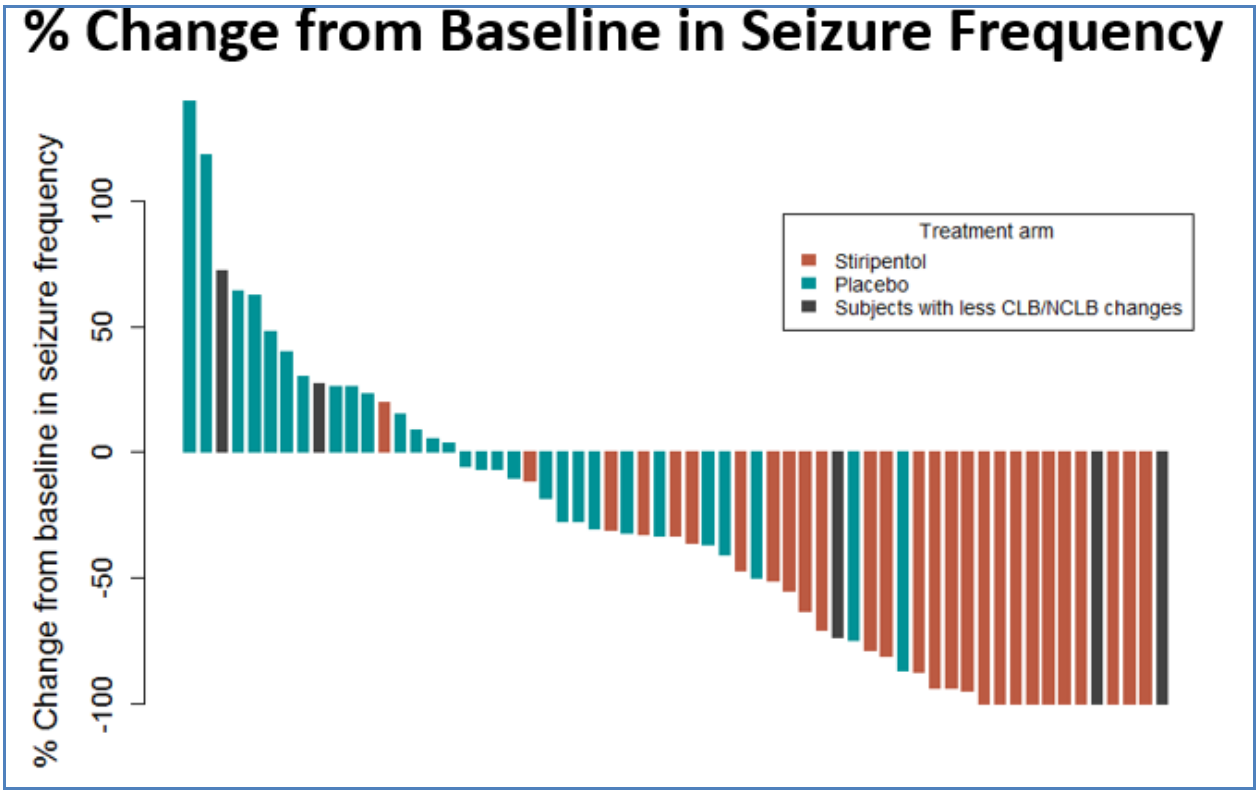
Figure 5 5 Patient STP Subset with Lowest CLB/NCLB Change from Baseline Exposure[27]



The cohort of 5 patients with minimal combined increase from baseline CLB and NCLB were examined in the context of all patients in their percent change from baseline seizure frequency. This analysis is shown in Figure 6.

[27] New Drug Rounds, 3/10/2017, OCP Review Team

Figure 6 All Patient % Change from Baseline Sz Frequency with Select 5 Patient Cohort shown as Black Bars in Histogram.[28]

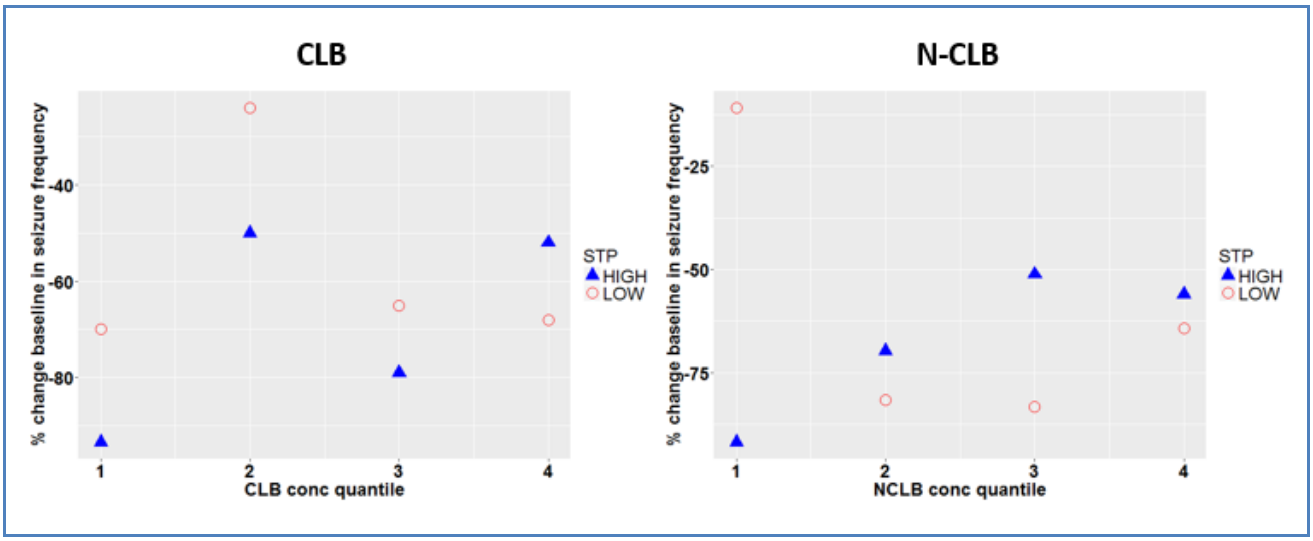


The next approach to test for an STP treatment effect independent of CLB/NCLB was to examine change from baseline seizure frequency among STP treatment patients divided into high and low STP exposure subgroups. These subgroups are placed into their respective quantile bins of CLB/NCLB exposure. The bins are then examined for efficacy response of the low and high STP patients within each bin. An expected response to support independent STP treatment effect would be observation of greater percent seizure reduction over baseline for high STP exposure compared to the low STP exposure patients. This effect was not observed. The CLB analysis revealed greater percent seizure reduction over baseline for high STP exposure over low exposure in quantiles 1 to 3 but in the highest CLB concentration quantile the effect reversed and the low STP exposure had the largest percent seizure reduction. The NCLB analysis revealed superior seizure reduction in the low STP exposure patients in the upper three NCLB exposure quantiles, see Figure 7. The n size of each quantile was small with narrow STP exposure ranges within each quantile that does not allow a large differentiation of STP

[28] New Drug Rounds, 3/10/2017, OCP Review Team

exposures. These characteristics reduce the reliability of this method.

Figure 7 STP Exposure Response Relationship by CLB and NCLB Exposure Quantiles.[29]



Considering these analyses, the OCP review team concludes "the currently available data appears insufficient to partition the efficacy contribution of STP and CLB/NCLB".[30]

Reviewer Comment: The exposure response curve of CLB and NCLB in LGS indicates the concentrations observed in the STICLO studies at baseline are below the plateau of maximum antiepilepsy effect. The pathologic mechanism of seizures is not necessarily the same in LGS and Dravet syndrome, therefore It is unknown if the CLB/NCLB concentration response profile in LGS is a predictor of concentration- response in Dravet syndrome. However, in view of the difference between the STICLO concentrations and the plateau of response, this is a conservative metric for assessment of concentration-response expectations in Dravet syndrome. This analysis supports a conclusion that a CLB/NCLB contribution to the treatment effect in the STP treatment arm cannot be excluded.

5 Sources of Clinical Data and Review Strategy

[29] New Drug Rounds, 3/10/2017, OCP Review Team
[30] Ibid.

5.1. Table of Clinical Studies

Features of Available Safety and Efficacy Data

There are 20 studies included in the sponsor tabular listing of all clinical studies in section 5.2 of the NDA application. Nineteen of these entries are clinical studies and 1 is a retrospective chart review. The 19 clinical studies submitted include DS and non-DS epilepsy patients. The sponsor initially submitted SAS transport, xpt datasets for only DS patients.

The composition of the data is not uniform across the 19 studies. None were performed under IND. Due to the diversity of study design, study objective, date of study, patient population, variation in definition of serious adverse events, variation in adverse event MedDRA coding and type of dataset, whether available as an SAS transport files (xpt) or only in table and narrative in pdf format, a category key has been created by the reviewer to facilitate understanding of the type of data available from each of the studies. This key is added as a column variable in the table of clinical studies, see Table 4 . The studies are assigned a category number (1 to 5) to allow the reader ease of reference to their data type in the ensuing sections and analyses.

There were two studies designed to evaluate STP treatment in DS patients in a prospectively randomized, placebo controlled parallel treatment studies. These were the STICLO France and STICLO Italy studies. These pivotal studies are designated category 1.

There were 2 open label clinical studies, STP-1 and TAU-EAP comprised of only DS patients and 1 additional PK study (STOPOP) that was comprised of DS patients only, these three studies constitute the category 2 designation. The category 2 designation indicates a non-pivotal study with DS patients only. These three studies contributed to the “non-Pivotal” studies group. Three remaining studies contribute to the “non-Pivotal” studies group. Two of these were open label, long term open label treatment studies of DS and non-DS epilepsy patients, these are the STILON and DIAVEY studies. One remaining single blind controlled trial of both DS and non-DS epilepsy patients contribute to the group of “non-Pivotal” studies. This is the STEV study. These studies constitute the designated category 3 studies for this review where their key characteristic is they are of a mixed population of DS and non-DS epilepsy patients. In the initial submission, only DS patients from the STEV, STILON and DIAVEY studies had datasets provided in xpt format. To expand the patient pool that could contribute to analysis with active xpt tables (as opposed to written tables in PDF documents) an information request was made to the sponsor to provide safety datasets in SAS transport, xpt format for the non-DS patients in the STILON and DIAVEY studies. These data subsequently contribute to the “non-Pivotal” safety population. All pivotal and non-pivotal studies with xpt datasets available are shown as shaded cells and are identified as category 1, 2, and 3 in Table 4.

The next groups of 7 studies in the application are identified as exploratory efficacy studies in non-DS epilepsy patients with safety data available as PDF tables and narratives in the ISS and individual study reports. This latter group of studies is assigned category 4. The defining feature of category 4 is that study patients are non-DS and study data is only available in PDF written text – table format. The remaining study group is comprised of 4 PK studies designated category 5. Category 5 studies are PK safety and tolerability studies of healthy volunteers with safety data presented in written PDF tables and narratives.

Table 4 Table of Clinical Studies

Study name	study number	Date*	category	type	objective	design	Test Product(s); Dosage Regimen; Route of Administration	population	n	duration	seizure type	Data presentation	comment
STIVAL	BC.481	2007	5	BA-PK	BA	OL-Crossover	STP 500 mg capsules and STP 500 mg powder for oral suspension (b) (4) 1,000 mg, Oral route	Healthy	24	single dose	none	PDF- Written	
Greig	BC.287	1993	5	BA-PK	PK	OL-Crossover	STP 300 mg capsules 1,200 mg R-STP, 1,200 mg S-STP, 1,200 and 2,400 mg racemic STP Oral route	Healthy	6	single dose	none	PDF- Written	
STIUNI	BC.337	2002	5	BA-PK	PK	OL-Crossover	STP 500 mg capsules 500, 1000, 2,000 mg Oral route	Healthy	12	single dose	none	PDF- Written	
Pons	BC.345	1995	5	BA-PK	CYP	OL	STP 500 mg capsules Day 1: 1,000 mg (500 mg twice a day) Day 2: 2,000 mg (1,000 mg twice a day) Day 3-13: 3,000mg (1,500 mg twice a day) Day 14: 1,500 mg in the morning, Oral route	Healthy	13	single dose	none	PDF- Written	
STIPOP	STP167	2008	2	BA-PK	PK	OL	STP 250 and 500 mg capsules and STP 250 and 500 mg powder for oral suspension (b) (4) 50 mg/kg/day, Oral route	DS	35	from other studies	DS	xpt	
STICLO France	BC.299	1998	1	STP efficacy, add on to VPA, CLB	DS efficacy	DB	STP 250 and 500 mg capsules 50 mg/kg/day, Oral route	DS	42	8 weeks	DS	xpt	
STICLO Italy	BC.385	2000	1	STP efficacy, add on to VPA, CLB	DS efficacy	DB	STP 250 and 500 mg capsules 50 mg/kg/day, Oral route	DS	23	8 weeks	DS	xpt	
STP-1	BC.609	2012	2	STP open label add on (Japan)	DS efficacy	OL	STP 250 capsules or STP 250 mg powder for oral suspension (b) (4) Up to 50 mg/kg/day, Oral route	DS	33	16 weeks, OL extension	DS	xpt	
TAU-EAP (ATU de COHORTE)	BC.458	2007	2	OL add on STP, long term safety, EMA temp authorization	DS safety	OL	STP 250 and/or 500 mg capsules and STP 250 and 500 mg powder for oral suspension (b) (4) 50-	DS	210	up to several years	DS	xpt	screened 272

Study name	study number	Date*	category	type	objective	design	Test Product(s); Dosage Regimen; Route of Administration	population	n	duration	seizure type	Data presentation	comment
							100 mg/kg/day, Oral route						
STEV	BC.288	1997	3	single blind STP add on after baseline	DS efficacy	SB	STP 250 and 500 mg capsules and 100, 250, and 500 mg powder for oral suspension (b) (4) 60 mg/kg/day for 28 days, then increased (as needed) up to 90 mg/kg/day for 56 days, Oral route	DS	25	12 weeks	DS	xpt	
STEV	BC.288	1997	3	single blind STP add on after baseline	non-DS efficacy	SB	same as DS	Refractory epilepsy, non-DS	202	12 weeks	POS, generalized	PDF- Written	
STILON	BC.387	2003	3	OL extension	OL Safety extension of STICAR, LENNOX, WOW, STEV, STISERV, STICLO	OL	STP 250 and/or 500 mg capsules or powder for oral suspension (b) (4) Maximum dose: 4,000 mg/day, Oral route	DS	45	up to several years	DS	xpt	
STILON	BC.387	2003	3	OL extension	OL Safety extension of STICAR, LENNOX, WOW, STEV, STISERV, STICLO	OL	same as DS	non-DS	110	up to several years	DS	xpt	xpt after IR
DIAVEY	BC.627	2012	3	OL post marketing	DS safety, STP add on to AEDs	OL	STP 250 and 500 mg capsules and STP 250 and 500 mg powder for oral suspension (b) (4) 50 mg/kg/day, Oral route	DS	153	up to several years	DS	xpt	
DIAVEY	BC.627	2012	3	OL post marketing	non-DS safety, STP add on to AEDs	OL	same as DS	non-DS	77	up to several years	POS, generalized epilepsy, LGS, multifocal, others	xpt	xpt after IR
Lennox-Gastaut	BC.274	1994	4	SB, ref period - PBO- add on to standard therapy	efficacy & safety of STP as add on	SB	STP 500 mg capsules and (b) (4) <29 kg: 2,000 mg/day, 29-<39 kg: 2,500 mg/day, >40 kg: 3,000 mg/day, Oral route	LGS	24	8 weeks	LGS	PDF- Written	

Study name	study number	Date*	category	type	objective	design	Test Product(s); Dosage Regimen; Route of Administration	population	n	duration	seizure type	Data presentation	comment
STICAR	BC.246	1990	4	add on to CBZ	efficacy	DB	STP 500 mg capsules 2,000 mg/day, Oral route	non-DS	62	8 weeks	epilepsy that is susceptible to carbamazepine, POS, 2nd generalized, absence, tonic, atonic, myoclonic	PDF- Written	
STISEVR	BC.484	2000	4	add on to CBZ	efficacy	SB-OL	STP 250 and 500 mg capsules and 100, 250, and 500 mg powder for oral suspension (b) (4) 50 mg/kg/day then increased (as needed) up to 90 mg/kg/day, Oral route	non-DS	32	12 weeks	POS type 1-3	PDF- Written	
WOW	BC.276	1994	4	add on to CBZ	efficacy	OL	STP 500 mg capsules 3,000 mg/day, Oral route	non-DS	64	70 days	POS, generalized	PDF- Written	
martinez-Lage	BC.244	1986	4	titrate off of existing therapy after 8 week basal period to STP monotherapy	efficacy	OL	STP at least 1,800 mg/day as monotherapy, adjusted when biotherapy, Oral route	non-DS	31	8 weeks transition to STP monotherapy, 8 weeks STP alone	POS , CP or 2nd generalized	PDF- Written	
Courjon	BC.109	1976	4	refractory patients receiving "some form of treatment",	efficacy	OL	STP 50 and 100 mg capsules 200-300 mg/day (increased or decreased accordingly), Oral route	non-DS	135	1 month to more than 6 months	POS, primary generalized	PDF- Written	
Loiseau	BC.243	1984	4	withdrawal of background AED over 5 to 8 weeks, then 12 weeks STP monotherapy	efficacy	OL	Up to 1800mg/day, oral	non-DS	44	12 weeks	POS	PDF- Written	

*Date of last patient or study report date in cases where last patient recruitment date is not provided

5.2. Review Strategy

Efficacy Review Strategy

Examine STICLO study efficacy based on seizure frequency data provided in the qs.xpt as medical history data by row name without 30 day adjustment and subsequently submitted adsf.xpt dataset where seizure frequency is provided as a column variable with 30 day adjustment. The relationship of seizure frequency to CLB, NCLB and VPA concentrations at 7 weeks and change from baseline to 7 weeks is also examined. Subset analysis by age, sex and SCN1A status is also examined.

To perform these analyses a master efficacy jmp dataset is constructed with column variables for study day, SCN1A status, and unadjusted seizure frequency (tonic-clonic and clonic) from the qs.xpt dataset, study arm from the adsl.xpt dataset, adjusted 30 day seizure frequency from the adsf.xpt dataset, clobazam, norclobazam and valproic acid concentrations from the pp.xpt dataset as well as completer/ discontinuation status from the ds.xpt dataset.

From the master efficacy dataset, the seizure frequency data from the qs.xpt and adsf.xpt datasets is cross checked for consistency. The change in seizure frequency from baseline to month 2 (M3 frequency entry) and resultant responder rate for all (ITT) and completers only is calculated and compared to sponsor entries as well as cross checked with the biometrics review. Subset analysis by age, sex and SCN1A is performed.

Safety Review Strategy

Due to the diversity of studies presented in this approval package a primary tool for safety review will be use of a safety data table template. As noted in the full discussion of safety review in section 7.2 there are 19 studies in the sponsor table of clinical studies as well as a single retrospective study, none conducted under IND. The retrospective study (Laux) will only occupy a paragraph in section 7 to include Deaths, discontinuations and serious adverse events. The remaining 19 studies were conducted in a timeframe from 1976 to 2012.

STICLO study adverse event and laboratory data analysis are performed using the adae.xpt and lb.xpt dataset.

Non-pivotal, category 2 and 3 , DS non-DS adverse event and laboratory data analysis is performed using the adae.xpt and lb.xpt datasets provided. Datasets are also pooled. Results are compared and supplemented by the individual study reports and ISS.

Category 4 and 5 safety is examined using the ISS and individual study reports.

5.3. STICLO France and Italy

5.3.1. Study Design

Overview and Objective

STICLO France and Italy had the same design. The objective in both was to demonstrate the efficacy of stiripentol combined with clobazam and sodium valproate in patients with Dravet syndrome (severe myoclonic epilepsy of infancy) where severe resistant tonic-clonic and myoclonic seizures are measured.

Trial Design

STICLO France and Italy were both parallel groups, placebo controlled, fixed dose (50mg/kg), randomized, double blind. Each was performed at multiple centers in France or Italy respectively.

Inclusion criteria: Age between 3 and 18 years, maximum weight 60kg, male or female (risk of pregnancy ruled out). Severe myoclonic epilepsy in infancy (SMEI) according to syndrome diagnostic criteria established by C. Dravet (1983). At least 4 generalized tonic-clonic or clonic seizures per month despite optimized therapy with valproic acid (VPA) and clobazam (CLB). Study enrollees were on obligatory clobazam at a dose of 0.5mg/kg/day with a maximum of 20mg/day. Progabide (Gabrene) and intrarectal valium were permitted. Normal CBC, Platelets, creatinine, ALT and AST were required at inclusion.

VPA at Study Entry

The valproate sodium dose was initially set at 20mg/kg/day upon study entry; however, this criterion was amended on May 2, 1997 after enrolment of 20 patients in STICLO France due to the large decrease in VPA dose that was required in patients who were receiving 30 to 40 mg/kg/day at study screening. In those patients at the higher dose range an increase in seizures was noted upon VPA reduction of 15mg/kg/day or more.

Study Blinding:
The active drug and the placebo were supplied with a strictly identical appearance as snap-fit capsules, and they were indistinguishable from each other. A jury to test resemblance was summoned. The jury judged the similarity of the products to be compared and the results were recorded in a certificate of resemblance. Certificates of resemblance are retained. Each investigator had a set of sealed, numbered envelopes at his/her disposal in case of emergency situations requiring breaking the blind.

Exclusion Criteria: other anticonvulsant medications except those permitted, asthma treated

with theophylline, parents unable to keep accurate seizure diary, inclusion in other therapeutic study.

Study Treatment: stiripentol (STP) 50mg/kg/day supplied as 250mg or 500mg capsules with maximum does of 3000 mg/day. STP is administered in divided doses two or three daily at meals. The dose is maintained as close as possible to 50mg/kg/day within the framework of delivering the calculated dose using 500mg and 250mg capsules.

Rescue Medication: option to provide intrarectal diazepam during the study should a long and severe seizure occur.

During the treatment period adjustment in VPA and CLB dose was allowed. In the event of severe decrease in appetite or weight loss the dose of sodium valproate could be decreased by 10mg/kg/day. In the event of severe drowsiness or hyperexcitability the dose of clobazam could be decreased by 25% then an additional 25% if the adverse event persists.

Study Chronology: (see Figure 8 and Table 5)
Visit 1: Pre inclusion/ screening- beginning of baseline
Laboratory studies, medication history- 3 weeks after visit 1
Visit 2: Randomization, one month after visit 2
Confirm inclusion and exclusion criteria
Telephone Visit 3:
One month after randomization- one month double blind period (called comparison period by protocol)
Visit 4: End of double blind study period (comparison period)
2 months after start of double blind period (2 months following start of comparison period)
Evaluation of efficacy and safety criteria
End of study drug treatment
All children begin open label STP for 30 days with treatment by investigator discretion thereafter.

Figure 8 STICLO Study Schematic / Timeline

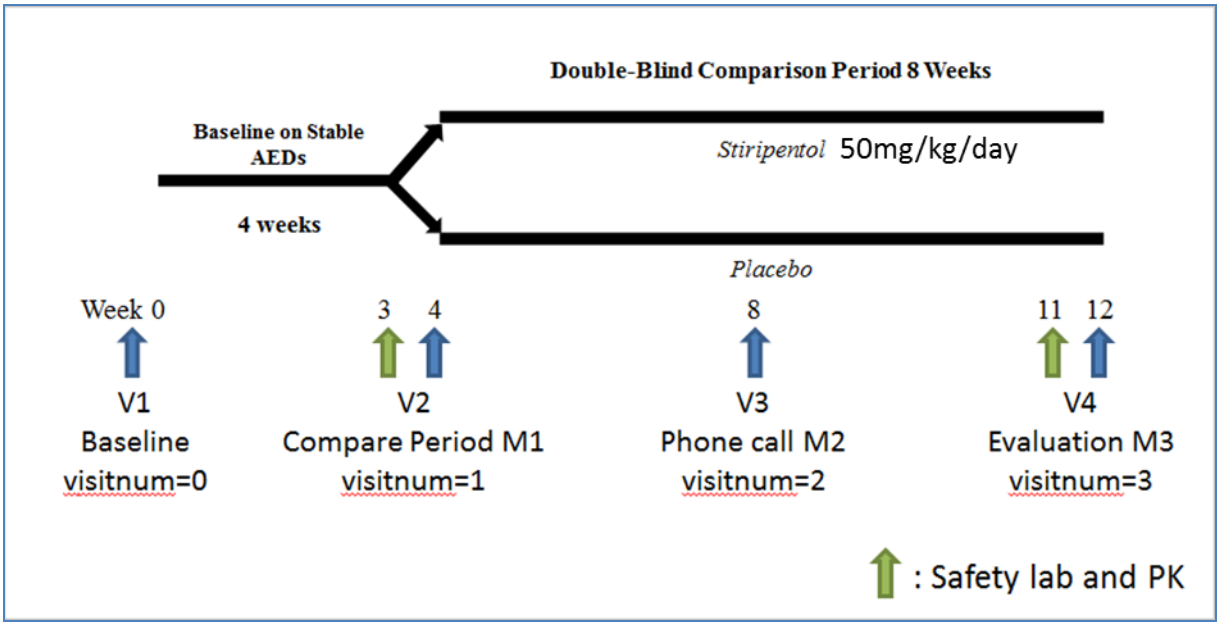


Table 5 STICLO Study Timeline Variables

VISIT variable in the QS dataset	Visit Code	Week	Visit name	Description
BASELINE	0	0	V1	Start of baseline period / pre-inclusion visit / C1
COMPARE PERIOD M1	1	3	V2	Baseline assessment for safety laboratory tests and
COMPARE PERIOD M1	1	4	V2	Start of comparison (double-blind) period / Baseline visit / C2
PHONE CALL M2	2	8	V3	Telephone consultation / the 1st month of comparison period / C3
EVALUATION M3	3	11	V4	End of study assessment for safety laboratory tests
EVALUATION M3	3	12	V4	End of the comparison (double-blind) period / the 2nd month of comparison period / C4

Study Endpoints

STICLO Primary Endpoint

A "responder" is defined as the primary endpoint. A responder is characterized by the absence of the following 4 non-responder criteria:

a. Patients having been treated and monitored for the 2-month comparison period, in whom the number of *generalized tonic-clonic or clonic seizures* during the 2nd month, adjusted to 30 days, has not decreased by at least 50% in relation to the number of seizures during baseline. *(this clause identifies the properties of a non-responder, thus patients who fulfill this criteria are non-responders*)
b. Patients having dropped out of the study because of the onset of status epilepticus. (status epilepticus nullifies the potential to be a responder)
c. Patients in whom the number of seizures has increased by more than 50% in relation to baseline, within a period of 0 to 20 days after entry into the comparison period. (*early seizure increase nullifies the potential to be a responder even if the 2 month, 30 day normalized seizure frequency would qualify this patient as a responder*)
d. Patients showing during baseline a more than 50% increase in the number of seizures in relation to the previous period and in whom the number of seizures has not returned to the number prior to baseline during the first month of comparison in the study. (an *unstable baseline seizure frequency with an increase during baseline that does not show improvement to pre-baseline frequency in 1st month of double blind treatment is a disqualifier for being a responder*)

Statistical Analysis Plan

Section 5.3.5.1, "Statistical Methods Interim Analysis Plan" for STICLO France is limited to the following entry:

> ***DOCUMENTATION ON STATISTICAL METHODS (sponsor)***
>
> *Data were recorded on four EXCEL tables (general information on patient included, plasma levels of stiripentol and anticonvulsants, clinical information and adverse effects). The first two tables were based upon single entry, with full proofreading of data needing to be checked. Double -entry was used for the other two tables.*
>
> *Tables were then exported in the form of text for statistical analysis.*
>
> *Statistical methods: comparison of frequencies of responders and of frequencies of cases with an adverse effect by the Chi-2 (X^2) test. Comparison of plasma levels of anticonvulsants by Mann and Whitney test."*
>
> *The sponsor does report a preliminary analysis was performed after enrolment of 42 patients. This analysis, performed as planned after enrollment of 42 patients without breaking the blind, showed that it was not necessary to enroll additional patients. Thus, the preliminary analysis can be considered as the final analysis.*

Section 5.3.5.1 for STICLO Italy has no entry for "Statistical Methods Interim Analysis Plan".

This study was planned as a supplement to STICLO France, to include 20 patients. No preliminary analysis is reported.

The primary endpoint analysis for both studies was based on the ITT population. In the ITT population patients with missing post baseline seizure data were considered treatment failures (could not be responders). In the per protocol (PP) analysis population the subjects missing post baseline number of seizures were excluded from analysis.

Comparison of stiripentol and placebo groups during treatment had to be performed based on the number of generalized clonic or tonic-clonic seizures during month 2 of the comparison period.

Responder proportion is analyzed using X^2 test.

STICLO Studies Interim Analysis

The STICLO study protocol included an interim analysis to examine the between group difference after enrollment of 20 patients in each arm. The interim analysis had the following design: This analysis was planned to examine for a significant difference at a significance level of alpha = 2.5% without deblinding. This level was considered a significant for the planned primary outcome measure. In the event the difference reached significance the study would be terminated. If found not to be the case the "placebo group" difference will be used to "precisely" determine the total number of patients to be included in the study per treatment group and the study would be continued until inclusion of this number of patients with a maximum of 100 patients or maximum inclusion time of 18 months.

The Biometrics reviewer examined STICLO France and Italy under the assumption that an interim analysis was performed in each study. The analysis used the O'Brien-Fleming spending function to test the significance outcome of each study performed using Fisher's Exact test. The nominal significance level using the O'Brien-Fleming spending function was calculated assuming accumulation of 40% (of total study) information for STICLO France and 20% (of total study) information for STICLO Italy.31 The analysis revealed the nominal significance level of the O'Brien-Fleming function for STICLO France was adequate to confirm the study outcome significance while the nominal significance level for STICLO Italy was insufficient to confirm significance (due to dilution by the interim look).

[31] Biometrics review, Junshan Qiu, Ph.D, page 7

Examine of STICLO Italy for alpha spending at 20% information is the most conservative approach. The actual interim analysis plan calls for an interim analysis at accumulation of 40% information. STICLO Italy had an enrollment of 23 patients when the study was ended. This is below the planned threshold for interim analysis. The STICLO Italy study report indicates that "This study being a supplement to the STICLO study in France, it was planned to include 20 patients" while there is no indication that an interim analysis was performed. The STICLO studies France and Italy were sequential studies with a separation of approximately 9 months between the end of STICLO France on August 17, 1998 and start of STICLO Italy on April 20, 1999.

Reviewer Comment: Both STICLO France and STICLO Italy have large separation between the STP and PBO treatment arms with high levels of significance upon testing with Fisher's exact test. The examination of STICLO Italy for alpha spending of an interim analysis is a conservative measure for interpretation of study significance. Because the threshold for interim analysis in the STICLO Italy had was not reached, there is no indication in the submission of an interim analysis was performed and the treatment to placebo separation in both STICLO France and STICLO Italy are in alignment both studies may reasonably serve as pivotal trials to support the efficacy of STP for the treatment of Dravet Syndrome.

Protocol Amendments

A single protocol amendment occurred. The protocol was amended in May 1997, seven months after the start of the study even though 20 patients had been enrolled. Two changes were proposed:

- The upper dosage limits that were imposed for valproate sodium i.e., 20 mg/kg/24hrs, before the study and 15 mg/kg/24hrs on entry in the baseline period (to minimize the risk of adverse events) were removed. Indeed, on one hand some patients who were receiving higher doses could not be enrolled, and on the other hand some patients experienced an increased number of seizures during the baseline period when valproate dosage was decreased. The aim of this amendment was to better protect the enrolled children by reducing the risk of an increased incidence of seizures as a result of the decreased dosage of valproate sodium and to facilitate patient recruitment.

- The primary endpoint criterion was replaced by a qualitative criterion, i.e. "success" or "failure". Definition of treatment failure was specified for children who would not have been followed throughout the entire comparison period (2 months) and also for those who would have been withdrawn from the study before the end of this comparison period.

- These changes allowed the possibility to retain in the analysis patients who would have been withdrawn from the study before the end of the comparison period, and especially the possibility for children experiencing frequent seizures to withdraw more easily from the study.

- The initially planned primary endpoint criterion became a secondary endpoint criterion.

- A new secondary endpoint criterion was added, i.e. the time elapsed until the same number of seizures as that of the 1-month baseline period, were experienced. This criterion should be analyzed using a survival analysis technique.

Data Quality and Integrity: Sponsor's Assurance

STICLO France and Italy are both non-US studies and were not conducted under and IND with no review of protocols prior to NDA submission.

STICLO France

This study was conducted at 14 centers in France. The sponsor provided the following discussion in the study report although the protocol does not contain any statement on quality assurance.

During the study, regular visits and phone contacts were performed by the monitor, in order to assist in the filling out of cases/dossiers, to verify source data and data consistency and to verify the patient's consent, etc.

A closing visit was organized in all centers at the end of the study. This visit consisted of a meeting with the center investigator(s) and the hospital pharmacist.

The investigators were informed that an audit of cases/dossiers relating to the study might be carried out, independently of monitoring visits, by the Quality Assurance Department of Laboratories BIOCODEX or by external auditors. In the end, this audit was not conducted.

The statistical reviewer identified a discrepancy in seizure frequency between the datasets and the sponsor's tabular efficacy data in Appendix 16.2.6 (5.3.5.1 STICLO France "Individual Efficacy Response Data") as follows:

"*For study STICLO France, the values of frequency of Tonic-Clonic and Clonic seizures out of 30 days for Subjects 56 and 11 for analysis visit "FOLLOW-UP M2" and for Subject 10 for analysis*

visit "Follow-UP" in the data set adsf.xpt: 10.83, 192, and 16.45 are not consistent with the corresponding ones reported in the Appendix 16.2.6: 0.00, 166.67 and 16.15."

STICLO France, Dataset Divergence

Due to these divergent findings the clinical reviewer performed an examination across the 4 sources of efficacy data provided by the sponsor. The datasets in SAS transport form were updated after initial submission due to missing seizure count dates and a format change was also performed in the individual STICLO studies and presented as a new adsf.xpt dataset to present seizure counts as a column variable, see Table 6.

In the STICLO France dataset there were 4 patients in the placebo arm with study visit M3 seizure count entries, both in the qs.xpt as unadjusted counts and adsf.xpt dataset as 30 day adjusted counts that were not present in the "individual efficacy response data" pdf table from the eCTD section 5.3.5.1 of the original submission. In this latter document there was a blank at the location for a numerical entry. All 4 of these patients discontinued from the study before the M3, final study visit where the month 2 seizure count for efficacy endpoint is captured. All of these patients were entered as non-responders for ITT analysis. In one of these four patients (STICLO - FRANCE (b) (6) who discontinued in addition to an M3 entry, there was an M2 study visit entry in all datasets, qs.xpt, adsf.xpt and "individual efficacy response data", however, the entry for M3 in the adsf.xpt dataset (166.67) was entered at M2 in the "individual efficacy response data". Both M2 and M3 were subsequent to patient discontinuation 8 days after the start of treatment interval.

A fifth patient (STICLO - FRANCE (b) (6)) in the STP treatment arm of the STICLO France study had an entry in the adsf.xpt dataset that did not agree with the "individual efficacy response data" at the M2 visit. This patient had an entry of "0" seizures in the "individual efficacy response data" and an entry of 10.83 seizures (30 day adjusted) at the M2 visit. The entry at M3, for ITT analysis, was in agreement in both datasets.

Reviewer Comment: These divergent entries did not affect primary endpoint calculations. In 4 of 5 patients the divergent entries occurred after the entry for study discontinuation that resulted in non-responder status for the ITT analysis. In the fifth patient, the discordant entry did not impact responder calculation and did not favor the STP treatment arm in the case of a higher seizure count in the M2 visit for adsf.xpt dataset.

Table 6 STICLO France, Presentations of Seizure Count (efficacy data) in the NDA Submission

Dataset name	Date	Dataset content and structure
qs.xpt	11/10/15 (initial submission)	Efficacy data as medical history in questionnaire domain dataset. Raw seizure counts for study intervals presented along with study day numbers

		and dates. No study date entries for M3 seizure count (end of treatment month 2 follow up)
qs.xpt	1/7/16	Updated content for section 5.3.5.3 "data from more than one study", with dates and study day for M3 seizure count
adsf.xpt	1/7/16	Revised efficacy data (seizure count format) with counts presented as column variable, 30 day adjusted with M1, M2 and M3 as rows for each patient.
Individual efficacy response data, pdf format	11/10/15 (initial submission)	Submitted with STICLO France study report in initial NDA submission

STICLO Italy

This study was conducted at 6 centers in Italy. The sponsor provided the following discussions from the study protocol and study report.

Section X (ten) of the protocol was entitled "Study Monitoring". This section indicated that monitoring would be undertaken by the Clinical Pharmacology Department of Saint- Vincent de Paul Hospital, Paris, under the supervision of Prof. G. Pons with the Clinical Research Associate (CRA) responsible for monitoring will assist the investigator in practical management of the study and will ensure that the investigator works in accordance with the protocol and within legal requirements covering clinical studies. The CRA will check all case report forms, which will require access to basic data on patients as well as study raw data. The investigator must provide all original documents on which case report form data are based.

There will be regular on-site monitoring visits. The time and space necessary must be organized in such a way as to optimize the efficacy of these visits. If a patient is excluded, the coordinator must be quickly informed and the corresponding case report form completed and recovered by the CRA. At each visit, the investigator will certify the accuracy of data by signing each case report form.

In the study report it is also noted in section 9.6 "Data Quality Assurance" that "A Contract Research Organisation (CRO), (b) (4) was in charge of the study from the opening of the centres to their closing."

Before starting the study, an information meeting was organized with the investigators. All centers had an opening visit. This visit included a meeting with the center investigator(s) and with the hospital pharmacist. The protocol, case report form and various procedures were explained; the directions for use the treatment were defined.

During the study, regular visits and telephone contacts were performed by the CRO, in order to

help in completing the files, to check the raw data, to make sure of the data coherence, to check the patients' consents, etc.

At the end of the study, all centers had a closing visit. This visit included a meeting with the center investigator(s) and with the hospital pharmacist. Investigators were informed of the possible audit of the files related to the study, apart from the follow-up visits, by the Quality Assurance department of Laboratories BIOCODEX or by external auditors. Finally, this audit was not performed.

STICLO Italy Dataset Divergence

The statistical reviewer also identified a discrepancy in seizure frequency between the datasets and the sponsor's tabular efficacy data in the study report Appendix 16.2.6, STICLO Italy "Individual Efficacy Response Data" as follows:

"*For study STICLO Italy, the values of frequency of Tonic-Clonic and Clonic seizures out of 30 days for Subjects 227 for analysis visit "FOLLOW-UP M2" and for Subject 217 for analysis visit "Follow-UP" in the data set adsf.xpt: 8.5 and 39.7 are not consistent with the corresponding ones reported in the list of individual efficacy data: 11.8 and 38.7*"

Due to these divergent findings the clinical reviewer performed an examination across the 4 sources of efficacy data provided by the sponsor. The datasets in SAS transport form were updated after initial submission due to missing seizure count dates and a format change was also performed in the individual STICLO studies and presented as a new adsf.xpt dataset to present seizure counts as a column variable, see Table 7.

Examination of the seizure count datasets reveals disagreement for two patient entries. In the first (STICLO - ITALY (b) (6)) there is an adsf.xpt dataset entry for visit M3 of 39.68 where the "individual efficacy response data" from the study report has an entry of 38.7. In the second case (STICLO - ITALY (b) (6)) the adsf.xpt dataset has an entry of 8.48 for the M2 visit where "individual efficacy response data" from the study report has an entry of 11.8.

Reviewer comment: The difference seen for either STICLO Italy patient does not alter the study report responder rate calculation.

Table 7 STICLO France, Presentations of Seizure Count (efficacy data) in the NDA Submission

Dataset name	Date	Dataset content and structure
qs.xpt	11/10/15 (initial submission)	Efficacy data as medical history in questionnaire domain dataset. Raw seizure counts for study intervals presented along with study day numbers and dates. No study date entries for M3 seizure

		count (end of treatment month 2 follow up)
qs.xpt	1/7/16	Updated content for section 5.3.5.3 "data from more than one study", with dates and study day for M3 seizure count
adsf.xpt	1/7/16	Revised efficacy data (seizure count format) with counts presented as column variable, 30 day adjusted with M1, M2 and M3 as rows for each patient.
Individual efficacy response data, pdf format	11/10/15 (initial submission)	Submitted with STICLO France study report in initial NDA submission

Reviewer Comment: Although there were seizure data discrepancies the statistical reviewer concluded "that the data that were submitted seem to be adequate in terms of the supporting documentation"[32]

Reviewer Conclusion, STICLO France and Italy Dataset Divergence:

The clinical reviewer tests the condition where those seizure count entries in STICLO France studies entered after patient discontinuation were analyzed as if the patients were treated as study completers. This would result in a change in responder count in the PBO arm. There would be a non-responder outcome (no-change) in 3 of the 4 PBO arm patients and a change to responder status in 1 of the 4 PBO patients. The divergence in the single STP arm patient would not alter the total STP responder rate outcome. If all the above patients were taken as study completers there would have been 1 additional responder in the STICLO France PBO arm. This would change the count from 1 responder and 19 non-responders in the PBO arm to 2 responders and 18 non-responders. Fishers Exact test is recalculated with these values. The result of the recalculation does not change the significance of the STP : PBO comparison from the result originally presented by the sponsor.

The data divergences seen in the STICLO Italy do not change the responder outcome status of the patients involved.

Overall, the cause of these data disagreements in this small study dataset is unclear. Examination of all remaining values across datasets does not reveal additional data entry disagreements or patterns of data entry that undermine confidence in the data quality.

5.3.2. **Study Results**

[32] Biometrics review, Junshan Qiu, Ph.D, page 8

Compliance with Good Clinical Practices

The sponsor attests that both STICLO France and STICLO Italy were conducted per GCP guidelines.

Financial Disclosure

The sponsor has submitted a signed form 3454 indicating no disclosable financial interest for all 20 investigators who enrolled patients in STICLO France and Italy, the covered efficacy studies.

Patient Disposition

In the STICLO France study there were 46 patients screened and 41 patients enrolled and while in the STICLO Italy study there were 23 patients screen with all patients identified as evaluable and contributing to the ITT population.

Protocol Violations/Deviations

STICLO FRANCE

There were 33 patients with protocol deviations in this study. The majority were laboratory abnormalities out of range low for study inclusion and treatment packs not returned to clinic (treatment packs not brought back).

The deviations of concern due to potential impact on the efficacy outcome were incorrect study drug dose. Two patients in the placebo arm received a dose less than intended. Two patients in the STP treatment arm also received less than intended dose. There is also one patient in the PBO treatment arm with truncated double-blind study period at 42 days. This patient day 42 seizure frequency is treated for analysis as LOCF.

STICLO ITALY

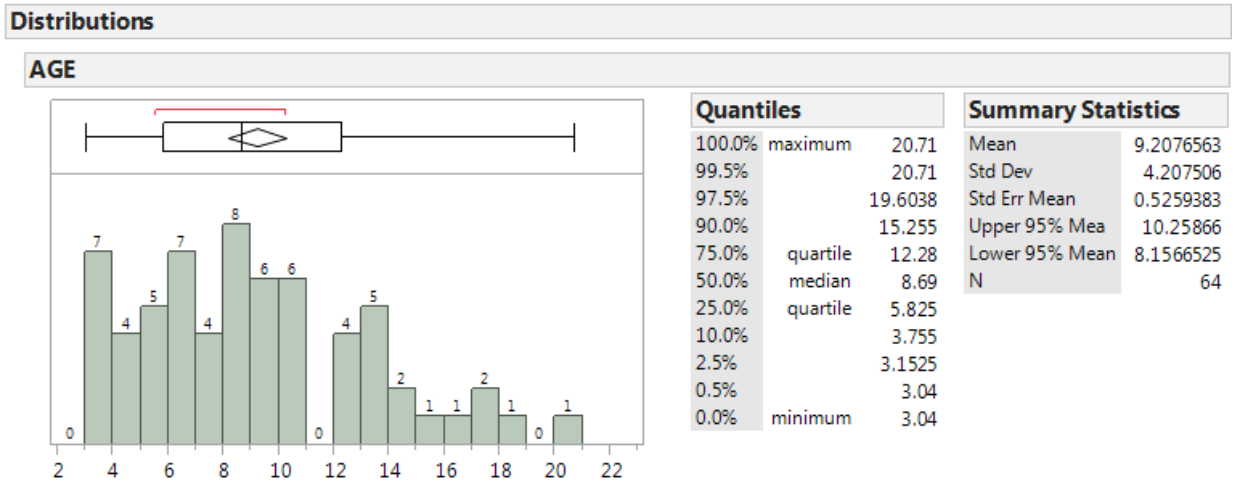
There were 3 patients with protocol deviations in the study. Two of these were mistiming of antiepilepsy drug levels that occurred 8 days before the patients dropped out of the study. A third patient in the STP treatment arm had a 2-month baseline period before inclusion into the study to allow for adaptation to ongoing treatment.
IR- “clarify adaptation of the doses”

Reviewer comment: the deviations related to medication dose bias the outcome away from success rather than toward false positive benefit.

Table of Demographic Characteristics

Demographics data for the STICLO France and Italy pivotal studies is limited to age and sex. The group mean and median ages were 9.2 and 8.7 respectively with a range of 3.04 two 20.7 years.

Figure 9 STICLO Pooled France and Italy age distribution



There were 34 (53%) females and 30 (47%) males in the pooled STICLO study demographic data. The mean and median ages for females were 9.9 years and 8.7 years respectively while for males these measures were 8.5 years and 8.7 years respectively.

The sex distribution of the individual STICLO France and Italy studies is shown in Table 8. There is a small increase in female over male study participants in STICLO France while in STICLO Italy there is a small increase in male over female study participants.

Table 8 STICLO Study Sex Distribution by country

Country	SEX	N Rows	%
France	F	24	58.5
France	M	17	41.5
Italy	F	10	43.5
Italy	M	13	56.5

Age distribution by sex and study ID (STICLO France and Italy) is shown in Table 9. The median age of female study participants in STICLO France is 1 year older than male participants while in STICLO Italy the median age of males and females is very close at 8.6 years and 8.4 years respectively.

Table 9 Distribution of patient age by STICLO Country and Sex

STUDYID	SEX	Patients	Mean	Median
FRANCE	F	24	10.0	9.8
FRANCE	M	17	8.5	8.8
ITALY	F	10	9.6	8.4
ITALY	M	13	8.5	8.6

Reviewer Comment: there is a modest inequality of sex distribution in the STICLO studies while age distribution in STICLO France reveals the female participants have an older mean and median age of 1.5 years and 1.0 year respectively. In the overall pooled STICLO studies there is a modest increase in females over males while mean and median age is 9.2 years and 8.7 years respectively. Given the background of a small sample size these differences from equality in distribution of sex and age across the STICLO studies is acceptable and not a challenge to the study outcome.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Age distribution Across Placebo and Stiripentol Treatment Arms

The age distribution of patients in the placebo and stiripentol treatment arms may potentially influence apparent seventy of the Dravet syndrome epilepsy. The interval of most severe and frequent seizures is between ages 1 to 5 years, termed the "catastrophic" stage. In this interval there are frequent seizures and events of status epilepticus. Although no differential effect of therapeutic antiepilepsy drugs is reported, greater difficulty in management in this interval is expected. The distribution of patients in this age range should be balanced to be sure there is no apparent gradient of treatment effect between treatment groups that is due to disease severity.

Table 10 Patient Age Group Distribution by Treatment Arm

	Arm				Mean Age		Median Age	
age group	**PBO**	**PBO %**	**STP**	**STP %**	**PBO**	**STP**	**PBO**	**STP**
3 to ≤5 yrs	6	19.4	5	15.2	3.9	3.9	3.8	3.7
5 to ≤10 yrs	16	51.6	14	42.4	7.8	7.6	8.1	7.9
10 to ≤15 yrs	5	16.1	12	36.4	11.9	12.5	12	12.8
15 < yrs	4	12.9	2	6.1	18.6	16.1	18.2	16.1

In addition, the number of patients who are in the 5 year old age group should be balanced between treatment arms because there may be stabilization during the treatment interval in this group. A large predominance of patients from this age group in the STP treatment arm may

result in an improved seizure count that is due to disease stabilization rather than study drug treatment effect. There were 3 placebo patients and 2 patients in the STP treatment group who were in the age range from 5.54 years to 5.72 years.

The distribution of patients in the 3 to ≤5 year and 5 to ≤10 year age groups is adequately balanced as is the distribution of the five patients between ages 5 and 6 years.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:

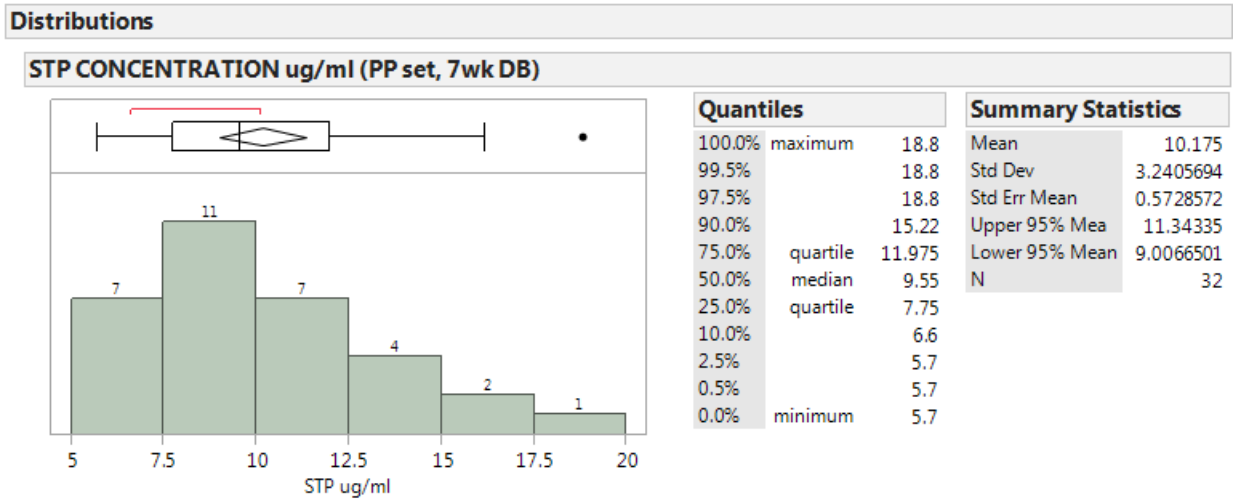
The sponsor indicates: "One patient in STICLO France who received at least 1 dose of STP was considered non-evaluable because of non-compliance with treatment and non-completion of the patient diary. This patient was totally excluded from efficacy and safety analyses because of missing data." This patient is not identified in any of the. xpt datasets. The disposition (DS) dataset identifies 41 patients in STICLO France with 5 early discontinuations including 2 patients due to lack of efficacy, 2 due to status epilepticus and 1 adverse event. The 42nd unevaluable patient is not presented. In the STICLO France subject level analysis dataset (ADSL) there are 46 entries including 5 screening failures but again no entry of an unevaluable patient due to missing data.

Treatment compliance was assessed by having patients return treatment boxes at end of study. The number of product capsules remaining was counted as well as plasma STP concentrations on week number 7 of the 8 week double blind treatment period. The sponsor indicates that compliance could not be evaluated in 19 out of 41 patients in the STICLO France study, 11 in the STP treatment arm and 8 in the placebo arm. These patients did not return all their medication bottles. From among the remaining 22 patient's compliance ranged from 57% to 164%, mean 100%. Those with compliance greater than 100% give the appearance of ingesting more than prescribed. The compliance calculation was based on the remaining capsule count reported at the end of treatment and could represent lost or discarded capsules. Overall capsule count in the STICLO France study was performed in 53% of patients. The STICLO Italy study report indicates that despite protocol recommendations, it was not possible to get the containers (medication) back to evaluate the compliance of treatment. There is a statement "However, thanks to the measure of blood concentrations, compliance appears to have been correct." The sponsor is thus relying on stiripentol blood levels for confirmation of compliance.

Stiripentol blood concentrations from patients in the STP arm at week 7 of the double-blind period are examined. The32 of the 33 patients in the STP arm have measurements available. One patient STICLO - FRANCE (b) (6) has only baseline Pk samples available. The mean and median concentrations of the remaining 32 patients were 10.18ug/ml and 9.55ug/ml respectively with a minimum and maximum of 5.7ug/ml and 18.8ug/ml respectively. The

distribution of STP concentrations is shown in **Figure 10**.

Figure 10 STP concentrations at week 7 double blind treatment period



Reviewer Comment: The compliance methodology using end of study tablet count yielded a 53% return for STICLO France patients and no counts available for STICLO Italy. This methodology does not appear to have been executed well. The results of STP concentrations obtained at week 7 of the treatment period demonstrate that treatment was ingested by 32 patients but does not provide information on the degree of individual compliance. The blood concentration measurement only identifies that treatment was taken but not the consistency and accuracy of daily intake. The possibility of inconsistent compliance is present but an erosion of the confidence on the study outcome is not expected because reduced compliance would not favor the STP arm and would reduce the STP – Placebo separation.

Concomitant medications

"Obligatory" concomitant treatments

Dravet syndrome is a highly pharmaco-resistant form of epilepsy.[33] As discussed in section 2.2, Analysis of Current Treatment Options, and section 4.2.2 Stiripentol – Clobazam Interaction,

[33] 7. Chiron C. Current therapeutic procedures in Dravet syndrome. Developmental Medicine and Child Neurology 2011;53:16-18.

first line agents include valproate and clobazam.[34] Inclusion in the STICLO trials required combined treatment with clobazam and sodium valproate.

Patients were stabilized, optimized antiepilepsy drug treatment at entry to 4-week baseline period. Clobazam and Sodium Valproate were "obligatory" concomitant treatments for the STICLO France and Italy studies. Clobazam 0.5mg/kg/day to a maximum of 20mg/day was prescribed in addition to sodium valproate. Following admission to the study a protocol driven reduction of VPA to 15mg/kg/day took place. In some patients, this reduction was associated with an increase in seizure frequency and after enrollment of 20 patients the protocol was modified. The modification allowed patients on VPA in the range 30 to 40mg/kg/day to have a reduction to 30mg/kg/day rather than 15mg/kg/day. If a patient had an associated seizure increase the patient was returned to their previous dose. Further exploration of the clobazam – stiripentol interaction and valproate dose change during the double-blind treatment period will be provided in section 5.3.2 **STP – CLB & VPA Interaction** .

Other Concomitant Medications

This group of concomitant medications will include non-AED concomitant medications and allowed non-obligator anticonvulsants, these included progabide (Gabrene) and intrarectal diazepam (IR) as a rescue medication. Although the STICLO protocol directs in section IV.3 that "All other anticonvulsants with the exception of progabide and IR diazepam will be forbidden throughout the study period", there are also entries in the dataset for nitrazepam (1 patient), phenobarbital (2 patients), phenytoin (1 patient) and clonazepam (1 patient).

There were seven patients treated with Gabrene. Two Gabrene treated patients were from the PBO cohort while 5 were in the STP cohort. The dataset provided by the sponsor reveals that two patients from the PBO cohort and two patients from the STP cohort were treated with progabide for a minimum of 1 year prior to the double-blind treatment period with a maximum of 11 years. The treatment duration is not provided for the remaining 4 patients from the STP cohort, therefore these patients may be considered to have been on a stable progabide dose for a minimum of 4 weeks, from the beginning of baseline (visitnum 0) until start of the double-blind treatment interval.

There were 11 patients who received 20 instances of IR diazepam treatment during the double-blind treatment period of STICLO France and Italy. Seven PBO patients had 16 instances of IR diazepam treatment while 4 patients in the STP treatment arm had 4 instances of IR diazepam treatment. None of the entries for the forbidden AEDs nitrazepam, phenobarbital, phenytoin and clonazepam occurred during the STICLO double blind treatment intervals. The distribution

[34] 8. Wallace A, Wirrell E, Kenney-Jung DL. Pharmacotherapy for Dravet Syndrome. Pediatric Drugs 2016;18:197-208.

and potential influence of progabide and IR diazepam will be explored further in section 5.3.2, **STP – CLB & VPA Interaction**

The STICLO protocols directed that any medications containing aspirin must be reduced by half. Prohibited medications were theophylline and any oral anticoagulant. The remaining panel of concomitant medications included Atarax, Exomuc, Levothyrox, Zynnat and a group of "other non-AED" medications. The composition of the group of "other non-AED" medications is shown in **Table 11**.

Table 11 Concomitant Medications, Other, non-AED Treatments

non-AED Treatments	# Patients	PBO	STP
ANTIBIOTIC	10	3	7
ACETAMINOPHEN	2	1	1
ANTITUSSIVE	1	0	1
DECONGESTANT	1	1	0
UNKNOWN	1	0	1
VITAMIN D	1	1	0

Reviewer Comment: The type and distribution of non-AED medications does not appear to have an influence on responder rate.

Stiripentol -Clobazam Interaction

As discussed in section Pharmacokinetics, no method has clearly differentiated augmentation of clobazam / norclobazam effect from stiripentol. In the several approaches the Pharmacometrics team has performed to examine this issue the resulting conclusion is that the currently available data appears insufficient to differentiate the efficacy contribution of STP and CLB/NCLB.

STP – CLB & VPA Interaction

As presented in "Obligatory" concomitant medications above, all patients were treated with CLB and VPA during the study. The mean blood concentration (Cmin) at end of baseline (day 0 of double blind treatment period) and week 7 (note; DB treatment period is 8 weeks) of the DB treatment period is examined for symmetry between the placebo and stiripentol treatment groups. Table 12 reveals no operative difference in the mean baseline VPA level between the PBO and STP cohorts while there is a 12.8% greater mean CLB Cmin in the STP arm compared to the PBO arm. In Table 13 examination of VPA values for PBO and STP treatment cohorts reveal

an 11.1% greater mean VPA level in the STP group compared to the PBO cohort while examination of the CLB blood level reveals that the STP cohort has a 53.5% greater mean value than the PBO treatment group. This large increase in CLB level is due to a known DDI between STP and CLB described in section 4.2.3 "Stiripentol – Clobazam Interaction".

These values show the VPA and CLB blood levels are approximately equal during the pre-treatment interval. In the STP arm there is an increase in the VPA and CLB levels during the treatment period due to an STP – VPA and STP- CLB drug-drug interaction (DDI) as previously described. This interaction has important implications for STP effectiveness with and without concomitant CLB treatment and has been discussed in section 4.2.3 above. The effect on NCLB is not included in this discussion where the goal is to evaluate the symmetry of parent drug treatment at baseline and during treatment but is also covered in section 4.2.3.

Table 12 End of Baseline, Mean and Median VPA and CLB Cmin Blood Levels

M1 period (day 0 DB treatment)	Mean conc. ug/ml			Median conc. ug/ml		
ARM	VPA	CLB	n	VPA	CLB	n
PLACEBO	72.2	0.191	29	69.6	0.171	30
STIRIPENTOL	74.5	0.215	32	67.8	0.180	32
STP – PBO **% Diff**	3.2	12.8		-2.7	5.3	

Table 13 Week 7 of Double Blind Treatment Period, Mean and Median VPA and CLB Cmin Blood Levels

M2 period, week 7 of 8 week DB interval	Mean conc. ug/ml			Median conc. ug/ml		
ARM	VPA	CLB	n	VPA	CLB	n
PLACEBO	73.1	0.200	28	75.3	0.2	28
STIRIPENTOL	81.2	0.301	32	81.4	0.2	32
STP – PBO **%** Difference	11.1	50.43		8.1	23.7	
Baseline to M2 STP arm % Difference	9.0	34.9				

Sodium Valproate Dose Adjustment

Sodium Valproate dose change during STICLO France and Italy double blind treatment period

As described in "Obligatory medication" above, patients entered the study on a stabilized dose of clobazam and sodium valproate. There was a planned sodium valproate dose reduction but an increase in seizure frequency was observed in some patients. A subsequent protocol modification allowed an increase to baseline dose. The distribution of VPA dose increase,

decrease and proportion of double blind treatment interval covered by the dose change is examined for the pooled cohort of STICLO France and Italy, see Table 14. In the PBO cohort 3 (9.7%) patients had a dose increase over a mean of 62% of the double-blind treatment interval while 2 (6.5%) patients had a dose reduction over a mean of 99% of the double-blind treatment interval. In the STP cohort no patients had a VPA dose increase while 7 (21%) patients had a dose reduction over a mean of 48% of the double-blind treatment interval. Individual patient dose reductions during the 8-week treatment interval are shown by study arm with associated comment,Table 15

Table 14 Patients by Treatment Arm with VPA Dose Adjustment and Proportion of DB Interval Covered by the Dose Change

Treatment arm	Direction of VPA Dose Adjustment	% of patients in treatment arm	Average % of treatment interval for patients with dose adjustment (proportion of DB interval)
STP (n=33)	Dose increase	0	
	Dose reduction	21.2	55
PBO (n= 31)	Dose increase	9.7	62
	Dose reduction	6.5	99

Table 15 VPA Dose Reduction by Individual Patient, STP and PBO Arms, at Each time Interval and Proportion of DB Treatment Interval with Comment, mean change and mean proportion of Interval.

USUBJID STP n = 33	Comment	% CHG BASE TO 1	% CHG 1 TO 2	% CHG 2 TO 3	Total % Dose change	Proportion % Base to 1	Proportion % 1 to 2	Proportion % 2 to 3	% of Treatment Interval , Total , any change	% tot STP / PBO
STICLO - FRANCE (b) (6) (b) (6)	VPA and CLB decreased due to hyperkinesia and hyperexcitability (onset between (b) (6) and (b) (6)).	-20	-12.5		-30	30	11		41	21.2
STICLO - FRANCE (b) (6) (b) (6)	VPA and CLB decreased due to loss of appetite, weight loss, abdominal pain, nausea, drowsiness (onset on (b) (6). Improved digestive symptom and behavior.	-28.6	-20		-43	6	28		34	
STICLO - FRANCE (b) (6) (b) (6)	VPA decreased due to abdominal pain (reported at Visit 4 on (b) (6).	-25			-25	63			63	
STICLO - FRANCE (b) (6) (b) (6)	VPA decreased due to anorexia and weight loss ((b) (6) to ongoing).	-33.3			-33	21			21	
STICLO - FRANCE (b) (6) (b) (6)	VPA decreased due to drowsiness and hypotonia.	-50	-20		-60	54			54	
STICLO - FRANCE (b) (6) (b) (6)	VPA decreased due to loss of appetite (b) (6) to ongoing) and weight loss (b) (6) to ongoing).	-16.7	-20	-12.5	-42	12	10	50	72	
STICLO - ITALY (b) (6)	VPA decreased due to loss of appetite (onset on (b) (6) and weight loss (onset on (b) (6)). Improved by decreasing VPA and CLB.	-10			-10	53			53	
Mean STP					-35				48.3	
PBO n = 31										6.5
STICLO - FRANCE (b) (6) (b) (6)		-25			-25	100			100	
STICLO - FRANCE (b) (6) (b) (6)		-16.7			-17	98			98	
STICLO - FRANCE (b) (6) (b) (6)		25			25	46			46	
Mean PBO					2.1				72	
STICLO - FRANCE- (b) (6)		25			25	44			44	

(b) (6)										

IR Diazepam

The STICLO France and STICLO Italy protocols included an option for the use of IR diazepam as a rescue medication during the double-blind treatment period "should a long and severe seizure occur".[35] The frequency of IR diazepam treatment in the PBO and STP arms as well as in study endpoint responders compared to non- responders was examined, see Table 16.

In total (both study arms) 11 patients had 20 instances of IR diazepam treatment during the double blind 8-week study interval. There were 7 (22.6%) patients in the PBO arm and 4 (12.1) patients in the STP treatment arm who were treated with IR diazepam rescue medication. In the PBO arm there were 5 non-responders treated and 2 responders while in the STP arm there were 2 patients each in the non-responder and responder group. Patients who received IR diazepam rescue medication in the PBO arm had more frequent instances of treatment per patient than among those in the STP arm. The PBO patients had a mean of 2.3 instances of treatment per patient while the PBO arm patients had a mean of 1 instance of treatment per patient.

Table 16 Frequency of IR Diazepam treatment by Treatment Arm by Responder Status

Treatment arm	RESPONDER GROUP, 0= NO, 1 = YES	# Patients	# Instances	% of treatment arm	Mean # Instances of rescue treatment per patient by arm	% of Treatment by arm
PBO (n= 31)	0	5	10	16.1	2.3	22.6
	1	2	6	6.5		
STP (n= 33)	0	2	2	6.1	1.0	12.1
	1	2	2	6.1		

Efficacy Results – Primary Endpoint

The primary endpoint for the STICLO France Italy studies was a 50% responder rate. A responder as, (see study design above, Primary Endpoint) was defined as a patient who

[35] STICLO France study protocol, section IV.3 (page 11), Permitted combined treatments.

experienced a ≥50% decrease in the frequency of generalized tonic-clonic or clonic seizures during Month 2 of the 8-week double-blind treatment period compared to baseline (i.e., 4-week placebo run-in). The results for STICLO France, STICLO Italy and the pooled study ITT population is shown in Table 17. The statistical reviewer was able to confirm the sponsor's primary efficacy endpoint results shown in Table 17 [36].

Table 17 Efficacy Results, Responder Analysis at the End of Treatment in the Intent-to-Treat Population across the STICLO France and STICLO Italy Pivotal Trials

	STICLO France N=41		STICLO Italy N=23	
	Stiripentol N=21	**Placebo N=20**	**Stiripentol N=12**	**Placebo N=11**
No of responders[a]/total	15/21	1/20	8/12	1/11
(Responder Rate)	(71%)	(5%)	(66.7%)	(9.1%)
[95% CI]	[52.1 – 90.7]	[0.0 – 14.6]	[34.9 – 90.1]	[0.0 – 41.3]
p-value (Fisher Exact Test)	<0.0001		0.009	

[a] Responder is defined as a patient with a greater than 50% decrease in frequency of generalized tonic-clonic or clonic seizures
CI=confidence interval

Both STICLO studies are strongly positive in favor of STP treatment. An additional consideration in the assessment of this efficacy result is the contribution of the "obligatory" concomitant medications. From the discussion in section 4.2.3 "Stiripentol-Clobazam Interaction", it has not been possible to separate the contribution of CLB and NCLB from the observed STP treatment effect seen in the STICLO Studies.

Subpopulations

Age

Treatment response by age is examined. This analysis reveals a consistently higher proportion of responders in the STP treatment arm than PBO arm in all age strata, see Table 18. When STP responder rate frequency was examined across age groups a lower responder rate frequency was seen in the cohort of patients ≥ 15 years of age than the younger age groups. Interpretation of this observation is limited by the very small number of only 2 STP treated patients in this group. In the remaining 4 age strata shown in Table 18 there was no notable difference in the percentage of STP responders across the age groups.

[36] Biometrics review, Junshan Qiu, Ph.D,

Table 18 Responder rate by Age Strata. Age Strata; 3- 6 yrs, 6< - 9 yrs, 9< - 12 yrs, 12< - 15 yrs, 15< yrs. STICLO France, STICLO Italy and Pooled STICLO Studies

	Age Group	3-6			6-9			9-12			12-15			15≤		
		R	N-R	% R	R	N-R	% R	R	N-R	% R	R	N-R	% R	R	N-R	% R
France	PBO	0	6	0	0	4	0	1	4	20	0	2	0	0	3	0
	STP	4	0	100	4	2	66.7	2	2	50	5	1	83.3	0	1	0
Italy	PBO	0	2	0	1	3	20	0	1	0	0	1	0	0	1	0
	STP	1	2	50	2	1	50	2	0	100	2	0	100	1	0	100
Pooled STICLO	PBO	0	8	0	1	7	11.1	1	5	16.7	0	3	0	0	4	0
	STP	5	2	71.4	6	3	60	4	2	66.7	7	1	87.5	1	1	50

Table 19 Sample Size (n) in each Age Strata

	Age Group	1	2	3	4	5
		Sample Size (n) per group				
France	PBO	6	4	5	2	3
	STP	4	6	4	6	1
Italy	PBO	3	5	1	1	1
	STP	3	4	2	2	1
Pooled	PBO	9	9	6	3	4
	STP	7	10	6	8	2

Sex

Treatment response by sex is examined. This analysis reveals no notable difference in response to STP treatment by sex.

Table 20 Responder Rate by Sex. STICLO France, STICLO Italy and Pooled STICLO Studies

		Male			Female		
		R	N-R	% R	R	N-R	% R
France	PBO	1	10	9.1	0	9	0
	STP	5	1	83.3	10	5	66.7
Italy	PBO	0	4	0	1	4	16.7
	STP	5	3	62.5	3	0	75
Pooled STICLO	PBO	1	14	6.25	1	13	6.7
	STP	10	4	71.4	13	5	68.4

Reviewer Comment: There is no difference in responder rate seen when examined by age group or sex.

SCN1A Status

From among the 33 patients in the STP treatment group there were 29 with known SCN1A mutation status. The responder rate in this subset with identified SCN1A lesion is examined, Table 21. There were 23 patients in the STP treatment group with a positive SCN1A mutation from among these patients 17 (74%)were positive responders to treatment. There were 6 patients in the STP treatment group with no identified SCN1A mutation. From among these patients 2 (33%) fulfilled criteria for a positive response. It is noted there are a large number of SCN1A mutations and assessment of the mutation status in these patients did not identify specific mutations, only the presence or absence of a mutation.

Table 21 Responder Rate by Presence of SCN1A mutation Status among STP treated Patients, STICLO France and Italy

	SCN1A POSITIVE	SCN1A NEGATIVE
n of group	23	6
Positive Responder	17	2
% Responder	73.9	33.3

The effect of SCN1A status on the seizure frequency at end of double blind treatment (M3) is examined. An analysis of covariance with final study visit seizure frequency (30 day adjusted) as outcome variable with baseline seizure frequency (30 day adjusted) and SCN1A status as covariates. Outcome and baseline values are log transformed where SCN1A mutation status is a binary variable. This analysis reveals the SCN1A status had an effect on the M3 seizure frequency where SCN1A positive patients, with baseline seizure frequency as covariate, had a lower seizure frequency than SCN1A mutation negative patients.

Table 22 Covariate Analysis of SCN1A Effect on Seizure Frequency in STP Treated Patients, Baseline Frequency and SCN1A as Covariates

Baseline Sz Frequency and % SCN1A status as Covariate	SCN1A Mutation Status	Least Sq Mean Sz Frequency (ln Transformed)	Least Sq Mean Sz Frequency (back transformed)	% reduction Sz Frequency $SCN1A^+$ over $SCN1A^-$ at end of study visit (M3)
Pooled STICLO France and Italy (n=29)	SCN1A negative (n=6)	2.6	12.6	

Baseline Sz Frequency and % SCN1A status as Covariate	SCN1A Mutation Status	Least Sq Mean Sz Frequency (ln Transformed)	Least Sq Mean Sz Frequency (back transformed)	% reduction Sz Frequency $SCN1A^+$ over $SCN1A^-$ at end of study visit (M3)
	SCN1A Positive (n=23)	1.2	2.2	82.5

Reviewer Comment: Examination of the effect of SCN1A status on responder rate and end of study seizure frequency reveals a greater effect on seizure reduction in the subset of patients with who are positive for an SCN1A mutation. This must be considered exploratory since the overall n size is small and the proportion of SCN1A negative patients was a small proportion of the group (n=29) with an identified SCN1A status. The observation is in alignment with the results of the STEV study where the Dravet patient subset had a notably better response to STP treatment than the other epilepsy subtypes in the study population.

STICLO France and Italy Pooled analysis

Results of the pivotal STICLO France and STICLO Italy are shown in Table 23.[37] The sponsor examined the validity of pooling the studies. It is noted that except for planned sample size the protocols are the same, patient populations are comparable with no statistical difference between demographic metrics. The numbers of patients that withdrew from each trial in the STP treatment and PBO groups were comparable. The mean STP plasma concentration at week 7 of the 8 week double blind treatment period were very similar in both studies. Analysis of the primary endpoint from the two studies using the chi-square test with a Type 1 error rate of 0.10 reveals no significant difference (responder analysis p=0.656)

Table 23 Efficacy Results at the End of Treatment in the Intent-to-Treat Population, Pooled Pivotal Trials STICLO France and STICLO Italy

STICLO Pooled Total (France, Italy)		
	Stiripentol n=33	**PBO, n= 31**
Responder Analysis*		
No of responders/total	23/33	2/31
Responder Rate	69.7%	6.5%
95% CI	54.0 – 85.4	0.0 – 15.1
P-value (Fisher's Exact test)	<0.0001	

[37] From sponsor Table 3-8, page 49, ISE

Percentage Change from baseline in seizure frequency**		
n	32	29
mean	-66	4.3
±SD	44.2	50.7
median	-84.4	-5.8
Min-max	-100 to 72.6	-87 to 140
P-value (Wilcoxon test)	<0.0001	
*Responder is defined as a patient with a ≥50% decrease in frequency of generalized tonic-clonic or clonic seizures		
** Frequency of generalized tonic-clonic or clonic seizures		

STICLO Secondary Endpoints

The protocol specified secondary endpoints for STICLO France and Italy are the same. These endpoints have no prespecified adjustment for multiplicity. These endpoints are presented to examine for alignment with the results of the primary endpoint but are not considered for labeling claims.

The STICLO secondary endpoints are as follows:

1. A percentage of children whose number of generalized clonic or tonic-clonic seizures during the last month of the comparison period, on a 30-day basis, decreased by at least 50% compared to the number of seizures, on a 30-day basis, during the baseline period.
    a. Note: this secondary endpoint is the opposite of part 1 of the 4-part primary endpoint. In part 1 of the primary endpoint was defined as exclusion of patients who did not have a decrease by at least 50% of baseline. The primary endpoint also had 3 additional elements.
    b. The data provided by the sponsor for this parameter is derived from the per-protocol population in the STICLO Italy study report, for consistency non-completer patients are excluded from the calculation for STICLO France.

2. Percentage of children withdrawn from the study in each treatment group.

3. Number of seizures during the comparison period (months 1 and 2 considered separately) in comparison to the number of seizures during the baseline period in each treatment group.

4. Time elapsed until the same number of seizures as that of the 1-month baseline period were experienced.

STICLO France

Decrease in seizures by at least 50%: The percentage of patients whose number of generalized clonic or tonic-clonic seizures during month 2 of the comparison period, on a 30-day basis, decreased by at least 50%, compared to the number of seizures, on a 30-day basis, during the baseline period was 75% in the stiripentol group and 6.25% in the placebo group (excluding non-completers, n based on completers only PBO= 16, STP= 20)).

Withdrawal from study: In the STP group, 1 child (5%) was withdrawn from the study, vs. 4 (20%) in the PBO group (also shown in section 7.4.3 "Dropouts and / or Discontinuations.

Comparison of number of tonic-clonic seizures during months 1 and 2 and relative change compared to the baseline period: In comparison to baseline the STP treatment arm had a larger mean decline in seizure frequency than the PBO arm in both month 1 and month 2, Table 24.

Table 24 STICLO France, Number of tonic-clonic seizures during months 1 and 2 and change compared to the baseline period*

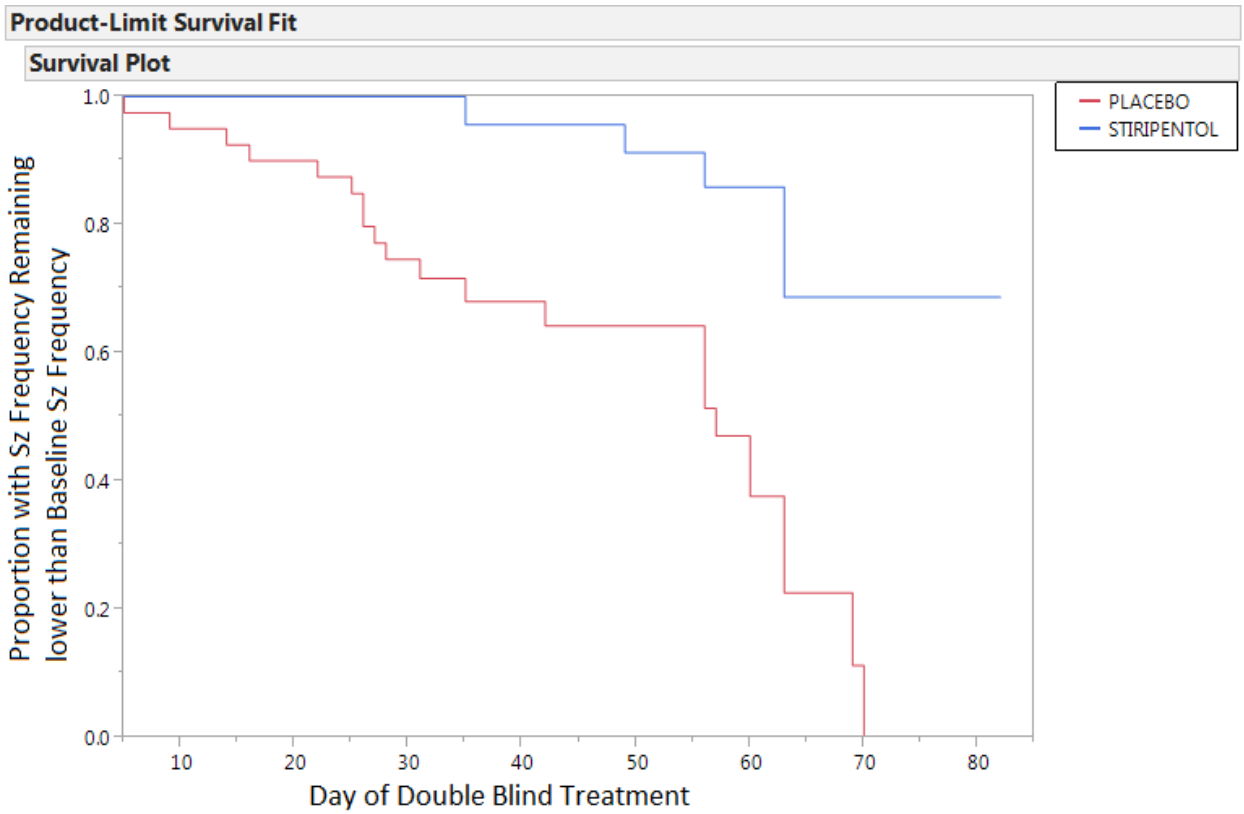
	STP, n=21	**PBO, n=20**
Baseline		
mean	17.9	18.5
SD	17.3	17.0
Median	11.4	14.4
Min, max	3.9, 72.9	4.1, 76.3
Month 1 of DB Treatment Period		
mean	3.2	25.1
SD	4.4	41.8
Median	0	10.1
Min, max	0, 13.3	3.9, 192
Month 2 of DB Treatment		
mean	6.4	23.6
SD	9.6	35.8
Median	2.1	15.5
Min, max	0, 32.1	2.6, 166.7

* Based on sponsor table 14, Sponsor STICLO France Study Report p43, derived by reviewer from ADSF.xpt dataset. Note-sponsor table month 2 does not include non-completers, this table includes data on all ITT patients and median value

Time Elapsed to Baseline Seizure Frequency

Time to return to baseline seizure frequency was identified as a secondary endpoint. The sponsor methodology for the survival plot in Figure 3 on page 44 of the STICLO France study report was unclear. The reviewer generated a survival plot for STICLO France based on return / no return to baseline seizure frequency for the study days provided as M2 and M3 visit days in the QS dataset (version 2, IR 1/7/16). Return to baseline seizure frequency or study non-completers were counted as failures and patients who continued to have seizure frequency less than baseline frequency to end of study were censored. The plot is presented for descriptive assessment without testing of significance shown since these survival plots were not identified with a prespecified methodology or correction for multiplicity. The survival curves reveal clear separation with the proportion of failures accruing more rapidly in the PBO arm, Figure 11.

Figure 11 STICLO France (n=41), Patients with Sz Frequency Remaining Lower than Baseline, STP vs PBO (Survival Plot)[38]



Time to event: DB
Censored by CENSOR
Censor Code 1
Grouped by TRTP (ARM-ADSF)

Summary

Group	Number failed	Number censored	Mean	Std Error
PLACEBO	23	17	49.3439	3.39068
STIRIPENTOL	4	38	60.798 Biased	1.54121
Combined	27	55	56.7924 Biased	2.18573

STICLO Italy

The percentage of patients having their number of generalized tonic-clonic seizures, experienced during the second month of the comparison period, adjusted to 30 days,

[38] Reviewer Generated, Based on Days in DB Treatment (Day M2- M1and M2-M1), Reported day where Seizure Frequency > Baseline frequency. Note: seizure measurement is not continuous but acquired at discrete time points M2 and M3 following baseline. Non-completers counted as failure at day of discontinuation (not censored).

decreased of at least 50% compared to the number of seizures at baseline, adjusted to 30 days, was 73% (8/11) in the stiripentol group and 11% (1/9) in the placebo group (excluding non-completers, n based on completers only PBO= 9, STP= 11))[39].

Withdrawal from study: In the STP group, 1 child (9%) was withdrawn from the study, vs. 2 (18%) in the PBO group (also shown in section 7.4.3 "Dropouts and / or Discontinuations".

Comparison of number of tonic-clonic seizures during months 1 and 2 and relative change compared to the baseline period: In comparison to baseline the STP treatment arm had a larger mean decline in seizure frequency than the PBO arm in both month 1 and month 2, Table 25.

Table 25 STICLO Italy, Number of tonic-clonic seizures during months 1 and 2 and change compared to the baseline period*

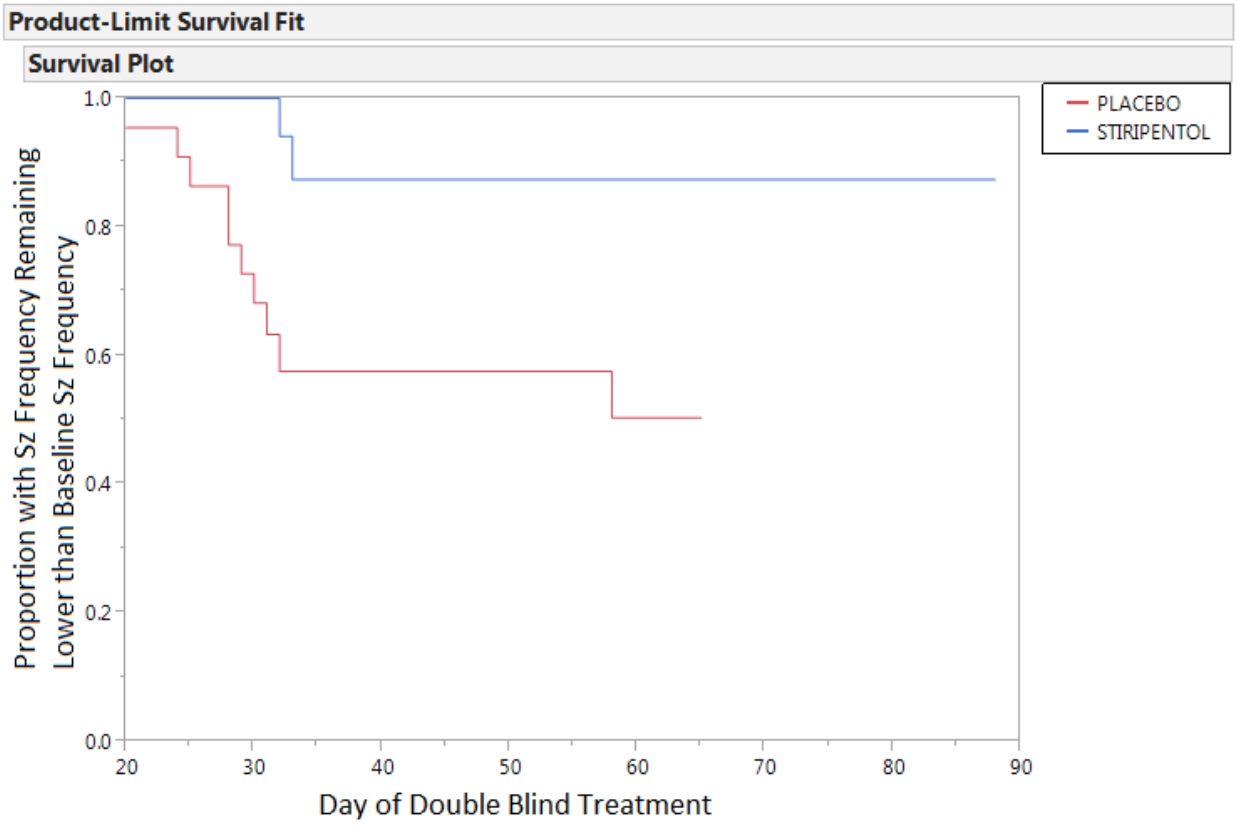
	STP, n=12	**PBO, n=11**
Baseline		
mean	33.6	27.5
SD	28.2	28.7
Median	30.2	20.7
Min, max	2.14, 86.1	3.75, 101.1
Month 1 of DB Treatment Period		
mean	4.4	29.1
SD	7.1	35.6
Median	1.0	16.5
Min, max	0, 24.2	0.94, 126.3
Month 2 of DB Treatment		
mean	9.9	16.7
SD	12.3	10.6
Median	6.0	19.3
Min, max	0, 39.7	0.5, 31.8
* Based on sponsor table 11, Sponsor STICLO Italy Study Report p31, derived by reviewer from ADSF.xpt dataset. Note-sponsor table month 2 does not include non-completers, this table includes data on all ITT patients.		

[39] STICLO Italy Study Report, page 30

Time Elapsed to Baseline Seizure Frequency

Time to return to baseline seizure frequency was identified as a secondary endpoint. The sponsor did not perform an analysis for STICLO Italy due to small sample size. The reviewer generated a survival plot for STICLO Italy based on return / no return to baseline seizure frequency for the study days provided as M2 and M3 visit days in the QS dataset (version 2, IR 1/7/16). Return to baseline seizure frequency or study non-completers were counted as failures and patients who continued to have seizure frequency less than baseline frequency to end of study were censored. The plot is presented for descriptive assessment without testing of significance shown since these survival plots were not identified with a prespecified methodology or correction for multiplicity. The survival curves reveal clear separation with the proportion of failures accruing more rapidly in the PBO arm, Figure 12.

Figure 12 STICLO Italy (n=23), Patients with Sz Frequency Remaining Lower than Baseline, STP vs PBO (Survival Plot)[40]



Time to event: DB
Censored by CENSOR
Censor Code 1
Grouped by TRTP (ARM-ADSF)

Summary

Group	Number failed	Number censored	Mean		Std Error
PLACEBO	10	12	44.1886	Biased	3.92911
STIRIPENTOL	2	22	32.9412	Biased	0.08071
Combined	12	34	49.643	Biased	2.34719

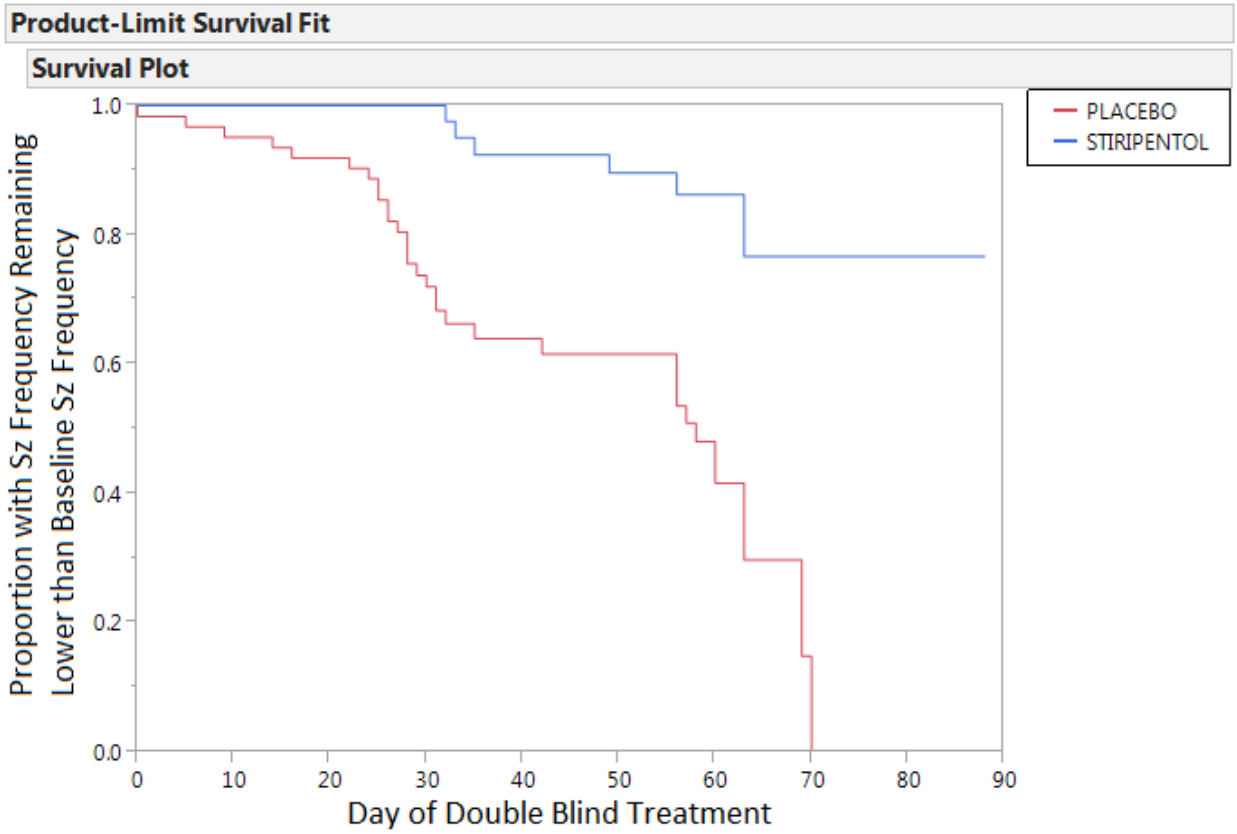
Pooled Results, STICLO France and Italy

[40] Reviewer Generated, Based on Days in DB Treatment (Day M2- M1and M2-M1), Reported day where Seizure Frequency > Baseline frequency. Note: seizure measurement is not continuous but acquired at discrete time points M2 and M3 following baseline. Non-completers counted as failure at day of discontinuation (not censored).

Pooled STICLO France and Italy Survival Plot of Patients whose Seizure Frequency Returns to ≥ Baseline

Time to return to baseline seizure frequency was identified as a secondary endpoint. The sponsor did not perform an analysis for pooled STICLO studies. The reviewer generated a survival plot for the pooled STICLO studies based on return / no return to baseline seizure frequency for the study days provided as M2 and M3 visit days in the QS dataset (version 2, IR 1/7/16). Return to baseline seizure frequency or study non-completers were counted as failures and patients who continued to have seizure frequency less than baseline frequency to end of study were censored. The plot is presented for descriptive assessment without testing of significance shown since these survival plots were not identified with a prespecified methodology or correction for multiplicity. The survival curves for pooled STICLO studies reveal clear separation with the proportion of failures accruing more rapidly in the PBO arm, Figure 13.

Figure 13 STICLO France & Italy (n=64), Patients with Sz Frequency Remaining Lower than Baseline, STP vs PBO (Survival Plot)[41]



Time to event: DB Treatment Day
Censored by CENSOR
Censor Code 1
Grouped by TRTP (ARM-ADSF)

Summary

Group	Number failed	Number censored	Mean	Std Error
PLACEBO	33	29	49.3017	2.79713
STIRIPENTOL	6	60	60.1276 Biased	1.42211
Combined	39	89	57.0275 Biased	1.81084

Seizure Freedom

[41] Reviewer Generated, Based on Days in DB Treatment (Day M2- M1and M2-M1), Reported day where Seizure Frequency > Baseline frequency. Note: seizure measurement is not continuous but acquired at discrete time points M2 and M3 following baseline. Non-completers counted as failure at day of discontinuation (not censored).

The reviewer examined seizure freedom. There is a notable difference in the proportion of patients who achieved seizure freedom in STICLO France, STICLO Italy and the pooled studies in the STP arm compared to the PBO arm. Analysis of STICLO France revealed that 52% of patients were seizure free at one month of treatment during the double-blind treatment interval with seizure freedom retained in 43% of patients at month 2 of the blinded treatment interval while no patients in the PBO treatment arm achieved seizure freedom, Table 26.

Analysis of STICLO Italy study revealed that 42% of patients were seizure free at one month of treatment during the double-blind treatment interval with seizure freedom retained in 33% of patients at month 2 of the blinded treatment interval while no patients in the PBO treatment arm achieved seizure freedom, Table 26.

Table 26 STICLO France, Italy and Pooled Studies, Proportion of Patients that Achieved Seizure Freedom during Double Blind Treatment Interval.

	n	Sz Free M2 Double Blind Treatment (visit number 2)	% Sz Free Month 1	Sz Free M3 Double Blind Treatment (visit number 3)	% Sz Free Month 2
France					
STP	21	11	52.4	9	42.9
PBO	20	0	0	0	0
Italy					
STP	12	5	41.7	4	33.3
PBO	11	0	0	0	0
POOLED					
STP	33	16	48.5	13	39.4
PBO	31	0	0	0	0

Reviewer Comment: The secondary endpoints are not protocol designed to assess statistical significance. Examination of study withdrawals reveals fewer in the STP arm than PBO arm in both STICLO France and Italy. Secondary endpoints that examined seizure frequency during the treatment interval compared to baseline reveal a notable reduction of frequency for patients in the STP arm compared to the PBO arm. The survival plot analysis reveals more rapid return of a larger proportion of patients to their baseline seizure frequency in the PBO arm compared to the STP arm in both studies. Analysis of seizure freedom reveals that a large proportion of patients in the STP treatment arm achieved seizure freedom at the end of month 1 of treatment that was sustained in 80% of patients in both studies at the end of month 2. No patients in the PBO arm achieved seizure freedom. All secondary endpoints are seen to be in alignment with the primary efficacy outcome.

Efficacy Conclusion

Stiripentol under the conditions of treatment in the STICLO Studies where sodium valproate and clobazam were obligatory concomitant medications is an effective treatment for the seizures of Dravet syndrome. The contribution of the concomitant treatment cannot be adequately separated to conclude that stiripentol alone is effective. The robust effect size and high level of significance demonstrate efficacy based on the STICLO France and STICLO Italy studies

Data Quality and Integrity – Reviewers' Assessment

The OSI report is discussed in section 4.1. Issues relating to data integrity were examined in the process of OSI site audit selection. There was no site identified with a disproportion of discontinuations, screen failures or outlier frequencies of adverse event reporting. Patient (b) (6) in STICLO France was considered unevaluable because treatment was taken irregularly and seizures were not recorded in the diary. The patient number (b) (6) places the patient at site (b) (6) (b) (6)

The quality of data on initial NDA submission was deficient due to inconsistent alignment of nomenclature for study visit dates. Datasets were submitted with differing nomenclature for visit dates. There were four patient visits from baseline to final visit. These were referenced as visit number (V1, V2, V3, V4), period (baseline, compare period M1, phone call M2, Evaluation M3), and (baseline, pre-inclusion, P1, P2) across study report documents and xpt datasets. Information requests were required to repair these nomenclatures that did not align. In the initial NDA submission, the date of visit 4 (evaluation M3) study visit was not provided in the qs.xpt dataset. Multiple information requests were required to rebuild workable datasets for review. Overall, once datasets were constructed with consistent alignment of study visit variable names and appropriate population of variable fields there was no substantial evidence of faulty data integrity.

The statistical reviewer did identify modest discrepancies between the SAS (.xpt) datasets and the study report tables for 5 patients. This issue is also covered in full above in STICLO France, Dataset Divergence, STICLO Italy Dataset Divergence and Reviewer Conclusion, STICLO France and Italy Dataset Divergence:.

Three of these patients were in STICLO France and two in STICLO Italy. These discrepancies are shown in Table 27. Where there was divergence identified the statistical reviewer used values from the sponsor study reports. Using these (study report) values the statistical review could repeat the sponsor's primary efficacy analysis.

Table 27 Divergence between the ADSF.xpt dataset and Study Report Individual Efficacy Data

STICLO France			**Study visit disparity, 30 day adjusted Sz Count**	
Subject	**ARM**	**Study Milestone (visit)**	**ADSF dataset**	**Study Report, Individual efficacy response data, Appendix 16.2.6**
(b) (6)	STP	M2	10.83	0
	PBO	M3	16.45	16.15
	PBO	M2	192	166.67
STICLO Italy				
(b) (6)	STP	M3	39.67	38.7
	STP	M2	8.48	11.8

Durability of Response

There were 33 STP treated patients in the STICLO trials. To assess durability of the STP treatment effect seizure frequency at the end of month 2 (M3 visit) of the double-blind treatment interval was compared to the frequency at the end of month 1 (M2 visit) of the double-blind treatment interval. The mean and median seizure frequency at the M2 assessment were 3.7 and 0.94 respectively per 30 day adjusted period while at the end of 8 weeks of double blind treatment (M3) the mean and median frequency of the 30 day adjusted interval were 7.6 and 3.7 respectively. Seventeen (52%) of the 33 patients had an increase in seizure frequency from month 2 to month 3 while 12 (36%) patients had no change and 3 (9%) patients had additional decline in frequency. Of the 17 patients that had an increase in seizure frequency between M2 and M3 visit there were 3 patients with an increase over baseline seizure frequency. The maximum increase over baseline was 73% observed in one patient. From the remaining 14 patients of the cohort with a positive change in the M2 to M3 interval all retained a decline in frequency compared to the baseline frequency. The mean percent decline of these 14 patients was 54%. None of the 16 patients with a stable or declining seizure frequency from month 2 to month 3 (M3 final study visit) had an end of study increase over baseline frequency.

Approximately half of patients had some loss of antiseizure effect (positive M2 to M3 slope) during the second months of treatment. At end of study (8 weeks) three of these patients had a 30-day seizure count greater than baseline. The seizure frequency by visit plot is shown for these patients in Figure 14. The remaining 14 patients retained a M2 visit seizure frequency less than baseline value (negative slope from baseline to M3). The plot of baseline, M2 and M3 seizure frequency for the 30 STP treatment arm patients with final study visit seizure frequency < baseline for the STICLO France and Italy pool is show in Figure 15.

In summary, at the second month of treatment there were 3 (9%) STP treatment patients who had a seizure frequency higher than at baseline. All patients (33) had a decline in seizure frequency from baseline at M2 (4 weeks of treatment) while 17 of these patients had a nadir at M2 with an increase between M2 and M3 (8 weeks). From among these 17 patients, 3 had an increase that exceeded baseline as noted above while the remaining patients retained a benefit. Two patients had continued reduction of seizure frequency from M2 to M3. Sixteen patients had a 30-day seizure count of 0 at M2. Fourteen of these patients continued to have seizure counts of zero at M3 while one patient discontinued.

Figure 14 Seizure Frequency by Study Visit of Those Patients with M2 (8 week treatment) Seizure Frequency > Baseline

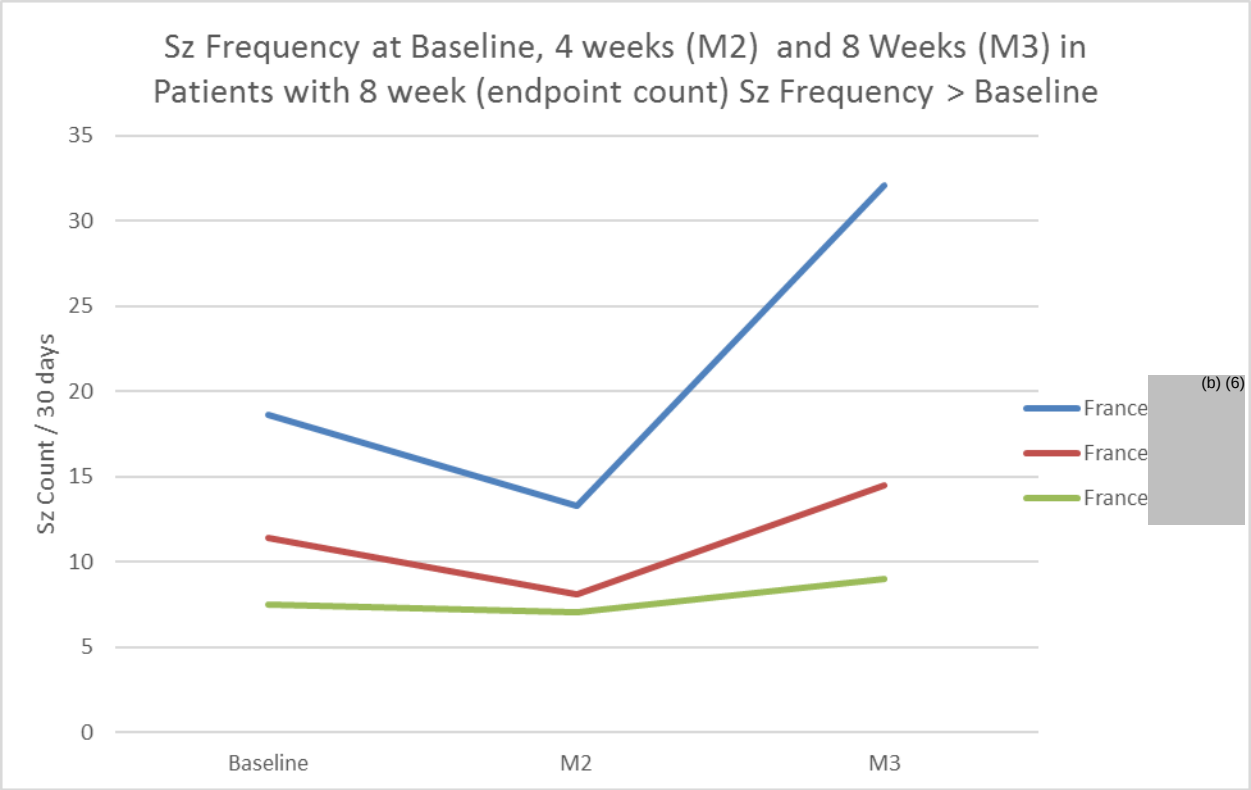
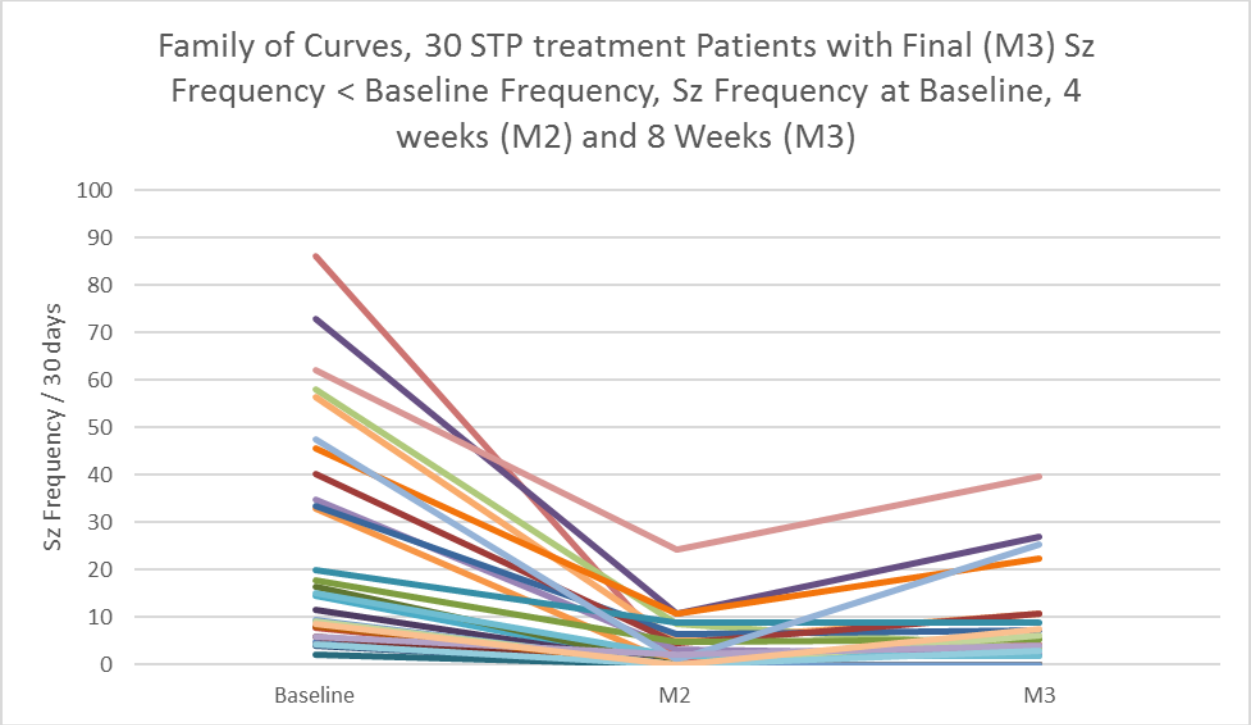


Figure 15 Seizure Frequency of all STP Treatment arm Patients (n= 30) with Final Study visit Sz Frequency < Baseline Sz Frequency. Frequency at 4 weeks (M2) and 8 Weeks (M3), STICLO France and Italy



Reviewer Comment: The therapeutic benefit of STP treatment is maintained in 91% of patients over the 8-week treatment period while 36% of patients retain a very significant benefit of a zero seizure count. The graphic visuals in Figure 14 and Figure 15 reveals an overall small upward slope from M2 to M3 while Figure 13 shows a clear separation in favor of STP treatment in a survival plot of return to baseline seizure frequency. The therapeutic benefit is durable through the 2 months of available treatment data.

Persistence of Effect (after cessation of treatment)

There is no data available for the STICLO pivotal study to assess persistence of effect.

Additional Analyses Conducted on the Individual Trial

ANCOVA Analysis, Reviewer Analysis of Outcome by Seizure Frequency using ANCOVA

Efficacy Analysis of Seizure Frequency at Baseline & End of Double Blind Treatment Examined by ANCOVA

The efficacy analysis is examined using an analysis of covariance with final study visit seizure

frequency (30 day adjusted) as outcome variable and baseline seizure frequency (30 day adjusted) and treatment arm as covariates. Outcome and baseline values are log transformed where treatment arm is a binary variable. The STICLO France study results are confirmed by the statistical reviewer. Both the STICLO France and pooled STICLO France and Italy results reveal a strongly positive percent reduction in seizure frequency, Table 28. These analyses are in alignment with the pre-specified responder rate analysis.

Table 28 Reviewer Analysis of % Change in Seizure frequency from baseline to Treatment interval comparing STP to PBO with baseline seizure frequency as Covariate

Baseline Sz Frequency and STP Treatment Status as Covariates	Treatment Arm	Least Sq Mean (ln Transformed)	Least Sq Mean (back transformed)	% reduction Sz Frequency over Baseline
STICLO France (n= 41)*	PLACEBO	2.70	13.9	
	STIRIPENTOL	1.29	2.6	81.3 (p<.0001)
Pooled STICLO France and Italy (n=64)	PLACEBO	2.7	14.3	
	STIRIPENTOL	1.4	3.0	79.0 (p<.0001)
*Confirmed in Statistical Review and Evaluation, Junshan Qiu, Ph.D., page 16				

6 Integrated Review of Effectiveness

6.1. Assessment of Efficacy Across Trials

This application is supported by two small pivotal trials, performed sequentially, of the same study design, using STP treatment for a rare disease. These trials have been presented in section 5.3 above. Additional studies that explore the therapeutic effect in Dravet syndrome will be presented in this section.

This examination will include the available legacy non-IND studies, including the STEV and STP-1 studies that have results in alignment with STP efficacy. The retrospective chart review by Laux et al. where there are a small number of Dravet patients identified that were not concomitantly treated with CLB). The sponsor also performed a covariate analysis to provide evidence of a differential effect of stiripentol, by demonstration of non-significant contribution of CLB and NCLB. Finally, the long term open label safety studies TAU-EAP, STILON, and DIAVEY will be briefly examined for any unexpected divergence from expected treatment benefit. This will

include the bassline to treatment seizure frequency and in the STILON and DIAVEY studies a comparison of discontinuation for “lack of efficacy” between the Dravet Syndrome and non-Dravet cohorts.

6.2. Additional Efficacy Considerations

6.2.1. Additional Study Data on STP

STEV Study

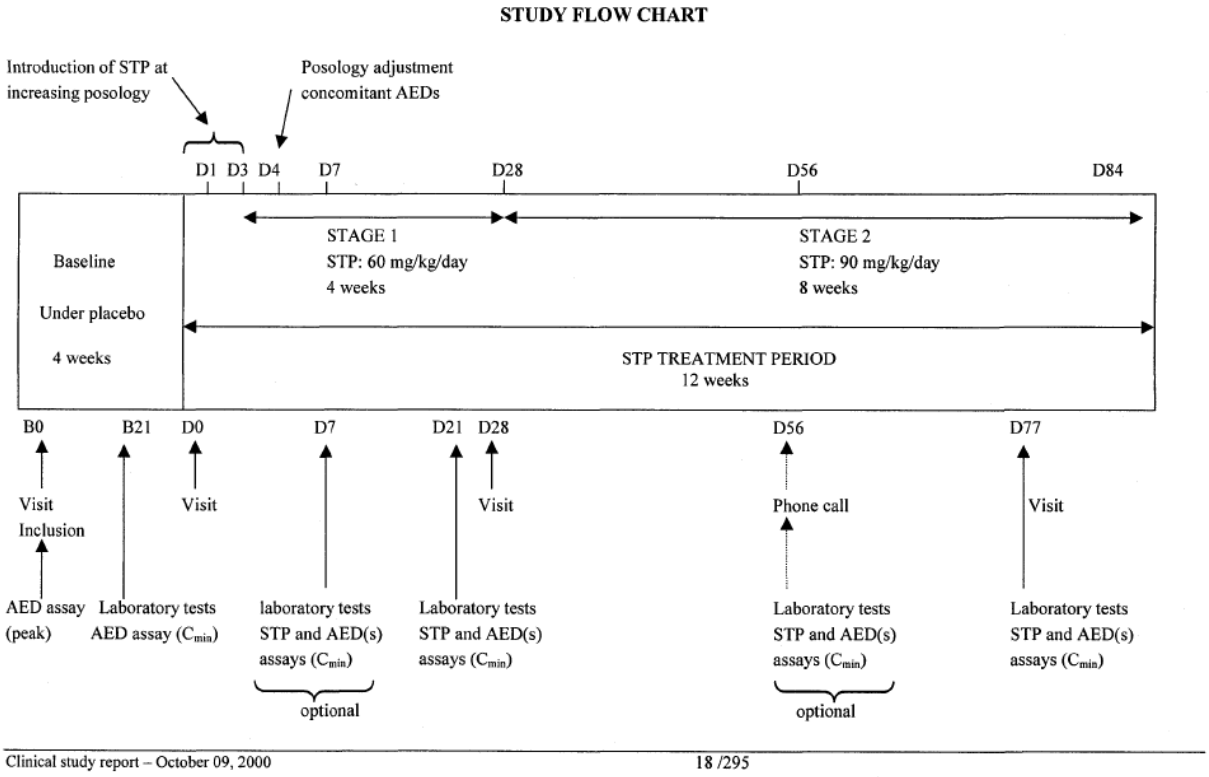
The STEV trial was the first clinical trial in which the efficacy of STP in Dravet syndrome was observed. This multicenter (2 centers in France), single-blind, add-on trial was conducted from 1992 to May 1997 in 233 children, 2 months to 15 years of age with severe refractory epilepsy treated with 1 or 2 AEDs. The objective of the trial was to identify which seizure types would respond to STP.

A total of 233 patients were enrolled, 227 received at least one dose of STP, and 157 completed the trial. Among the 233 children enrolled, 24 had Dravet syndrome. The response rate of Dravet syndrome patients was notably higher than non-Dravet patients. In addition, 30% of Dravet syndrome patients achieved seizure freedom at day D28 (28 days) of treatment (confirmed by reviewer).

Trial Design

The protocol specified that following a 1-month single-blind placebo run-in (baseline), patients were to be treated with STP for 12 weeks. Patients were blind to treatment, placebo during the 4-week run-in; STP during the remaining 12 weeks of the trial. The protocol specified that STP was to be administered at a dose of 60 mg/kg/day from treatment Day 1 to Day 28 (first treatment period), given in 2 to 3 divided doses. Thereafter the STP dose could be increased up to 90mg/kg/day.

Figure 16 STEV Study Schematic / Flow Chart



Demographic Characteristics

Examination of demographic characteristics reveals a higher proportion of males than females, mean age of 5.7 years where 58% of patients are between ages 1 to <6 years. There is a higher proportion of patients with clonic seizures than tonic-clonic.

Demographic Characteristic	**N=24**
Gender (n, %)	
Males	17 (70.8 %)
Females	7 (29.2 %)
Age (years)	
Mean ± SD	5.7 ± 5.3
Median	3.5
Min – Max	0.9 – 18.5
Age Group (n, %)	
< 1	3 (12.5%)
1 to < 6	14 (58.3%)
6 to < 12	3 (12.5%)
12 to < 17	3 (12.5%)
>= 17	1 (4.2%)
Weight (kg)	
n	20
Mean ± SD	25.7 ± 18.5
Median	19.5

Demographic Characteristic	N=24
Min - Max	9.0 – 79.0
Missing data	4
SCN1A mutation (n, %)*	
n	18
Mutation	15 (83.3%)
No mutation	3 (16.7%)
Disease Duration (years)	
n	23
Mean ± SD	5.6 ± 5.3
Median	3.3
Min – Max	0.3 – 18.0
Seizure Type (n, %)	
Generalized Seizures	
Clonic	16 (66.7%)
Tonic	1 (4.2%)
Tonic-Clonic	6 (25.0%)
Myoclonic	7 (29.2%)
Atonic	0 (0.0%)
Absence	0 (0.0%)
Unspecified generalized seizure	5 (20.8%)
Partial Seizures	
Simple Partial	1 (4.2%)
Complex Partial	1 (4.2%)
Secondary Generalized	0 (0.0%)
Number of tonic-clonic or clonic seizures during baseline	
n	20
Mean ± SD	25.9 ± 65.1
Median	10.5
Min – Max	1 – 300
Daily Dose CLB (mg/kg/day) at baseline	
n	21
Mean ± SD	0.8 ± 0.3
Min – Max	0.3 – 1.4
Daily Dose VPA (mg/kg/day) at baseline	
n	20
Mean ± SD	30.4 ± 9.5
Min – Max	15.1 - 51.6

Withdrawals and Discontinuations

During the trial, 3 of 24 (12.5%) Dravet syndrome patients were withdrawn on due to SUDEP and 2 due to adverse events.

Dose of STP

The mean dose of STP at day 28 from among 23 patients with available data was 60.5mg/kg/day. Dose adjustment to 90mg/kg/day after day 28 was allowed however the sponsor did not provide a mean dose at end of study D84 and calculation

Seizure Reduction

The sponsor reports (ISE) a mean change from baseline seizure frequency for 20 Dravet syndrome patients with data available at treatment day 28 of (-65%). There were also 16 of 20 (80%) positive responders (patients with ≥ 50% reduction over baseline Sz frequency). A seizure frequency reduction at D84 is not provided by the sponsor and could not be calculated using data in the QS.xpt dataset. As noted in the above summary there were 6 patients who achieved seizure freedom at day 28. This was confirmed by the reviewer from the QS.xpt dataset. The age of these 6 patients was examined. The exam revealed that 4 of the 6 patients were less than age 6. This age range is the interval of most severe seizure frequency in Dravet syndrome. The remaining two patients were 7.5 years and 11.2 years old. By contrast, the 50% responder rate was low (25-30%) in the non-Dravet patients.

Clobazam (CLB) Concomitant Treatment

The reviewer performs an analysis of mean CLB concentration at visit day D28 and D84, visit day 28 days and end of study respectively. The group mean trough CLB concentration at the D28 visit for 19 available patients is 0.358 ug/ml while the mean concentration for data available from 14 patients at end of study is 0.27 ug/ml.

Reviewer Comment: The seizure reduction data from the STEV study data are in alignment with the findings in the STICLO France pivotal trial. The CLB trough levels at D28 are somewhat higher than the end of study values from the STICLO France and Italy end of study values. Although concordant with the STICLO study results this study does not allow differentiation of STP augmented CLB level as the basis for seizure reduction from an independent treatment benefit of STP.

STP-1 Study

Study Summary

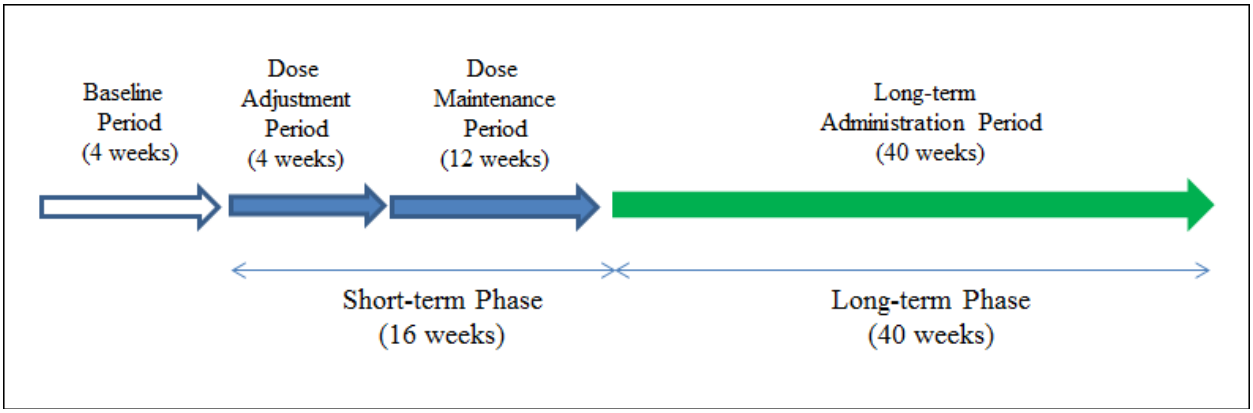
This study was conducted at 11 centers across Japan from May 2010 to January 2012. The study had a 4-week baseline, 4 week STP dose adjustment and 12-week maintenance phase where STP was added to background CLB, VPA and optional bromide in STP naive patients. There was a long term 40-week extension period after the dose maintenance phase. The pre-existing background treatment of CLB and VPA that had been increased to maximum tolerated dose of 0.5mg/kg/day CLB and 30mg/kg/day VPA where bromide (Br) could also be administered. Background AEDs were stable for 4 weeks. In this study, unlike the STICLO studies, there was a dose adjustment period for STP. During the first 4 weeks of STP treatment (dose adjustment period), the initial dose of 20 mg/kg/day of STP was gradually increased by 10 mg/kg/day every week up to a maximally tolerated dose or up to 50 mg/kg/day, whichever came first. Following the dose adjustment period, patients were treated at their best dose for 12 weeks (maintenance period). Seizure frequency was evaluated at the 3rd interval of the maintenance period (4 weeks) compared to baseline. There were 24 patients in the treatment population

divided into two groups by age. Group 1 patients were age 1 to 18 years and group 2 patients age 19 to 30 years. A third analysis group 3 of 6 patients already on ongoing STP treatment entered the STP-1 study for the long term component of the study, at end of maintenance period. These patients did not contribute to the 12-week experimental STP maintenance period examined for efficacy. The sponsor defined efficacy outcome for this study was a non-inferiority design to compare the lower bound confidence (CI) of the Group 1 responder rate (50% ≤seizure reduction over baseline) to the STICLO France and Italy mean placebo responder rate of 6.5%. Group 1 had a point estimate 65% reduction over baseline (13/20, 95% CI: 40.8-84.6%). By this measure the study was successful outcome for STP treatment.

A total sample size of 30 in this study is reported due to the 3rd group of 6 patients who entered a long-term extension of STP-1 after the maintenance period. The extension period is not included in this presentation.

STP- 1 Trial Design

Figure 17 STP-1 Trial Design Timelines



STP-1 Demographic Characteristics

Examination of STP-1 Group 1 and 2 demographic characteristics reveals a larger proportion of males than females, with a mean age of 8.9 years and range of 1.3 to 24.6 yrs. Seventeen patients (71%) had testing for SCN1A mutation. A positive SCN1A mutation was identified in 94.1% of group 1 & 2 patients who had testing performed while 1 patient tested was mutation negative. Disease duration had a mean and median of 8.4 and 5.0 years respectively while the predominant seizure type was tonic-clonic events, .

Table 29 Study STP-1 Demographic Characteristics*

Demographic Characteristic	Group 1&2 N=24
Sex	
Males	15 (62.5 %)
Females	9 (37.5 %)
Age	
Mean ± SD	8.9 ± 7.6
Min – Max	1.3 – 24.6
Age Group	
< 1	0 (0.0%)
1 to < 6	14 (58.3%)
6 to < 12	4 (16.7%)
12 to < 17	1 (4.2%)
>= 17	5 (20.8%)
Weight (kg)	
n	24
Mean ± SD	25.3 ± 14.6
Min – Max	10.0 – 54.6
SCN1A mutation (n, %)	
Mutation	16/17 (94.1%)
No mutation	1/17 (5.9%)
Not done/unknown	7
Disease Duration (years)	
n	24
Mean ± SD	8.4 ± 7.6
Median	5.0
Min – Max	0.9 – 24.1
Seizure Type (n, %)	
Generalized Seizures	8 (33.3%)
Clonic	21 (87.5%)
Tonic-Clonic	5 (20.8%)
Myoclonic	5 (20.8%)
Unspecified generalized seizure	
Number of tonic-clonic or clonic seizures during baseline (/month)	
n	24
Mean ± SD	17 ± 30.7
Median	10.1
Min – Max	4.6 – 158
CYP2C19 Genotype(n, %)	20 (83.3%)
Extensive metabolizer	
Poor metabolizer	4 (16.7%)
Daily Dose CLB (mg/kg/day) at baseline	24
n	
Mean ± SD	0.4 ± 0.2
Min – Max	0.1 – 0.8
Daily Dose VPA (mg/kg/day) at baseline	
n	24

Mean ± SD	26.6 ± 8.9
Min – Max	8.8 – 40.8
Daily Dose Bromides (mg/kg/day) at baseline	
n	14
Mean ± SD	38.4 ± 13.3
Min – Max	12.1 – 59.0
*From sponsor ISE, table 3-15, ISE page 59	

Withdrawals and Discontinuations

No patients withdrew during the maintenance phase of STP-1

Dose of STP

The mean dose of STP in groups 1 &2 during the maintenance phase was 47.8 mg/kg/day with a median of 48.9mg/kg/day and a range of 41.2 to 53.5mg/kg/day.

Efficacy Results

Table 30 STP-1 Efficacy Results, Change in Seizure Frequency Compared to Baseline, Responder Rate*

	Group 1&2 N=24
Percentage Change from baseline in seizure frequency	
n	24
Mean ± SD	-57 ± 30.9
Median	-60.0
Min - Max	-100 – 0.0
Responder analysis*	
Responder/total number	16/24
(%)	(66.7%)
95% CI	47.8 – 85.5
*50% ≤seizure reduction over baseline	

Table 31 STP-1 Study, Baseline and End of Treatment CLB, NCLB and VPA levels

AED	**Baseline**	**End of Treatment**
CLB (mg/L)		
n	20	20
Mean ± SD	0.109 ± 0.073	0.187± 0.165
Min - Max	0.014 – 0.275	0.023 – 0.631
NCLB (mg/L)		

n	20	20
Mean ± SD	1.091 ± 1.938	2.667 ± 1.986
Min – Max	0.062 – 8.010	0.346 – 7.360
VPA (mg/L)		
n	24	22
Mean ± SD	66.40 ± 30.17	70.37 ± 28.90
Min – Max	21.10 – 133.1	14.70 – 128.4

Reviewer Comment: The STP-1 study reveals improvement in seizure frequency during STP treatment over baseline. Although not stated explicitly in the protocol the study endpoint had a non-inferiority type design where success was considered if the lower bound of the responder rate 95% CI was greater than the pooled STICLO France and Italy placebo responder rate of 6.5%. The study was successful on that basis with a lower bound CI of 40.8% for Group 1 (1-18 years old), and 19.4% for group 2 (age 19-30 years). The study did not have a parallel control group with efficacy based only on comparison to baseline. The study was also intended to have patients on maximum tolerate clobazam prior to start of STP treatment, however the group mean baseline CLB level is lower than the STICLO France (0.182mg/L) and STICLO Italy (0.279mg/L). There were insufficient SCN1A mutation negative patients to examine the treatment response difference between mutation positive and mutation negative groups. In conclusion, the study shows alignment with the pivotal STICLO study but also does not allow differentiation of STP augmented CLB level as the basis for seizure reduction from an independent treatment benefit of STP.

Laux Retrospective Chart Review

The most pressing concern in the assessment of STP efficacy is differentiating the DDI interaction that increases CLB and NCLB levels when STP is introduced. This interaction raises the possibility that an augmented CLB effect rather than independent STP effect may account for the benefit seen in STP therapy. No prospective study of STP alone is available to inform this possibility.

The Laux study is a retrospective chart review that contains documentation of seven rare Dravet syndrome patients that do not have ongoing treatment with CLB at the time STP is added to their therapeutic regimen.

In the US, Dravet syndrome patients have been treated with STP (b) (4) (b) (4) since 2002. The charts of 130 consecutive Dravet syndrome patients (b) (4) from 2002 to 2012 were reviewed. To be eligible for STP treatment, patients had to have a diagnosis of Dravet syndrome, to present with seizures despite optimized antiepileptic treatment, to present with severe Dravet syndrome and to be able to afford STP. A total 31 of these 130 (22%) patients were found to have been eligible and advised to start treatment with STP; 29 started on STP

and were followed up for 3 to 12 months, the remaining 2 patients who were advised to start STP treatment were lost to follow up and it is unknown whether they started STP treatment or not, but further information is lacking. Thus, a total of 29 patients with Dravet syndrome treated with STP are included in the chart review. Only the results of the first 3-12 months of treatment with STP are included in this analysis.

Three groups of patients were identified according to the treatment they received before STP initiation:

- Group 1 (N=16): treated with AEDs and CLB; patients in this group were first subjected to an upward titration of the CLB dose, until no further efficacy was observed, or until dose-limiting adverse events (AEs) were observed, or until 3-times the therapeutic dose was reached, whichever came first; 14 of these 16 patients experienced severe sedation (lethargy) at the highest CLB reached prior to STP treatment;

- Group 2 (N=6): treated with AEDs and CLB: patients in this group were not subjected to an upward titration of CLB; and

- Group 3 (N=7): treated with AEDs but not with CLB.

Information on patient response to STP (number of seizures; number of episodes of status epilepticus) was collected in the patient medical record at the time of each visit and was extracted from the hospital records for this analysis. Patient diaries were not used; the investigator questioned the parents on seizure frequency since the last visit.

The initial dose of STP was 15 mg/kg/day (in 2 divided doses) for patients weighing less than 20 kg, titrated up by weekly increments of 15 mg/kg/day, up to maximum efficacy or to AEs or to 100 mg/kg/day, whichever came first. Table 32 summarizes by treatment group the number and percentage of patients on a given final dose range of STP. Final dose was the best dose following initial upward titration of STP dose.

Table 32 Laux Chart Review, Final STP Dose Range by Treatment Group in 29 Dravet Syndrome Patients *

Final Dose of STP (mg/kg/day)	Number (%) of Patients		
	Treated with CLB (N=22)		
	Group 1 Titrated Up to Maximum Dose of CLB (N=16)	Group 2 Not Titrated Up to Maximum Dose of CLB (N=6)	Group 3 Not Treated with CLB (N=7)
10 to <30	6 (38%)	3 (50%)	0 (0%)
30 to <50	5 (31%)	3 (50%)	3 (43%)

50 to 100	5 (31%)	0 (0%)	4 (57%)
* from Sponsor ISE, Table 3-36, P79			

Individual characteristics of the 7 group 3 patients reveal that 4 patients are age 5 years or below. Three of these 4 patients had a greater than 50% reported response to STP treatment. One 5 year old patient was treated with an STP dose > 50mg/kg/day. These 4 patients are of special interest because they are in the age range of highest seizure frequency usually observe in the natural history of Dravet syndrome, see Table 33.

Table 33 Group 3 Patient Characteristic Listing with Age, Concomitant AED, STP Dose and Observed Seizure Reduction*

Patient ID	Age	Current AED	STP dose (mg/kg/day)	Efficacy (percent reduction in Seizure frequency)
(b) (6)		VPA, AZM	50	<50% GTC, HC
		FBM, CZP, VNS	50	>50% GTC
		KD, VNS	62	>50% Partial, Absence >90% GTC
		VPA	33	>50% GTC
		KD	35	>50% GTC, Partial
		VPA, TPM, ESM	42	>50% Partial M, A >90% GTC
		VPA	80	<50% GTC
AED & Seizure type abbreviation key: GTC=generalized tonic-clonic; HC=hemi-clonic; VPA=valproate; TPM=topiramate; FBM=felbamate; ESM=ethosuximide; AZM=acetazolamide; CZP=clorazepate; VNS=vagal nerve stimulation; KD=ketogenic diet.				
*From sponsor Laux report, table 9-6, page 28				

Overall response to STP treatment was assessed by questioning parents at each medical visit (note; study is based on ongoing medical care). Patients judged to have a ≥ 50% reduction in seizure frequency were considered responders. Results are shown in Table 34.

Table 34 Reduction in Seizure Frequency by Treatment group in 29 Dravet Syndrome Patients (Laux Chart Review)*

Reduction in Seizure Frequency		Treated with CLB (N=22)		Group 3 Not Treated with CLB (N=7)
		Group 1 Titrated Up to Maximum Dose of CLB (N=16)	Group 2 Not Titrated Up to Maximum Dose of CLB (N=6)	
Non-Responder	<50%	4 (25%)	2 (33%)	2 (29%)
Responder	>50% and < 90%	6 (38%)	1 (17%)	3 (43%)

	≥90%	6 (38%)	3 (50%)	2 (29%)
* sponsor ISE, table 3-39, p 81				

Reviewer Comment: This study has multiple limitations. It is based on a retrospective review of data from medical care charts and the assessment of seizure frequency was based on questioning of caregivers without attempted quantitative capture of seizure frequency from real time diaries. In addition, the duration of treatment before patients achieved the reported seizure reduction is not provided. The investigator only indicates the first 3 – 12 months of treatment with STP are included in the report. The contribution of this data is the observation of seizure frequency reduction in 7 patients who were not on concomitant CLB treatment. The overall group of 7 had a 72% response rate while three of 4 patients who were age 5 or under had a greater than 50% response. Although anecdotal, the observations in this report do not contradict the potential that an independent therapeutic effect of STP present in the treatment of seizures in Dravet syndrome.

Sponsor Covariate Analysis

To examine the influence of CLB and NCLB on the treatment effect seen in the STICLO studies the sponsor performed a covariate adjusted analysis. This analysis is 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 C_{min} concentrations of CLB and NCLB are used as covariates or potential contributing factors in the analysis with the logistic model used to calculate the odds ratio as well as the p-values that establish the contribution of each factor (STP-PBO treatment difference and covariates). CLB and NCLB covariates were examined individually and again as combined covariates for the STICLO studies.

Analysis of Change in Plasma CLB Baseline to Treatment as Covariate

Analysis of the data using logistic model after adjusting for the change of plasma concentration of CLB shows a significant treatment effect is retained when accounting for the clobazam as covariate and the contribution of the covariate (CLB) does not have significance. The results for STICLO France, STICLO Italy and both studies pooled all have similar results for the STP -PBO treatment difference and the CLB effect as covariate, Table 35.

Table 35 STP – PBO Treatment Difference Adjusted for CLB as Covariate, Covariate Significance and STP:PBO Odds Ratio*

	P -value		
Study	**Treatment Difference**	**Covariate**	**Odds Ratio (STP : PLB)**
STICLO - France and Italy	0.0002	0.4777	23.83
STICLO - France	0.0028	0.8835	39.95
STICLO - Italy	0.0225	0.344	16.88
* from sponsor, "Stiripentol Project", prepared (b) (4), Table 5-2, page 9			

Analysis of Change in Plasma NCLB Baseline to Treatment as Covariate

Analysis of the data using logistic model after adjusting for NCLB plasma concentration shows a significant treatment effect is retained when accounting for the clobazam as covariate and the contribution of CLB does not show significance for STICLO France and STICLO France - Italy pooled. The p value for the STICLO Italy treatment difference moves just outside of the significance threshold. The contribution of the CLB covariate does not reach significance for STICLO Italy while the Odds ratio remains strongly in favor of STP treatment benefit for STICLO Italy, Table 36.

Table 36 STP – PBO Treatment Difference Adjusted for NCLB as Covariate, Covariate Significance and STP:PBO Odds Ratio*

	P -value		
Study	**Treatment Difference**	**Covariate**	**Odds Ratio (STP : PLB)**
STICLO - France and Italy	0.004	0.6141	19.79
STICLO - France	0.0345	0.3199	17.61
STICLO - Italy	0.0573	0.6938	28.62
* from sponsor, "Stiripentol Project", prepared (b) (4), Table 5-3, page 9			

Analysis of Change in Plasma CLB and NCLB Baseline to Treatment as Combined Covariates

Analysis of the data using logistic model after adjusting for both CLB and NCLB plasma concentrations in one model shows a significant treatment effect is retained when accounting for clobazam and norclobazam together as covariates and the contribution of both covariates (CLB & NCLB) do not have significance for STICLO France and STICLO France - Italy pooled. The p value for the STICLO Italy treatment difference moves just outside of the significance threshold. The contribution of CLB and NCLB do not reach significance for STICLO Italy while the Odds ratio remains strongly in favor of STP treatment benefit, Table 37.

Table 37 STP – PBO Treatment Difference Adjusted for CLB and NCLB as Combined Covariates, Covariate Significance and STP:PBO Odds Ratio

	p- value			
Study	**Treatment Difference**	**CLB**	**NCLB**	**Odds Ratio (STP : PLB)**
STICLO France and Italy	0.0055	0.5038	0.6628	18.17
STICLO - France	0.0308	0.6152	0.2722	20.01
STICLO - Italy	0.0584	0.3496	0.6808	28.00
* from sponsor, "Stiripentol Project", prepared (b) (4), Table 5-4, page 10				

A summary of the odds ratios and associated confidence intervals is provided in Table 38. The results point to a retained STP-PBO treatment effect as the upward shifting, confounding influence, of CLB and NCLB levels as covariates are introduced. The odds ratios do not shift rapidly toward 1 as the CLB and NCLB covariates are introduced into the examination. The minimum ratio of 17 is seen for STICLO Italy adjusted for CLB. The lower bound confidence intervals remain > 1 for covariate analysis of STICLO France and the pooled STICLO France – Italy examination, although the STICLO Italy lower bound CI for NCLB and combined CLB/NCLB covariate adjustment drops below 1.0.

Table 38 Summary of odds ratios and 95% Confidence Intervals, adjusted for the Impact of CLB and NCLB*

	STICLO (France and Italy) Odds (95% CI)	**STICLO France Odds (95% CI)**	**STICLO Italy Odds (95% CI)**
Adjusted for CLB	23.8 (4.53 - 125.42)	39.9 (3.56 - 448.45)	16.9 (1.49 - 191.46)
Adjusted for NCLB	19.8 (2.59 - 151.54)	17.6 (1.23 - 251.77)	28.6 (0.90 - 909.40)
Adjusted for CLB & NCLB	18.2 (2.34 - 141.04)	20.0 (1.32 - 303.33)	28 (0.89 - 883.02)
* from sponsor, "Stiripentol Project", prepared (b) (4), Table 5-5, page 10			

Reviewer Comment: This analysis to examine the effect of CLB and NCLB on the stiripentol treatment difference (STP-PBO) supports a conclusion that STP has an antiepilepsy benefit that is independent of the augmentation of CLB and NCLB levels induced during stiripentol treatment. However, this analysis has the shortcoming that it is a post-hoc analysis not designed on a prespecified basis to test the significance of STP and CLB/NCLB separation. The method is not necessarily powered to detect significance of CLB, NCLB or CLB-NCLB effect.

While this analysis cannot prove an independent STP antiepilepsy effect it does not directly contradict independent STP effect that would manifest as no significant treatment difference, significant covariate effects of CLB and NCLB and a more rapid shift of odds ratios toward 1.0 with the introduction of the CLB and NCLB covariates.

Long Term Open Label Studies, TAU-EAP, STILON, DIAVEY (post marketing)

These studies are primarily directed at acquisition of safety data; however, seizure frequency data was also captured in a format consistent with medical care rather than in more exacting clinical trial methodology. The DIAVEY and STILON studies had cohorts of both DS and non-DS patients that offer the opportunity to compare discontinuations due to lack of efficacy and seizure frequency. The STILON study is found to have seizure frequency entries at baseline and again after, on average, 2.8 years. Due to the long interval between capture of seizure frequency this data is not examined further in the STILON study. Variables such as the natural history of disease may intervene and have a large effect on the seizure frequency at time number 2.

TAU-EAP

Discontinuations, Lack of Efficacy

In the TAU-EAP cohort there were 7 (3%) discontinuations for lack of efficacy. The mean and median study day of discontinuation were 581 and 560 respectively with a minimum of 115 days.

Figure 18 TAU-EAP, Distribution of Standardized Disposition Terms

Disposition Term	# Patients
ADVERSE EVENT	3
COMPLETED	190
DEATH	5
LACK OF EFFICACY	7
OTHER	4
STATUS EPILEPTIC	1

Seizure frequency

Figure 19 TAU-EAP Seizure Frequency Compared to Baseline from Among 55 patients with Baseline (preinclusion day -1) and 6, 12 and 18 month Follow up Visits

Month of follow up	Median % Reduction seizure frequency, Tonic – Clonic Seizures	N remaining in group *
6	-4.17	36
12	0	29
18	-16.67	23
* proportion of cohort with a baseline and 6month, 12 month and 18 month follow up seizure frequency value.		

STILON

In the DS group there were 6 (13%) patients discontinued for lack of efficacy while in the non-DS cohort there were 18 (16%) patients discontinued for lack of efficacy. The DS mean and median study day of discontinuation were 283 and 542 respectively with a minimum of 92 days. The non-DS mean and median study day of discontinuation were 660 and 598 respectively with a minimum of 239.

DIAVEY

The DIAVEY protocol indicates the Primary objective of the survey states: "To proactively collect Adverse Drug Reactions (ADRs) and safety information for patients newly prescribed DIACOMIT® for the treatment of Severe Myoclonic Epilepsy in Infancy (SMEI).". The secondary objective is stated: "To proactively collect ADRs and safety information for patients newly prescribed DIACOMIT® for the treatment of any other epilepsy". Because seizure frequency is not identified as an objective of the DIAVEY post marketing survey the seizure frequency results will not be presented to add support for efficacy but rather to examine the dataset for evidence of STP efficacy durability.

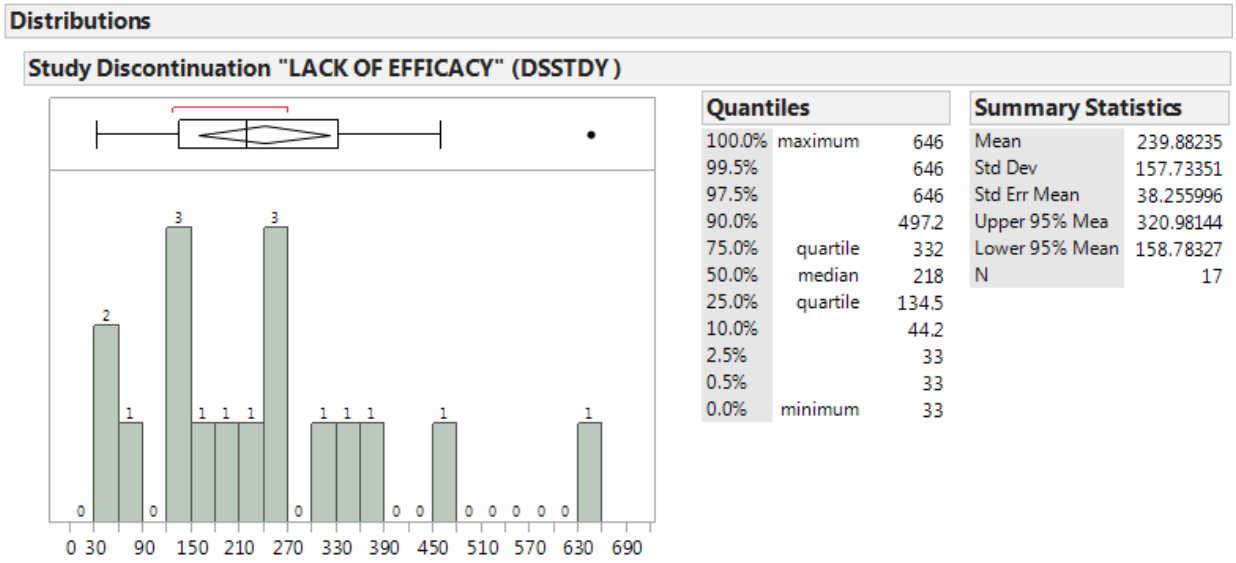
Patients who enrolled in the DIAVEY study were evaluated yearly for a target duration of five years. The frequency of discontinuation for lack of efficacy will be examined in addition to seizure frequency per month entries during the course of the study. It is noted that examination of the protocol the reviewer did not identify the methodology used for patients to keep track of their seizure frequency such as a seizure diary. However, a field for seizure frequency per months is present in the CRF for each follow up visit.

Discontinuations

DIAVEY discontinuations among Dravet patient's due to are examined. There were 111 patients (73%) identified as completers, 20 (13%) patients identified as discontinued due to lack of efficacy and 21 (14%) patients discontinued due to adverse events including 4 deaths. Three deaths were due to SUDEP while 1 was unrelated to treatment.

The cohort of completer patients had a mean and median study participation of 805 and 733 days respectively with a minimum of 110 days and a maximum of 1576 days. The cohort of patients discontinued due to lack of efficacy had a mean and median study participation of 285 and 233 days respectively with a minimum of 33 days and a maximum of 1058 days.

Figure 20 DIAVEY, Dravet Patients, Distribution of Discontinuations due to Lack of Efficacy. Patient DIAVEY-NL-226 excluded where study day = 1058 for better view of distribution.



As a comparator, discontinuations in the non-DS patient cohort of the DIAVEY study due to "Lack of efficacy" are examined. In this group 30% of patients discontinued. The mean and median day of discontinuation were 240 and 218 respectively with a minimum of 10 days.

Seizure frequency, Tonic-Clonic in Dravet syndrome

Follow-up visit 2 and 4 are examined

At follow up visit 2, there were 79 patients with a baseline and follow up # 2 seizure frequency entry. The mean and median study day were 249 and 200 respectively. There were 44 (56%) patients who retained a reduction in seizure frequency, 12 (15%) patients with no change and 22 (29%) patients with an increase in seizure frequency ranging from 14% to 900%. The median percent seizure reduction for the group of 79 patients was 30%.

At follow up visit number 3 there were 60 patients with a baseline and follow up seizure frequency entry. 35 (58%) patients retained a reduction in seizure frequency while 7 (11.6%) patients had no change from baseline and 18 (30%) patients had an increase in frequency over baseline. The range of seizure increase was from 18 to 2900%. There were three extreme outliers who had a 29x, 15x and 11x increase in frequency respectively. The patient with 29 x increase had 1 seizure per month at baseline and 30 at follow up 3. All the outlier patients were less than 3 years of age. The median percent reduction for the group of 60 patients was 39%.

The mean and median duration of treatment at follow up number 3 were 369 and 304 days respectively.

Reviewer Comment: Entries for lack of efficacy in the three long term open label studies are examined. In the TAU-EAP study 3% of patients are reported to have discontinued due to lack of efficacy. In the STILON study DS group 13% of patients discontinued due to lack of efficacy while in the non-DS cohort 16% of patients discontinued due to lack of efficacy. In the DIAVEY study 13% of patient discontinued due to lack of efficacy in the DS group compared to 30% in the non-DS cohort. There is a trend toward a higher frequency of discontinuation due to lack of efficacy in the non-DS cohorts that supports the early observation in the STEV study where there was a selective benefit in Dravet syndrome.

Exploratory Efficacy Study, Lennox-Gastaut Syndrome (LGS)

LGS (year 1989)

This was a single-blind, multicenter trial of STP in combination with standard treatment in 24 patients, 16 with Lennox-Gastaut syndrome and 8 with symptomatic generalized epilepsy of the Lennox-Gastaut type. The trial was conducted at 4 centers in France, from January 1989 to August 1993. To be enrolled, patients were required to be between 2 and 20 years of age, and to have at least 1 seizure per week despite optimized antiepileptic treatment (no more than 3 concomitant AEDs). Mean age at enrollment was 8.6 years. Upon enrollment, patients were subjected to a 1-month baseline period during which they continued on their AEDs, followed by a 1-month placebo run-in, followed by a 2-month treatment period with STP (dose adjusted to body weight, but no more than 3,000 mg/day). Patient baseline (with PBO run in) was compared to month 2 of STP treatment. There was no PBO arm. Two patients were considered non-evaluable: 1 patient with Lennox-Gastaut was withdrawn for AEs (anorexia, vomiting, loss of equilibrium, sleepiness) after beginning treatment with STP and 1 patient with symptomatic generalized epilepsy began treatment with STP during the baseline period (i.e., during the placebo run-in).

There were 15 evaluable patients with Lennox-Gastaut syndrome. The study report indicates that seizure count included tonic-clonic, absence, seizures with falls and sleep seizures. The unit of time for the reported seizure count is not provided. It is unclear if the time period is per week, month or the entire STP treatment interval. The overall results identified some benefit for LGS where 60% of patients were responders (based on 50% responder rate). There was a mean +62% seizure reduction (actual mean increases due to a single very large outlier) and median -80% reduction from baseline.

CLB analysis: Clobazam (CLB) was identified as a concomitant medication. Not all patients were treated with CLB. The reviewer performed and analysis from the seizure frequency result table

and concomitant medication table. Seizure reduction was examined by presence / absence of CLB. The 50% responder rate was 71% among the 7 patients not on CLB and 50% among the 8 patients on concomitant CLB. The median percent seizure reduction from baseline was -80% among the 7 patients not on CLB and -64% among those 8 who were on concomitant CLB.

Table 39 LGS Study, Responder rate by Concomitant Clobazam (CLB) Based on % reduction from baseline PBO run in period

CLB	Responder	# Patients	% of Group
NO	NO	2	28.6
NO	YES	5	71.4
YES	NO	4	50
YES	YES	4	50

Table 40 LGS Study Mean and Median % Seizure reduction by Concomitant Clobazam (CLB)

		Baseline to end of 60 day STP treatment	
CLB	# Patients	Mean % Reduction	Median % Reduction
NO	7	-66.0	-80.3
YES	8	174.9*	-64.5

*Influence by an outlier patient with seizure frequency of 11 at end of PBO run in and count of 209 at end of 2 month STP treatment. Baseline frequency was 203 (prior to PBO run in)

Reviewer Comment: This legacy study with a small sample of LGS patients reveals a larger 50% responder rate among patients not treated with concomitant CLB. Interpretation of this result is clouded by the inclusion of 3 LGS seizure types as well as “sleep seizures”. A home based count of this broad spectrum of epilepsy events may be difficult to perform accurately. There was also no identified time denominator for the seizure count in the study report, however with these limitations acknowledged this observation hints at an independent STP effect in LGS.

Efficacy Below Age 3 years.

The pivotal studies did not enroll patients below age 3 years. There is no controlled data to explore effectiveness of STP in patients less than age 3 years. There are two open label studies were STP was introduce as an open label treatment. The STEV study where STP was compared to a 4 week baseline PBO treatment period and DIAVEY a post marketing safety study where seizure frequency was followed at each 6 month visit.

The cohort of patients under age 3 years in the STEV study was examined. There were 8 patients with DS. At D28 of the study patients had been treated for 4 weeks with STP 60mg/kg/day. All patients were on clobazam. One of these patients was age 2.6 years while the remaining 7 were under age 2 years. The 2.6 year old patient had a reduction in clonic seizures of -33% at D28. No patient had an increase in seizures. The mean and median percent seizure reduction in the measured seizures were -66% and -55% respectively.

The cohort of patients in the DIAVEY study was examined. Patients were treated with STP 50mg/kg/day. There were 11 patients in the age from 2 years to <3 years who also had a 1st and 2nd visit entry with a seizure count. Eight of these patients have clobazam as a concomitant medication. The mean and median interval from visit 1 to visit 2 were 63 and 46 days respectively. From among these 11 patients there were 6 (55%) with a decline in seizure frequency, 3 (27%) with no change in seizure frequency and 2 with an increase in seizure frequency. The mean and median percent reduction in seizure frequency were +16% and -40% respectively. All patients <3 years of age were examined for change in seizure frequency between visit 1 and visit 2. There were 33 patients with seizure frequency entries for both visits. Eighteen patients had a reduction in seizure frequency while 10 had no change and 4 had an increase. The mean and median change in seizure frequency from visit 1 to visit 2 were -2.6% and -33% respectively.

Reviewer Comment: Overall in the exam of available data from open label study of patients newly introduced to STP treatment reveals the majority of patients had a reduction in seizure frequency.

6.2.2. Considerations on Benefit in the Postmarket Setting

As discussed in section 4.2.3 Stiripentol - Clobazam Interaction, stiripentol was administered with adjunctive use of clobazam and valproic acid in the pivotal study and all studies presented by the sponsor in the NDA submission examined stiripentol in patients treated with concomitant clobazam and valproic acid (b) (4)

(b) (4)

6.2.3. Other Relevant Benefits

At the time of this NDA review there remains an unmet medical need for treatment of Dravet syndrome. There are no approved treatments. The severity of Dravet syndrome epileptic

encephalopathy causes severe disability in some patients where the availability of stiripentol powder for oral suspension (submitted NDA 207223) may provide improved administration over the capsule form in some patients.

6.3. Integrated Assessment of Effectiveness

The indication is supported by two small pivotal trials with large treatment to placebo effect size, performed sequentially, of the same study design, using STP treatment for Dravet Syndrome. These studies had small sample sizes of 41 patients for STICLO France and 23 patients for STICLO Italy. These samples are commensurate with the limitations to recruitment of patients from the small population of this rare disease (see section 2.1). In the case of this rare disease, considered refractory to available therapy, the evidence provided by these two robust studies is acceptable as expressed in the evidence of effectiveness guidance.[42] As shown in the subsequent discussion these pivotal trials revealed benefit with a similar responder rate, in addition the ancillary data is seen to be in alignment with an STP therapeutic benefit. The ancillary data, although open label with additional descriptive information are in alignment with the pivotal trial.

The pivotal STICLO studies were of the same design and included patients with a clinical diagnosis of Dravet syndrome. STICLO France included 41 patients, 21 in the STP treatment arm and 20 in the PBO arm while STICLO Italy include 23 patients, 12 in the STP treatment arm and 11 in the PBO arm. Enrolled patients were age 3 to 18 years of age. Patients entered the study without previous stiripentol (STP) treatment. As a protocol inclusion criterion, patients were on established stable treatment with clobazam (CLB) and sodium valproate (CLB), see "Obligatory" concomitant medications. Patients entered a 1 month baseline interval to capture seizure frequency using a seizure diary. During the 1 month baseline, ongoing dosing of CLB and VPA was assessed with a goal to reduce VPA dose to 15mg/kg/day. This goal was modified, by protocol, after enrollment of 20 patient's due to adverse effect of increase in seizure frequency (during baseline) after rapid VPA dose reduction in those patients who had been treated in the high dose range of 30 to 40mg/kg/day at start of baseline interval.

At conclusion of the 1 month baseline interval patients were randomized to add STP at a dose of 50mg/kg/day, without titration, or an identical appearing placebo to ongoing VPA and CLB treatment. After randomization patients enter an 8-week double blind experimental interval. Patients had an onsite evaluation at start of the double-blind period, a telephone call assessment with capture of seizure frequency at approximately day 30, and a final study site

[42] Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. May 1998. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf

visit at approximately day 60 of STP treatment.

The STICLO study prespecified outcome endpoint was responder rate. A responder is identified by a decrease in the number of generalized clonic or tonic-clonic seizures during month 2, on a 30-day basis by >50%, see STICLO primary endpoint (although criteria define non-responders as cases that do not count as responders). At end of the 8 week double blind experimental interval the STICLO France pivotal study the STP treatment arm had 15 (71%) responders while in the PBO arm there was 1 (5%) responder while the STICLO Italy study the STP treatment arm had 8 (66.7%) responders while in the PBO arm there was 1 (9.1%) responder. The difference in both studies was statistically significant, see Table 17.

The Biometrics review team identified an issue in the STICLO study protocol. This was due to a planned interim analysis for sample size assessment of STICLO studies, see "STICLO Studies Interim Analysis" and the Biometrics review. Unless examined with the most conservative assumption of a hypothetical interim analysis (not scheduled at the 20% information threshold), STICLO Italy is a significant pivotal study.

The beneficial effect of stiripentol in both STICLO studies was achieved when used in combination with clobazam and sodium valproate concomitant treatment. This feature is identified clearly in the "Study Objective and Method" in the STICLO France protocol and the stated objective of the STICLO Italy study report where it is stated that "The objective of this study is to demonstrate the efficacy of stiripentol combined with clobazam and with sodium valproate in patients with SMEI and severe and resistant clonic seizures." As noted in section 5.3.2, "Stiripentol – Clobazam Interaction" the Cmax and AUC of clobazam are significantly increased by the addition of stiripentol. This creates the possibility the beneficial effect of stiripentol may be due to augmentation of clobazam concentration. In addition, although the increase in sodium valproate is much less than CLB, some additional, perhaps pharmacodynamic effect of sodium valproate could contribute to the benefit of stiripentol across all studies where clobazam and sodium valproate have been administered concomitantly with stiripentol.

As discussed in section 4.2.3 Stiripentol – Clobazam Interaction, a successful approach for confirming an independent antiepilepsy effect of stiripentol in Dravet syndrome has not been established. The benefit of stiripentol may rely on augmentation of clobazam and norclobazam levels or a pharmacodynamic effect of CLB, VPA and STP working together or a combination of both. There is little data in the submission where STP treated patients are not administered concomitant CLB. There is a retrospective chart review, from a medical care setting, where 7 patients with DS are identified who were treated without concomitant CLB. Five (71%) of these patients had a notable benefit from STP. Two patients had a >90% reduction in generalized tonic-clonic seizures in addition to a >50% reduction in partial and absence seizures while 3 of the remaining responders had a >50% reduction in generalized tonic-clonic seizures or partial

seizures. Two of 7 patients did not achieve a > 50% reduction in seizure frequency.

There is a plausible indication that STP may be selectively beneficial for treatment of DS. The pooled STICLO France and Italy responder rate of STP treated patients compared by SCN1A mutation positive or mutation negative status is examined. The SCN1A mutation positive STP treated patients (total n= 23) had a 74% responder rate compared to a 33% responder rate in the SCN1A mutation negative group (total n=6). The overall patient group is small with an even smaller SCN1A negative comparator but the observation is in alignment with the early findings in the STEV study where a disproportionally greater benefit of STP was seen in DS patients compared to the overall population of patients with other forms of epilepsy. If confirmed, such a selective STP mechanism, would suggest a treatment benefit that is independent of concomitant CLB and VPA.

In the STEV study a total of 233 patients were enrolled, 227 received at least one dose of STP, and 157 completed the trial. Among the 233 children enrolled, 24 had Dravet syndrome. Twenty-one of these patients have a concomitant clobazam level recorded in the dataset. The 50% responder rate of Dravet syndrome patients was notably higher at 80% than non-Dravet patients where it was seen to be 25% to 30%.

The 24 patients new to STP treatment of groups 1 and 2 of the STP-1 study reveals a 50% responder rate of 67%. There was no parallel PBO arm in this study. Responder rate was calculated by comparison of patient baseline seizure frequency to the 3rd month of the (3 month) experimental observation interval.

The long term open label safety studies of STP were the TAU-EAP, STILON and DIAVEY studies. The TAU-EAP enrolled only DS patients while STILON and DIAVEY (post-marketing) enrolled both DS and non-DS patients on STP treatment. In the TAU-EAP study 3% of patients are reported to have discontinued due to lack of efficacy. In the STILON study DS group 13% of patients discontinued due to lack of efficacy while in the non-DS cohort 16% of patients discontinued due to lack of efficacy. In the DIAVEY study 13% of patient discontinued due to lack of efficacy in the DS group compared to 30% in the non-DS cohort. Discontinuation due to lack of efficacy was generally less frequency in DS than non-DS patient cohorts. These are additional findings that are observational and descriptive across the STP-1, STEV, the open label extension studies and the post-marketing study that are in alignment with an STP benefit for treatment of DS, again in concert with CLB and VPA treatment.

Examination of the available data for DS patients in the age range from 2 to <3 years in the STEV and DIAVEY studies reveals the majority of patients have a reduction in seizure frequency. There is no evidence of a sharp change in effect below age 3 years. This observation suggests that treatment of DS at age 2 years, the generally recognized age of DS diagnosis is acceptable.

The responder rate identified with STP treatment in this refractory epilepsy syndrome as well as continuation of large proportion of patients in the extension studies indicates the treatment benefit is clinically meaningful. In addition, there were many instances of patients remaining on STP treatment due to the observed reduction of seizure frequency, although there were challenging adverse events.

The evidence presented in labeling should be the STICLO study responder rates. Responder rate was the prespecified outcome endpoint of the STICLO protocols. Acceptance of this endpoint was not declined by DNP. Pooled STICLO France and Italy should not be placed in labeling. Pooling was not prespecified.

7 Review of Safety

7.1. Safety Review Approach

See section 7.2 below

7.2. Review of the Safety Database

The methodology to analyze safety data across the entire NDA package of 20 clinical studies is not uniform due to differences in safety data format available across the panel of studies. From among the category 1, 2 or 3 studies (see safety study key, Table 41) patients have data entries in SAS (xpt) transport files available and there can be independent counts of deaths, serious adverse events, discontinuations and common adverse events as well as examination of relationships between variables. Adverse event entries for these patients are coded to MedDRA version 19.0. Safety signal analysis may be performed to examine for overall frequency of events as well as by age, duration of treatment, seizure worsening, event term splitting, and close inspection of significant adverse events. In the remaining categories, 4 and 5 conclusions are based on ISS and study report presentation.

The study categories identified in Table 4, list of clinical studies, will be referenced in the safety review subsections to keep track of data provided by each study type that is relevant to the subsection, for example; SAEs (7.4.2) and discontinuations (7.4.3),

Characteristics of Individual Safety Data Sources

Studies with parallel adjunctive placebo and STP treatment arms, identified as category 1, allow a controlled comparison of adverse effects are the STICLO trials. However, these studies

comprise a small population “n” of 64 patients, thus placebo comparison is limited. In total, the STICLO studies were composed of 31 placebo arm patients and 33 patients in the STP treatment arm.

The next categories to consider are the non-pivotal studies of only Dravet syndrome patients where xpt datasets for independent analysis are provided. These are labeled “category 2”. These include STIPOP, a Pk study of STP where the majority of exposures are only one day but 7 patients had exposures ranging from 7 to 28 days. The second category 2 study is STP-1, a Japanese study that enrolled 30 patients in short term and open label extension treatment to examine efficacy, safety and pharmacokinetics of continuous administration of STP. The mean and median exposure in this study was 341 and 390 days respectively. The final category 2 study of DS only patients was TAU-EAP. The key descriptor of this study is the acronym “TAU” for Temporary Authorization for Use. This study allowed the medicinal product to be used prior to the obtaining an MA (medical authorization in the EU) for STP. This was a multicenter clinical trial conducted at 77 sites in France. Dravet syndrome patients were enrolled in TAU-EAP for long term open label treatment to document safety. There were 272 patients enrolled in TAU-EAP with 210 patients who entered STP treatment. The mean and median exposure was 2.5 and 2.6 years respectively. Patients in TAU-EAP could enter from other follow up studies of STP in Dravet syndrome. Of the 210 STP treated patients, 103 were previously treated with STP. Thirty-four of these 103 patients had participated in other Biocodex-sponsored studies. These studies include STEV, STICLO and STILON while the remaining 69 patients had been treated with STP on a compassionate use basis. These 34 patients were not identified in datasets, thus when adverse event date is identified, the full duration of the STP treatment timeline does not include the portion from previous studies.

The next group of studies are termed as category 3 by the reviewer. These were long term open label studies with both DS and non-DS patients. This grouping includes the STEV, STILON and DIAVEY studies. The STEV study was a controlled trial where seizure frequency during a 28 day baseline placebo interval was compared to seizure frequency during a 60 day STP treatment interval. This study included a spectrum of epilepsy patients including a small number with DS (25 patients). Only the 25 DS patients have SAS transport (xpt datasets) included in the application to allow independent analysis while the safety information on the non-DS patients is covered in the text ISS discussion. The content of the ISS is partitioned into separate sections for the DS and non-DS patients.

The remaining category 3 studies are the STILON and DIAVEY studies. On initial submission only xpt dataset for DS patients were included. There was a later submission, in response to IR, of xpt datasets for non-DS patients in the STILON and DIAVEY studies.

These two studies were comprised of both DS and non-DS patients and SAS transport datasets (xpt) for all patients were provided for independent analysis of safety information (as compared to STEV where only DS patients had xpt dataset). STILON is a long term open label follow up study comprised of both DS and non-DS patients that participated in prior STP studies (OL safety extension of STICAR, LENNOX, WOW, STEV, STISERV, STICLO, see Table 41 for characteristics of these studies). The STILON patients who entered from prior ongoing long term studies do not have an analysis dataset that contains specific study identifier or date variables for those prior studies. This causes an inability to compute the STP treatment duration prior to an adverse event. The absence of a mechanism to track the continuity of STP exposure through prior study exposures does not allow computation of the complete duration of STP treatment (*prior study + STILON*). Mean and median exposure to STP in the STILON treatment interval (not including patient exposure in prior studies) was 2.6 and 2.9 years.

The DIAVEY study was a post-EMA approval, EU-wide, multicenter clinical trial that enrolled Dravet (N=153) and non-Dravet (N=77) syndrome patients who had never been treated with STP. The trial was conducted at 57 centers across Europe.

The next group of studies in the application have been termed category 4 by the reviewer are also presented in Table 41. These were exploratory, early efficacy studies in non-DS patients. Adverse event data is available only in table and text form in the ISS pdf and individual written study reports with no datasets (xpt) provided for independent analysis.

The biopharmaceutic and pharmacokinetic studies in healthy volunteers are evaluable only via text study reports and the ISS. These are identified in the study key as “category 5”.

A final study included in the sponsor’s “tabular listing of all clinical studies”, section 5.2 is the “Laux” study. This is not included in Table 4, list of clinical studies or Table 41, the safety study key. This is a retrospective chart review to assess whether efficacy of STP can be explained only by increased plasma concentrations of CLB and NCLB. Safety information from this study is limited to the subsequent two paragraphs:

“No deaths were reported in the 29 patients included in this retrospective chart review. By comparison, 4 of the remaining 101 (4%) Dravet syndrome patients seen at (b) (4) (b) (4) between January 2002 and January 2012 died of sudden unexplained death in epilepsy (SUDEP) or a prolonged seizure.

No serious laboratory abnormalities requiring intervention were observed in the 29 patients included in this chart review.”

Table 41 Safety Study Key

STUDY identifier (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	BA	OL-Crossover	10.1	Healthy= 24	Single dose
BC.287 *Greig (1993)*	5	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	cyp	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	DS only	DB	19.0	DS= 42	2 MONTHS
BC.385 (LP 2000) STICLO Italy	1	DS only	DB	19.0	DS= 23	2 MONTHS
Non-Pivotal Studies in Dravet Syndrome Patients						
BC.609 *(LP 2012)* *STP-1*	2	DS only	OL	19.0	DS= 33	16 wk, (>52 wks)
BC.458 *TAU-EAP (LP 2007) (ATU de COHORTE)*	2	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 multi seizure type	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	SAFETY – LONG TERM, post marketing	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 CBZ	SB-OL	Not provided	Non-DS= 32	3 month
BC.276 *WOW (LP 1991)*	4	EFFICACY, ADD 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 week maximum
*LP = Last Patient complete date, SR = Study report date						

7.2.1. **Overall Exposure**

Sources of Exposure Data

Twenty studies of divergent design, form of epilepsy, population characteristics, and available data spanning an interval of 36 years, are presented by the sponsor in this submission. These studies are performed across a timespan ranging from 1976 to 2014. SAS transport .xpt exposure datasets adequate for computation of duration and dose are present only for the STICLO studies, STP-1 study and 13 Dravet patients from the STEV study. Exposure is therefore extracted from the information provided in the sponsor presentation. The compilations of exposure have been extracted from three sources, the ISS, the STILON study report and the DIAVEY study report.

Table 42 Sources of Exposure Data

Sources of Exposure Data						
STUDY	OBJECTIVE	DESIGN	POPULATION	DURATION	COVERED IN	category
Biopharmaceutic and Pharmacokinetic Studies in Healthy Volunteers-						
BC.481 *STIVAL*	BA	OL-Crossover	Healthy	Single dose	NONE	Small exposure and or numbers, not extracted
BC.287 *Greig*	PK	OL-Crossover	Healthy	Single dose	NONE	Small exposure and or numbers, not extracted
BC.337 *STIUNI*	Pk	OL-Crossover	Healthy	Single dose	NONE	Small exposure and or numbers, not extracted
BC.345 *Pons*	cyp	OL	healthy	14 days	NONE	Small exposure and or numbers, not extracted
Biopharmaceutic and Pharmacokinetic Studies in Dravet Syndrome Patients						
STP167 STIPOP	PK	OL	DS = 35	From other studies	ISS P 65	DS only
Double-Blind, Placebo-Controlled Pivotal Studies in Dravet Syndrome Patients						
BC.299 *STICLO France*	DS only	DB	DS= 42	2 MONTHS	ISS P 65	DS only
BC.385 STICLO Italy	DS only	DB	DS= 23	2 MONTHS	ISS P 65	DS only
Non-Pivotal Studies in Dravet Syndrome Patients						
BC.609 *STP-1*	DS only	OL	DS= 33	16 wk, (>52 wks)	ISS P 65	DS only
BC.458 *TAU-EAP (ATU de COHORTE)*	DS only	OL	DS= 272	Years	ISS P 65	DS only
Non-Pivotal Studies in Dravet Syndrome and Non-Dravet Syndrome Patients						

Sources of Exposure Data						
STUDY	OBJECTIVE	DESIGN	POPULATION	DURATION	COVERED IN	category
BC.288 *STEV*	EFFICACY multi seizure type	SB	DS= 25 Non-DS= 202	12 weeks	STILON	DS + other Sz type, extension
BC.274 *Lennox- Gastaut*	EFFICACY LGS	SB	Non-DS= 24	2 month	STILON	DS + other Sz type, extension
BC.246 *STICAR*	EFFICACY, add on to CBZ		Non-DS= 62	2 month	STILON	DS + other Sz type, extension
BC.484 *STISEVR*	EFFICACY, ADD CBZ	SB-OL	Non-DS= 32	3 month	STILON	DS + other Sz type, extension
BC.276 *WOW*	EFFICACY, ADD TO CBZ	OL	Non-DS= 64	70 days	STILON	DS + other Sz type, extension
BC.387 *STILON*	OL Safety extension of STICAR, LENNOX, WOW, STEV, STISERV, STICLO		Non-DS= 110 DS= 45	years	SELF	DS + other Sz type, extension
BC.627 *DIAVEY*	SAFETY – LONG TERM, post marketing	OL	DS=153 non DS=77	Up to several years	Self-contained although no exposure breakout by patient / unit time only mean and median months exposure	DS + other Sz type, post-marketing
BC.244 *Martinez- Lage* (study report date 1986)	EFFICACY	OL	Non-DS= 31	16 week	NONE, no tabular summary or individual patient data found in study report	Not extractable
BC.109 *Courjon* (study report date 1976)	EFFICACY	OL	Non-DS 135	1 month to more than 6 months	NONE, study report contains individual duration of treatment by patient. Units not defined	Not extractable
BC.243 *Loiseau (study report date 1984)*	EFFICACY	OL	Non-DS = 44	16 week maximum	NONE, no tabulation of exposure found in report	Not extractable

The ISS provides exposure information for the STIPOP, STICLO FRANCE AND ITALY, STP-1 AND TAU-EAP (ATU de COHORTE) studies. Dose and duration of treatment information is extracted from the tables on page 64 & 65 of the ISS shown in Table 43 and Table 44 below.

There were 237 patients with STP dose between 40 and <60mg/kg/day while 116 patients were exposed to a dose between 60 to < 100mg /kg /day. There were 357 Dravet patients with exposure for 6 months or longer and 310 patients with exposure for 1 year or longer. This exposure is captured from the long term open label studies those patients included from the

short term STICLO, STP-1 and STEV studies.

Table 43 (Sponsor Table 3-12, ISS p65) Overall Exposure to STP by Treatment Duration, in Trials that Enrolled Dravet Syndrome Patients

		STICLO**							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

Table 44 (Sponsor Table 3-11, ISS p64) Overall Extent of Exposure to STP by Dose in Pivotal and Non-Pivotal Biocodex-Sponsored Clinical Trials in Dravet Syndrome Patients

		STICLO								
	STEV	France	Italy	STILON	STIPOP	STP-1	TAU-EAP	DIAVEY	TOTAL	
	N= 24	N=21	N=12	N=45	N=35	N=30	N=210	N=152	N=529	%
mg/kg/day										
n	23	21	12	45	35	30	207	151	524	
Mean ± SD Median	60.5 ± 10.8	48.8 ± 2.8	50.2 ± 4.7	43.3 ± 16.0	49.6 ± 14.9	49.0 ± 7.4	55.2 ± 24.7	40.1 ± 19.2	49.2 ± 21.2	
median	62.9	49.3	51.1	41.8	44.6	48.9	54.6	40.3	48.4	
Min – Max	40.0 – 82.4	43.3 – 54.4	39.2 – 57.0	5.8 – 72.9	27.1 – 89.3	35.7 – 75.5	3.7 – 122	3.9 – 115	3.7 – 121.9	
>= 0 and < 40	0	0	1	18	10	1	57	73	160	30.2%
>= 40 and < 60	9	21	11	20	15	27	73	61	237	44.8%
>= 60 and < 100	14	0	0	7	10	2	68	15	116	21.9%
>= 100 and < 150	0	0	0	0	0	0	9	2	11	2.1%
>= 150 and < 200	0	0	0	0	0	0	0	0	0	0.0%
>= 200	0	0	0	0	0	0	0	0	0	0.0%
MISSING	1	0	0	0	0	0	3	1	5	0.9%

The STILON study is examined for exposures in Dravet syndrome, partial onset seizures and

other epilepsies in total. There were 148 patients exposed for greater than two years and up to 13 years, Table 45. There were 71 Patients ≤16 years of age who received 40mg/kg/day or more STP with a mean dose of 56.8 for patients < 10 years of age and 59.4 mg/kg/day for patients between 10 and 16 years of age, Table 46. Exposure data from the DIAVEY study, a long term post-marketing study in the EU[43], reveals that 152 Dravet patients had a mean and median of 22.4 and 20.1 months of exposure respectively, while all 227 enrolled epilepsy patients had a mean and median exposure of 20.3 and 17.4 months of exposure respectively, Table 49.

Table 45 STILON Study Exposure, duration by years and Epilepsy Type

Overall duration of exposure- STILON	SMEI		Partial epilepsy		Other epilepsies		Total		Total minus SMEI (Dravet)	
	N	%	N	%	N	%	N	%	n	% non-DS
Missing data			2	2.5	1	3.4	3	1.9	3	2.7
Less than 1 year			1	1.2			1	0.6	1	0.9
Between 1 and 2 years			3	3.7			3	1.9	3	2.7
Between 2 and 3 years	1	2.2	2	2.5			3	1.9	2	1.8
Between 3 and 4 years	1	2.2	2	2.5	1	3.4	4	2.6	3	2.7
Between 4 and 5 years	4	8.9	7	8.6			11	7.1	7	6.4
Between 5 and 6 years	16	35.6	6	7.4	1	3.4	23	14.8	7	6.4
Between 6 and 7 years	13	28.9	7	8.6	2	6.9	22	14.2	9	8.2
Between 7 and 8 years	7	15.6	8	9.9	3	10.3	18	11.6	11	10.0
Between 8 and 9 years	1	2.2	11	13.6	3	10.3	15	9.7	14	12.7
Between 9 and 10 years			2	2.5	4	13.8	6	3.9	6	5.5
Between 11 and 12 years	2	4.4	10	12.3	8	27.6	20	12.9	18	16.4
Between 12 and 13 years			8	9.9	1	3.4	9	5.8	9	8.2
Over 13 years			12	14.8	5	17.2	17	11	17	15.5
Total	45		81		29		155		110	

Table 46 STILON Number of Patients by Dose and Epilepsy Type, Patients ≤16 Years of Age

STILON, STP dose exposure, children ≤16	SEMI		Partial Epilepsy		Other Epilepsies			Non DS
	< 10yrs	10-16	< 10yrs	10-16	< 10yrs	10-16	total	Total minus SEMI
	N	N	N	N	N	N	N	
missing data			1	1	1	1	4	4
Less than 40 mg/kg/day (not included)	6	6	3	1	2	2	20	8
Between 40 and 60 mg/kg/day	14	8	15	10		4	51	29
More than 60 mg/kg/day	4		6	5	4	1	20	16

[43] DIAVEY was a post-EMA approval, EU-wide, multicenter clinical trial that enrolled Dravet (N=153) and non-Dravet (N=77) syndrome patients who had never been treated with STP.

Total	24	14	25	17	7	8	95	57

Table 47 STILON, Dosing Descriptive Statistics in Patients ≤16 Years of Age by Epilepsy Type

STILON, Children ≤16, STP dose exposure (mg/kg/day)	SMEI		Partial epilepsy		Other epilepsies	
	Under 10 years of age	Between 10 and 16 years	Under 10 years of age	Between 10 and 16 years	Under 10 years of age	Between 10 and 16 years
Mean	49.6	42.5	58.1	63.2	56.8	59.4
Standard deviation	13.8	10.1	19.9	15.2	23.3	28.3
Minimum	18.4	25.9	21.4	38.8	24.7	39.0
Maximum	75.6	64.8	97.2	97.0	88.1	125.0
Median	47.2	40.8	54.9	62.7	63.2	52.0
n	24	14	24	16	7	8
Missing data	0	0	1	1	0	0

Table 48 STILON, Daily Dose by Number of Adult Patients and Epilepsy Type

STILON (adult) STP dose exposure (mg)	SMEI	Partial epilepsy	Other epilepsies	Total	Total non-DS
Patients over 16 years of age	N	N	N	N	
Less than 1000 mg	1	1		2	1
Between 1000 and 2000 mg	2	12	7	21	19
Between 2000 and 3000 mg	4	20	5	29	25
Between 3000 and 4000 mg		5	2	7	7

Table 49 DIAVEY, Duration of Exposure Descriptive Statistics, by Seizure Type

(DIAVEY) Stiripentol, treatment Exposure (months)	Dravet syndrome	Other types of epilepsy	Total analyzed patients
Overall	N=152	N=75	N=227
Mean (SD)	22.4 (13.8)	15.9 (13.7)	20.3 (14.1)
Median	20.1	11.3	17.4
Min, Max	1 ; 53	0 ; 51	0 ; 53

Reviewer Comment: Although Dravet syndrome is a rare disease the STP exposure, see Table 43, exceeds the recommended threshold for 3 months and 1 year identified in ICH E1 guideline. Exposure by dose also demonstrates adequate number of patients (353) have been exposed to

dosing in the range of proposed dosing. There were 163 DS patients under the age of 3 years in long term open label studies. Data from long term extension studies of patients with Dravet and other seizure types also identifies additional STP dose and duration of exposure to support safety assessment.

7.2.2. **Relevant characteristics of the safety population:**

STICLO Studies

Examination of the baseline characteristics of total STICLO studies (both treatment arms) reveals a small excess of male patients (4%) over female in the pooled PBO group while there is a larger difference in the STP treatment group with a 16% excess of female over male. In the individual studies STICLO France STP treatment arm the females are present in 40% excess over male patients while in STICLO Italy males are present in a 34% excess over males. Examination of age across treatment arms of the two studies reveals a very similar mean with all treatment arms having the highest frequency of patients in the 6 to < 12 yo age range. The age range of most frequent seizures, 1 go < 6 years is populated in a range of 19% to 30% of total study patients, where the pooled STICLO distribution in this age range is 21% in STP and 29% in PBO arms. Baseline weight is similar across STP and PBO treatment arms of both studies, Table 50.

Table 50 Demographic Characteristics of STICLO Studies*

Baseline Characteristic	STICLO France N=41		STICLO Italy N=23		STICLO Total N=64	
	STP N=21	Placebo N=20	STP N=12	Placebo N=11	STP N=33	Placebo N=31
Gender (N, %)						
Male	6 (29%)	11 (55%)	8 (67%)	5 (46%)	14 (42%)	16 (52%)
Female	15 (71%)	9 (45%)	4 (33%)	6 (54%)	19 (58%)	15 (48%)
Age (years)	9.4 ± 4.0	9.3 ± 4.9	9.2 ± 3.6	8.7 ± 4.4	9.3 ± 3.8	9.1 ± 4.6
Mean ± SD Min-Max	3.0 – 16.7	3.2 – 20.7	3.7 – 15.5	3.5 – 18.9	3.0 – 16.7	3.2 – 20.7
Age Group (N, %)						
< 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1 to < 6	4 (19%)	6 (30%)	3 (25%)	3 (27%)	7 (21%)	9 (29%)
6 to < 12	10 (48%)	9 (45%)	6 (50%)	6 (54%)	16 (48%)	15 (48%)
12 to < 17	7 (33%)	2 (10%)	3 (25%)	1 (9%)	10 (30%)	3 (10%)
> 17	0 (0%)	3 (15%)	0 (0%)	1 (9%)	0 (0%)	4 (13%)
Weight (kg)						
Mean ± SD	31.8 ± 12.7	30.5 ± 14.4	31.9 ± 11.7	29.2 ± 9.0	31.8 ± 12.1	30.0 ± 12.6
Min – Max	14 - 60	15 - 70	16 - 55	18 - 49	14 - 60	15 – 70

* From Sponsor ISS, Table 3-21, page 77

Reviewer Comment: Overall, given the small sample size of the studies, the distribution of age ranges is not unexpected while the variation in distribution is not sufficient to meaningfully

influence expected outcome of either treatment arm.

Non-Pivotal Trials

Examination of baseline demographic characteristics across non-pivotal studies is shown in Table 51. There is divergence in male – female distribution in the STEV and STP-1 studies, however, in the much larger populations of TAU-EAP and DIAVEY the distribution is close to even. Age distribution in the important high seizure frequency age 1 to <6 yo range in the clinical trials STEV and STP1 (group 1 & 2) is approximately 58% of the population while in the larger long term OL studies TAU-EAP and DIAVEY the proportion in this age range is approximately 45%. Mean weight is similar in the studies with a higher proportion of younger patients with a mean weight near 25kg, while in the studies STILON and STP-1 group 3 there is a higher mean weight of near 34 kg that reflects a shift to an older population in these studies.

Table 51 Baseline Demographic Characteristics across Non-Pivotal Trials (Dravet Syndrome Patients)

Baseline Characteristic	STEV N=24	STP-1		STILON N= 45	TAU-EAP N= 210	DIAVEY N= 152
		Group 1 & 2 N= 24	Group 3 (LT OL only) n= 6			
Gender						
Male	17 (71%)	15 (62 %)	2 (33%)	22 (49 %)	108 (51 %)	73 (48 %)
Female	7 (29%)	9 (38 %)	4 (67%)	23 (51 %)	102 (49 %)	79 (52 %)
Age (years)						
Mean ± SD	5.7 ± 5.3	8.9 ± 7.6	14.0 ± 6.1	11.0 ± 4.9	7.1 ± 6.4	6.4 ± 5.6
Min-Max	0.9 – 18.5	1.3 – 24.6	6.9 – 24.5	4.1 – 23.1	0.5 – 32.0	0.5 – 25.2
Age Group (%)						
< 1	3 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0)	25 (11.9)	16 (10.5)
1 to < 6	14 (58.3%)	14 (58.3%)	0 (0.0%)	7 (15.6)	93 (44.3)	71 (46.7)
6 to < 12	3 (12.5%)	4 (16.7%)	3 (50.0%)	20 (44.4)	49 (23.3)	36 (23.7)
12 to < 17	3 (12.5%)	1 (4.2%)	2 (33.3%)	13 (28.9)	23 (11.0)	22 (14.5)
>= 17	1 (4.2%)	5 (20.8%)	1 (16.7%)	5 (11.1)	20 (9.5)	7 (4.6)
Weight (kg)						
N	20	24	6	45	186	150
Mean ± SD Min –	25.7 ± 18.5	25.3 ± 14.6	34.4 ± 10.3	33.1 ± 13.0	24.5 ± 16.6	24.0 ± 15.8
Max	9.0 – 79.0	10.0 – 54.6	19.5 – 49.0	13.0 – 65.0	6.2 – 83.0	6.0 – 86.0
Missing	4	0	0	0	24	2
From Sponsor ISS, Table 3-22, page 78						

Reviewer Comment: The demographic features of the non-pivotal, primarily long term extension studies have a distribution of ages and sex that are appropriate for safety assessment relevant to the population of the proposed indication.

7.2.3. Adequacy of the safety database:

Taken in total the safety database is adequate with the following comments. The patient population is small as noted in the analysis of condition. This property has resulted in a study population in this submission that is fragmented across a mix of clinical studies. The only parallel controlled data is available from the pivotal and supporting STICLO France and STICLO Italy studies that have a population of only 64 patients. Additional supporting safety data in this application is available from a compilation legacy efficacy studies, long term pre-market extension studies and a long term European post marketing study. Overall, the composite safety data is large and adequately robust when considering small population of patients with this rare disease.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

Dataset structure was not typical for recent submissions. This added a layer of difficulty where direct reviewer assessment of efficacy and safety assessment were performed. The ISE and ISS content and structure were adequate for assessment.

7.3.2. Categorization of Adverse Events

As noted in "sources of exposure data" the safety dataset is composed of a panel of non-IND studies conducted in the EU. The adverse event reporting was not directed by the safety reporting requirements of 21 CFR 312.32 or the "Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE studies. The individual safety characterization methodology for the STEV and DIAVEY studies was extracted from the ISS due to limited relevant content in the study protocols. Methodology for adverse event collection and categorization for STICLO, STILON, TAU-EAP, STP-1, and STIPOP studies was extracted from the study protocols and show below with a summary for presented in Table 62.

STEV Study

All side effects were to be recorded, as well as the possible relationship between their occurrence and study drug. A side effect notification form was to be completed by the Investigator. Side effects were to be classified by intensity as severe, moderate, or mild.

STICLO Studies

The nature, date of onset and duration, severity, any possible corrective treatment and casual relation with the study treatment will be noted routinely in the case report form of each intercurrent event.

Severity will be graded as follows:

Slight: not affecting activity
Moderate: sufficient discomfort to interfere with activity
Severe: impossible of carrying out usual activities, leading to a decrease I the dose of combined medicine or even immediate withdrawal of a medicine and potentially requiring specific treatment

Investigators must express an opinion regarding the existence of a causality relation between the intercurrent event and study treatment:

definite: the event is certainly linked to the study treatment
probable: the event appears to be linked to the study treatment
possible: there may be a relation between the study treatment and the event, but it is difficult to definitely establish such a relation
unrelated: the event is not related to the study treatment
not known: the investigator has no available information which would enable the confirmation or ruling out of a causality relation.

Serious Intercurrent Events

Any of the following are serious intercurrent events:

- with a fatal outcome or life-threatening
- leaving sequelae
- requiring hospitalization or its prolongation
- involving a congenital abnormality or cancer
- requiring the immediate withdrawal of treatment when there is a "reasonable possibility" that
- the event has been caused by the medicine.

From ISS:

Across both STICLO trials, AEs were monitored using a symptom checklist:

- gastro-intestinal disorders (loss of appetite, weight loss, abdominal pain, nausea, vomiting, diarrhea, weight gain),

- behavioral disorders (drowsiness, hyperkinesia, agitation, irritability, insomnia, nightmares),

- neurological disorders (hypotonia, ataxia, dysarthria, tremor)

The protocol specified that all AEs occurring (whether part of the checklist or not) were to be recorded on the AE CRF and relationship to study drug (definite, probable, possible, unrelated, not known) was to be evaluated by the Investigator. Relationship to study drug was to be given by the investigator in an open-text field at the bottom of the CRF page. (Note that relationship to study drug was not always reported on the CRF; for the analysis when relationship was missing the AE was categorized by default as drug-related.)

STILON Study

AEs were collected from spontaneous notifications by the Investigator and from the patients' self-evaluation diaries, regardless of whether the event was judged to be related to STP or not. Causality was rated as unlikely, possibly, or probably related to STP.

Serious adverse events, the following were considered SAEs:

- death,
- hospitalization or prolonged hospitalization,
- life threatening event,
- event resulting in permanent disability,
- overdose.

STP-1 Clinical Study

<u>Definition of adverse events and side effects (from protocol)</u>

An adverse event can be any unfavourable and unintended sign, (includes an abnormal laboratory finding) symptom, or disease temporally associated with the use of a test drug whether or not considered to be related to this test drug. However, in the following cases, it is not an adverse event.

As a symptom or a symptom associated with the disease being treated, in this case the events are expected from the condition of the test subject before starting the administration of test drug.
Newly expressed events from the start till the end(discontinuation) of test drug administration, are considered the adverse events.

Among the adverse events which occur in test subjects, if it is judged not to be a Cause and Effect relationship "4. There is no relationship", these adverse events are the side effects. (Refer to "10.2 7) Cause and Effect relationship with the test drug")

1) Subjective and objective symptoms
When exacerbation or expression of subjective and objective symptoms and exacerbation of complications is noticed, these are considered as adverse events. The symptoms which already exist before the administration of test drug, or exacerbated symptoms are considered as adverse events.

2) Physiological test, weight, electrocardiogram, brain wave
Principal investigator or sub investigator compares the test result at the time of start of administration, during the administration and at the end (discontinuance) of administration, and judges the changes. These are judged to be clinical problems as abnormal variations, by considering range of physiological change and clinical significance of each test subject.

When judged as an abnormal variation, these are considered as adverse events.

3) Clinical examination (haematological tests, biochemical examination of blood, Urine test)
<Definition of each normal and abnormal test value>
Test value which deviates from the reference value of each medical institution is considered as an abnormal value.
<Judgment of the presence of an abnormal variation of each test item>
Principal investigator or sub investigator compares the test value at the time of start of administration, during the administration and at the end (discontinuance) of administration, and judges the changes. These are judged as clinical problems with abnormal variations, by considering range of physiological change and clinical significance of each test subject.
When judged as abnormal variations, these are considered as adverse events.

TAU-EAP

ADVERSE EVENT: “A harmful, unwanted reaction occurring at normal dosages in humans, for the prophylaxis, diagnosis or treatment of a disease, or a change in a physiological function or the result of misuse of the medicinal product or product”.
SERIOUS ADVERSE EVENT: An event is considered as serious if it is an event: “which is lethal or may be life-threatening, or results in a disability or incapacity or results in or prolongs hospitalisation”.
UNEXPECTED ADVERSE EVENT: “An event not mentioned by its type, severity or frequency in the summary of product characteristics (SmPC)”.

Reporting of Adverse events:

Every doctor, pharmacist, dentist or mid-wife or who observes a serious or unexpected adverse event which may be due to DIACOMIT must report it immediately and within 24 hours at the latest to BIOCODEX by means of the Adverse Event report form (Annex D).
He or she similarly can notify any event that he or she considers relevant to report.

STIPOP Clinical Trial

The investigator was asked to assess the severity of the adverse event (clinical or biological) using the following categories: Mild, Moderate and Severe. This assessment was subjective and the investigator had to use medical judgment to compare the reported adverse event to events of similar type observed in clinical practice. Guidelines for severity assessment were the following:

Mild – Symptom(s) barely noticeable to the patient or did not make the patient uncomfortable. The adverse event did not influence performance or functioning. Prescription drugs were not ordinarily needed for relief of symptom(s).

Moderate – Symptom(s) of a sufficient severity to make the patient uncomfortable. Performance of daily activities was influenced. Treatment of symptom(s) could be needed.

Severe – Symptom(s) of a sufficient severity to cause the patient severe discomfort. Severity could cause cessation of treatment with STP. Treatment for symptom(s) could be given.

The investigator promptly recorded all observed or reported adverse events from the inclusion of the patient in the study through study completion or early termination. The nature, the severity, date of onset, date of resolution, seriousness, action taken with regards to study drugs, any corrective treatment given, and the investigator's assessment of the relationship to STP administration were recorded in the patient's record, then transcribed onto the case report form (CRF).

Serious Adverse Event

A serious adverse event (SAE) was defined as any adverse event that resulted in any of the following outcomes (European Directive #2001/20/CE dated 04 April 2001):

- Death
- Life-threatening event
- Required inpatient hospitalization or prolonged existing hospitalization

- Persistent or significant disability/incapacity
- Congenital anomaly
- Important medical event that could jeopardize the patient and could require medical or surgical intervention to prevent one of the outcomes listed above.

Life-threatening event: Any adverse event that placed the patient, in the view of the reporter, at immediate risk of death from the adverse event as it occurred.

Persistent or significant disability/incapacity: The adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions.

Important medical events: Adverse events that could not result in death, be life-threatening, or require hospitalization could be considered as serious adverse event, when, based upon appropriate medical judgment, they could jeopardize the patient and could require medical or surgical intervention to prevent one of the outcomes listed above. Some examples of such events (noted in ICH E2A) are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Cancer, pregnancy, overdosage and drug abuse were also considered as SAE.

DIAVEY

Only AEs judged to be drug related were collected on the AE CRF. The nature, severity (mild, moderate, severe), date of onset, relationship to study drug, treatment and outcome were noted. The Investigator judged whether the AE was serious or not.

Reviewer Comment: Although not performed under IND, the STICLO, STILON, STP-1, TAU-EAP, and STIPOP studies have SAE definitions that approximate 21 CFR 312.32, see summary Table 62. In the open label DIAVEY post marketing study the definition of SAE was judged by the investigator. The less prescribed mechanism for SAE and TEAE capture in the DIAVEY study is acceptable for a post-marketing study implemented over a large population of practitioners. Overall the methodology for capture and categorizing SAEs and treatment emergent events is adequate for assessment of the safety database.

7.3.3. Routine Clinical Tests

Reviewer Comment: The STICLO studies had a smaller set of clinical testing compared to typical NME application packages. These studies had only ALT and AST chemistries obtained, height and weight vital signs, with a full hematologic profile. These studies, although containing the pivotal efficacy data, do not provide a comprehensive profile of clinical testing. This role is taken up by the STP-1 study that has a full chemistry and hematologic profile as well as ECGs and a vital sign panel including blood pressure, temperature, heart rate, height and weight both during the study maintenance period and extension phase. Baseline and periodic samples for chemistry, hematology and vital signs, in abbreviated panels, are available for the long term extension studies TAU-EAP, STILON, and the DIAVEY post marketing studies, see Table 52 and Table 53. In combination, the array of clinical studies is adequate for assessment of safety.

Table 52 Clinical Laboratory Parameters Obtained Across Studies

	Category 1 Studies	**Category 2 & 3 Studies**					
	STICLO	**STIPOP**	**TAU-EAP**	**DIAVEY**	**STEV**	**STILON**	**STP1**
Hematology							X
Basophils	X					X	X
Eosinophils	X					X	X
Erythrocytes	X				X	X	X
Hematocrit	X				X		X
Hemoglobin	X						X
Leukocytes	X				X		X
Lymphocytes	X					X	X
Monocytes	X					X	X
Neutrophils	X			X		X	X
Platelets	X					X	X
Chemistry							
Alanine Aminotransferase (n=438)	X	X	X	X	X	X	X
Alkaline Phosphatase						X	X
Aspartate Aminotransferase	X	X	X	X	X	X	X
Bilirubin					X		X
Blood Urea Nitrogen							X
Chloride							X
Cholesterol							X
Choriogonadotropin Beta							X
Creatinine						X	X
Gamma Glutamyl Transferase				X			X
Glucose							X
Lactate Dehydrogenase							X
Potassium						X	X
Protein							X

	Category 1 Studies	Category 2 & 3 Studies					
	STICLO	**STIPOP**	**TAU-EAP**	**DIAVEY**	**STEV**	**STILON**	**STP1**
Sodium						X	X
Urobilinogen							X

Table 53 Vital Sign Parameters obtained Across Clinical Studies

	Category 1 Studies	Category 2 & 3 Studies					
	STICLO	**STIPOP (PK short term*)**	**TAU-EAP**	**DIAVEY**	**STEV**	**STILON**	**STP1**
Systolic Blood pressure						X	X
Diastolic Blood Pressure						X	X
Heart rate						X	X
Height	X	X (baseline day only)	X	X		X	X
Weight	X	X (baseline day only)	X	X		X	X
Body temperature							X
ECG							

* STIPOP, maximum treatment duration 35 days in a single patient, 28 patients had only a single day STP treatment for Pk analysis

7.4. Safety Results

7.4.1. Deaths

In this submission, data available from the stiripentol development program was divided into pivotal studies of Dravet syndrome patients and non-pivotal studies. From among the non-pivotal studies there were two additional study groups, those composed of only Dravet syndrome patients (category 2) and studies with mixed patient populations of Dravet and non-Dravet syndrome epilepsy patients (category 3). In any category 2 or 3 studies the Dravet syndrome patient cohort had a panel of. xpt (SAS transport files) datasets provided, including adverse event (AE) datasets. The non-DS cohorts of the STILON and DIAVEY studies had SAS.xpt datasets provided. Non-Dravet patient participants in the category 3 STEV study were not included in the. xpt datasets, death and adverse event data provided only in PDF format study report documents for this study. A 4th category of studies was characterized by a patient population comprised entirely of non-Dravet patients. The sponsor identifies these studies as

exploratory efficacy studies in non-Dravet epilepsy patients. This group of studies had death and adverse event data provided only in PDF format study report documents. These are designated category 4. The 5th category of patients evaluated were healthy volunteer participants in biopharmaceutical and PK studies where death and adverse event data were provided in PDF format study report documents (category 5). All deaths are shown in a tabular format by study with core characteristics of each study, see Table 54.

Table 54 Overall Table of Death events in Stiripentol Studies by Study Category*

STUDY identifier (Sponsor Study Number) (Name) (Year)	category	OBJECTIVE	DESIGN	POPULATION	DURATION	Seizure type	Deaths
	Biopharmaceutic and Pharmacokinetic Studies in Healthy Volunteers-						
BC.481 *STIVAL (2007)*	5	BA	OL-Crossover	Healthy= 24	Single dose	Healthy volunteer	0
BC.287 *Greig (1993)*	5	PK	OL-Crossover	Healthy= 6	Single dose	Healthy volunteer	0
BC.337 *STIUNI (2002)*	5	Pk	OL-Crossover	Healthy= 12	Single dose	Healthy volunteer	0
BC.345 *Pons (1995)*	5	cyp	OL	Healthy= 13	14 days	Healthy volunteer	0
	Biopharmaceutic and Pharmacokinetic Studies in Dravet Syndrome Patients						
STP167 STIPOP (2008)	2	PK	OL	DS = 35	From other studies	DS	0
	Double-Blind, Placebo-Controlled Pivotal Studies in Dravet Syndrome Patients						
BC.299 *STICLO France (1998)*	1	DS only	DB	DS= 42	2 MONTHS	DS	0
BC.385 STICLO Italy (2000)	1	DS only	DB	DS= 23	2 MONTHS	DS	0
	Non-Pivotal Studies in Dravet Syndrome Patients						
BC.609 *STP-1 (2012)*	2	DS only	OL	DS= 33	16 wk, (>52 wks)	DS	0
BC.458 *TAU-EAP (ATU de COHORTE) (2007)*	2	DS only	OL	DS= 272	Years	DS	5
	Non-Pivotal Studies in Dravet Syndrome and Non-Dravet Syndrome Patients						
BC.288 *STEV (1997)*	3	EFFICACY multi seizure type	SB	DS= 25 Non-DS= 202	12 weeks	DS	1
						Non-DS	4
BC.387 *STILON (2003)*	3	OL Safety extension of STICAR, LENNOX, WOW, STEV, STISERV, STICLO		Non-DS= 110 DS= 45	years	DS	0
						Non-DS	3

BC.627 *DIAVEY* *(2012)*	3	SAFETY – LONG TERM, post marketing	OL	DS=153 non DS=77	Up to several years	DS	5
						Non-DS	2
BC.274 *Lennox- Gastaut* (1994)	4	EFFICACY LGS	SB	Non-DS= 24	2 month	Non-DS	0
BC.246 *STICAR* *(1990)*	4	EFFICACY, add on to CBZ	DB	Non-DS= 62	2 month	Non-DS	1
BC.484 *STISEVR* *(2000)*	4	EFFICACY, ADD CBZ	SB-OL	Non-DS= 32	3 month	Non-DS	0
BC.276 *WOW*	4	EFFICACY, ADD TO CBZ	OL	Non-DS= 64	70 days	Non-DS	0
BC.244 *Martinez- Lage* (study report date 1986)	4	EFFICACY	OL	Non-DS= 31	16 week	Non-DS	0
BC.109 *Courjon* (study report date 1976)	4	EFFICACY	OL	Non-DS 135	1 month to more than 6 months	Non-DS	0
BC.243 *Loiseau* *(study report date 1984)*	4	EFFICACY	OL	Non-DS = 44	16 week maximum	Non-DS	0
Total Reported Death							21

*Study Categories: **1**- pivotal studies of Dravet syndrome patients with xpt datasets available, **2**- studies comprised of only Dravet syndrome patients (xpt datasets available), **3**- studies with mixed patient populations of Dravet and non-Dravet syndrome epilepsy patients (xpt datasets available for DS patients only), **4** studies with a patient population comprised entirely of non-Dravet patients (no xpt datasets available, data only available in written format), **5** biopharmaceutical and PK studies in healthy volunteers (no xpt datasets available, data only available in written format).

Dravet Patients

Pivotal Studies

No deaths occurred in STICLO France and STICLO Italy

Non-Pivotal Studies of Dravet Syndrome only (Category 2, Table 54)

In the set of Dravet patient's death occurred only in the TAU-EAP study where there were five deaths, Table 55. In review, this was a long term open label safety study of stiripentol. The shortest latency from start of stiripentol treatment to death was 54 days in patient (b) (6) while in the remaining patients the minimum duration of stiripentol treatment was 227 days prior to death. The mean and median duration of treatment until death were 489 and 393 days respectively. All patients were under 7 years of age, Table 55. All deaths in this study are judged to be probable or possible SUDEP based on the proposed unified SUDEP definition and

classification[44].

Table 55 Death in non-pivotal studies with only Dravet patients

Death in NPDS patients								
Patient ID	**Age**	**sex**	**Preferred Term**	**Treatment Duration (days)**	**Circumstances**	**Age of DS Diagnosis**	**Dose at death**	**Cause of Death sponsor, [reviewer]**
ATU de COHORTE-(b) (6)	2.88	F	SUDDEN DEATH	1040	Died in Sleep	8 months	Not specified	SUDEP [P]
ATU de COHORTE-(b) (6)	1.48	F	SUDDEN DEATH	733	Found in dead in morning	5 months	750 mg (60mg/kg)	SUDEP [P]
ATU de COHORTE-(b) (6)	5.31	M	DEATH	54	Died in sleep	6 months	1000 mg (57 mg/kg)	SUDEP [possible]
ATU de COHORTE-(b) (6)	3.62	F	DEATH	227	Sudden death during seizure	6 months	750 mg	SUDEP [possible]
ATU de COHORTE-(b) (6)	.09	M	DEATH	393	Died after interva of somnolence and fever post vaccination. No further detail.	7 months	Not specified	SUDEP [possible]

Dravet Patients from Non-Pivotal Studies of Dravet and Non-Dravet Patients (Category 3, Table 54)

In this set of Dravet patients treated with stiripentol there were six deaths, Table 56. The shortest duration of exposure before death was 55 days while the remaining five patients were on stiripentol treatment between 398 and 829 days. The mean and median exposures were 457 and 456 days respectively. The youngest patient was 1.2 years old while the oldest was 14.1. The circumstances of death are not provided for two patients. From among these patients 3 were judged to be probable or possible SUDEP by the unified SUDEP definition.

Table 56 Death in non-pivotal studies of mixed Dravet, non-Dravet patients, Count of Dravet patients only.

Death in NPDS/non-DS Studies		

[44] 9. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;53:227-233.

Patient ID	Age	sex	Preferred Term	Treatment Duration (days)	Circumstances	Age of DS Diagnosis	Dose at death	Cause of Death Sponsor [reviewer]
DIAVEY (b) (6)	6	F	Death	463	Discovered dead in AM	6 months	1000mg (45mg/kg)	SUDEP [P]
DIAVEY (b) (6)	2.4	F	Sudden unexplained death in epilepsy	829	Died (no further detail)	7 months	750mg (47mg/kg)	SUDEP [possible]
DIAVEY (b) (6)	14.1	M	Death	398 (approximate)	No detail provided	2 months	2250mg/kg (58mg/kg)	Only report via parents of Death, Parents refused further information to sponsor (insufficient data)
DIAVEY- (b) (6)	2.7	M	Death	449	No detail provided- only sudden death	4 months	750mg (47mg/kg)	Only reported died unexpectedly- post mortem available
DIAVEY (b) (6)	2.7	M	Death	547	Hospitalized, recurrent chest infection (9 months after cessation of STP)	4 months		infection
STEV (b) (6)	1.2	M	Sudden unexplained death in epilepsy	55	Died during sleep. MH: hypotonia, mental deficiency, hyperkinesia	Not provided	750mg (79mg/kg)	SUDEP [P]

The TAU-EAP study was an open label extension study with a population of only Dravet syndrome patients while DIAVEY and STILON were open label extension studies that contained both Dravet syndrome and non-Dravet syndrome patients. Duration of treatment was available for each patient. This allowed a calculation of event per person year of exposure which was then converted to event per 1000 patient years as a more common comparator. Study population size, number of deaths / SUDEP, patient years of exposure and events /1000 patient year are shown in Table 57 and Table 58 below.

All deaths in the TAU-EAP study were judged to be probable or possible SUDEP so that total deaths equal SUDEP deaths. The SUDEP rate was calculated to be 9.6/1000 patient years with an overall death rate in the TAU-EAP cohort of 1.8%.

The DIAVEY study was a post marketing long term open label study. There were 152 Dravet syndrome patients exposed for a total of 278 patient years and 77 non-DS patients with 93 patient years of exposure. The calculated incidence of death in the DS cohort was 18 per 1000

patient years with a SUDEP rate of 13.1 per 1000 patient years. The incidence of death in the non-DS cohort was 21/1000 patient years with a SUDEP incidence of 10.8/1000 patient years. Death occurred in 3.1% of the overall study population. Two patients from DIAVEY have very limited information from time of death, see Table 56. If these patients were to qualify as SUDEP the incidence would increase to 26 / 1000 patient years.

The STILON study was an open label extension study that captured patients from several pivotal and exploratory efficacy trials including STICAR, LGS, WOW, STEV, STISERV, STICLO and others. Therefore, the observation interval in STILON does not represent the full STP treatment interval for these patients. The calculation of death and SUDEP incidence is based only on the interval while patients were in STILON. Detailed exposure for each patient from the parent studies is not available. This study was comprised of 45 Dravet syndrome patients and 110 non-Dravet patients with 131 and 268 patient years of exposure respectively. The incidence of death in the DS cohort was 0 while in the non-DS cohort it was 11/1000 patient years. There were 2 SUDEP deaths in the non-DS cohort with an incidence of 7.5/1000 patient years. Death occurred in 1.9% of the overall study population.

Table 57 All Deaths in TAU-EAP, DIAVEY and STILON studies

All Deaths				
Study	**n**	**# deaths**	**Pt years of exposure**	**Death /1000 pt year**
DS				
TAU-EAP	272	5	519	9.6
DIAVEY	152	5	278	18
STILON	45	0	131	0
Non DS				
DIAVEY	77	2	93	21
STILON	110	3	268	11
Total All Death, DS & non-DS				
TAU-EAP	272	5	519	9.6
DIAVEY	229	7	371	18.8
STILON	155	3	399	7.5

Table 58 SUDEP in TAU-EAP, DIAVEY and STILON studies

SUDEP				
Study	**n**	**# deaths**	**Pt years of exposure**	**SUDEP/1000 pt year**
DS				
TAU-EAP	272	5	519	9.6
DIAVEY	152	2	278	13.1
STILON	45	0	131	0
Non DS				
DIAVEY	77	1	93	10.8
STILON	110	2	268	7.5

SUDEP				
Study	**n**	**# deaths**	**Pt years of exposure**	**SUDEP/1000 pt year**
Total DS & Non-DS SUDEP				
TAU-EAP	272	5	519	9.6
DIAVEY	229	3	371	8.1
STILON	155	2	399	5

In Table 59 the TAU-EAP and DIAVEY studies are partitioned by patient age to examine the incidence of death and SUDEP by patient year and percent of total cohort. Age six years is chosen as the age of partition because the stabilization stage of Dravet is considered to be after age 5. An additional year was added to allow a margin to best capture patient in the "catastrophic" stage of Dravet between 1 and 5 years old where seizures are most frequent where risk of death from SUDEP and status epilepticus are more likely.[45] In the TAU-EAP study all deaths are SUDEP, these all occur in the cohort ≤6 years with no deaths in the >6 year old cohort while patient years of exposure was greater in the older cohort. In the DIAVEY study 80% of the deaths of which 2 were SUDEP occurred in the ≤6 year old cohort while 1 death occurred in the >6 year old cohort. The preponderance of death events occurred in the less than six year old age band. This observation is in alignment with the known catastrophic stage of Dravet syndrome where epilepsy severity is greatest.

Table 59 Studies TAU-EAP and DIAVEY, Death Shown by Cohorts Aged ≤6, >6 years. Total Patient years of Exposure with Death per 1000 Patient year, SUDEP per 1000 patient years.

Study	**Deaths (SUDEP)**	**Total Patient years exposure (DS)**	**Death / 1000 person year**	**SUDEP / 1000 patient year**	**DEATH % of DS Cohort**
TAU-EAP					
AGE ≤6 n=118	5 (5)	247	20	20	4.2
Age >6 n=92	0	272	0	0	0
DIAVEY					
AGE ≤6 N=87	4 (2)	164	24	12	4.6
Age >6 N=65	1 (0)	114	8.8	0	1.5

Non-Dravet Patients, Studies from Category 4, Table 54)

[45]10. Oguni H, Hayashi K, Awaya Y, Fukuyama Y, Osawa M. Severe myoclonic epilepsy in infants - a review based on the Tokyo Women's Medical University series of 84 cases. Brain & Development 2001;23:736-748.

Non-Dravet patients were enrolled in trials of mixed Dravet and Non-Dravet patients. Non-Dravet patients were also enrolled in trials with only non-Dravet epilepsy types. From among these studies there were 10 deaths in 781 study patients. Four of these studies were controlled trials while the remaining 6 were open label. Several of these studies did not provide any exposure information, these included STICAR, LGS, STISEVR, WOW, Martinez-Lage, and Loiseau, where only planned study duration was provided thus incidence per patient years could not be calculated see Table 60.

Table 60 Death events in Studies of non-Dravet Patients in both controlled and open label treatment*

Study	Deaths	# non-DS patients	Exposure	Death % of non-DS Patients
STEV	4	202	Mean 60 days	2
STICAR	1	62	Plan 8 weeks, not reported	1.6
Lennox-Gastaut	0	24	Planned 2 months, Not reported	0
STISEVR	0	32	Plan 16 wk, not reported	0
WOW	0	64	Planned 70 days, not reported	0
Martinez-Lage	0	31	Planned 8 wk, not reported	0
Courjon	0	135	1 mo: 30 patients 2-3 mo: 75 patients >6 mo: 30 patients	0
Loiseau	0	44	Planned 12 wk, not reported	0
Total	10	781	Mixed duration of treatment	1.28

*no exposure report available for STICAR, LGS, STISEVR, WOW, Martinez-Lage, and Loiseau, only planned study duration.

In Table 61 a brief summary of clinical information on deaths in non-Dravet patients is provided.

STEV Study

In the STEV trial two deaths were in infants approximately 10 months old. One of these was a SUDEP. Both had a diagnosis of “cryptogenic partial epilepsy”. From the narrative both patients had severe epilepsy. The child classified as SUDEP had a notable decline in seizure frequency

after starting treatment with STP. The remaining two deaths in STEV occurred in a ten year old female and 13 yo male. The female had an underlying mitochondrial encephalopathy and presented with severe hypokalemia and hypothermia. The 13 year old died during non-terminating seizures. In the STEV trial, the duration of treatment was 37 days or less in three of the patients and just over 3 months in the remaining patient. Two patients were very young with very severe epilepsy at baseline; one patient had a mitochondrial encephalopathy. The incidence of death in the non-Dravet STEV study population was 2.0%. This likely reflects severity of underlying illness in three of the patients. All deaths occurred during the STP treatment phase of the study and a concurrent placebo arm is not available for comparison.

STICAR

The single death in this trial was due to accidental injury

DIAVEY

There were two deaths in the non-Dravet cohort of this long term open label postmarketing study. One a SUDEP occurred at approximately 10 months, the second a death from severe infectious illness after 1.7 years of treatment. The extended treatment in these cases argues against a temporal relationship between STP and the death event. In the second case 1.7 year treatment interval and death following a severe infectious illness makes causality unlikely.

STILON

There were 3 deaths in the non-Dravet cohort of the long term, open label extension STILON study. Two of these events occurred after long treatment intervals of 2 and 2.8 years. One of these patients had severe underlying respiratory illness. The second of these patients had LGS with severe cognitive impairment. In the third patient, a SUDEP occurred after 73 days in the study, however the patient had a prior treatment interval on STP of 6 years following the STEV study. These deaths do not have features supportive of a causal relation to STP.

Table 61 Clinical Information on Non-Dravet Patient Deaths during Clinical Trials

Study	Deaths	Patient ID	Age (years)	Sex	cause	Treatment duration (days)	Circumstances	Epilepsy Diagnosis (from study report narrative)	Dose at Death
STEV		STEV							
	4	(b) (6)	10	F	Probable mitochondrial encephalopathy	37	K 2.5mmol/l, temp 34 C.	Mitochondrial encephalopathy	1250mg/day Wt 18kg 69 mg/kg
			13	M	Death due to a cardiac and respiratory arrest during serial	103	cardiac arrest and a respiratory depression during serial	symptomatic partial epilepsy	2750mg/day, weight not provided

					generalized cyanotic seizures		generalized cyanotic seizures.		
		(b) (6)	0.8	F	Death during night at home, probably related to a bronchial congestion SUDEP [p]	21	Death occurred at home during the night and was probably related to a bronchial congestion	cryptogenic partial epilepsy	900mg/day Wt 9kg 100mg/kg
			0.8	F	Apnea with bradycardia and cyanosis of undetermined origin, leading to cardiac and respiratory deficiency and death	11	presented apnea with bradycardia and cyanosis of undetermined origin, leading to cardiac and respiratory deficiency and death	cryptogenic partial epilepsy	900mg/day Wt 3.3kg 272mg/kg?
STICAR					**STICAR**				
	1	(b) (6)	15	M	accidental death following a cranial injury causing an acute sub-dural haematoma	79		Lymphoid leukemia with post-radiation epilepsy	PBO
DIAVEY					**DIAVEY**				
	2	(b) (6)	1.7	F	SUDEP [p]	296	found dead in her bed in the morning	Multifocal partial epilepsy	1000mg Wt 9kg 111mg/kg
			12	F	Severe pneumonia	636	Comfort treatment: O_2, prednisone, antibiotics	LGS	1500mg Wt 26kg 58mg/kg
STILON*					**STILON**				
	3	(b) (6)	6	M	Cardiac arrest	1004 (not including 3 yr in STEV no cross referenced ID)	6 month hospitalization for respiratory insufficiency.	Generalized tonic seizures 2nd to cerebral malformation. Hypotonic, pyramidal syndrome, mental retardation	2500mg/day 21kg 119mg/kg
			13	M	"severe epilepsy-related encephalopathy"	730 (not including interval following LGS trial where treatment info. Not provided)	Not provided	LGS	2500mg Wt 45kg 56mg/kg
			18	M	SUDEP (S)	75 (not including 6 years in STEV trial, no cross reference	Not provided	Doose Syndrome	3000mg Wt 72.5kg 41mg/kg

						ID)			
Total	10				3 SUDEP				
* treatment duration in STILON does not include interval prior to entry where details of stiripentol treatment are not provided									

Summary

There were 21 total deaths in all multidose, patient studies. In these studies there were a total of 1409 DS and non-DS patients. The raw death incidence without expression by duration of treatment or dose was 1.5 percent of all DS and non-DS patients. There were 11 (1.75%) deaths from among 628 Dravet syndrome patients participating in multiple dose trials and 10 (1.28%) deaths among 781 non- Dravet patients.

In the TAU-EAP study there were 5 deaths, all SUDEP. From among the DS patients in mixed trials (DS and non-DS patients) there was 1 SUDEP in the STEV trial from among 25 DS patients. There were 5 deaths, 2 SUDEP, 2 with insufficient information for judgment and one due to infection from among the 152 patients in the DIAVEY trial.

From among the non-DS patients in the mixed DS and non-DS trials there were 4 (2%) from among the 202 patients in the STEV trial, 2 (2.6%) in the DIAVEY study, 3 (2.7%) in the STILON study, and 1 (1.6%) in the STICAR study.

Examination of Death and SUDEP in the TAU-EAP, DIAVEY and STILON studies where patient level duration of treatment were available reveals an incidence of Death (*per*) / 1000 patient years that is lower in the Dravet cohort of the DIAVEY and STILON studies then in the non-Dravet cohort. The SUDEP rate is similar in DIAVEY for both the Dravet and non-Dravet cohort while in STILON it is higher in the non Dravet cohort.

All death and death from SUDEP are examined by age strata in the TAU-EAP and DIAVEY long term studies. Two age strata are designed; ages ≤6 and age>6 years. These strata were chosen to divide the severe epilepsy and stabilization interval of Dravet syndrome. In the TAU-EAP study all SUDEP (all death) occur in the ≤6 age interval while in the DIAVEY study 80% of deaths and all SUDEP occurred in the ≤6 age interval with 20% of death and no SUDEP in the >6 age interval. The incidence per 1000 patient year of SUDEP was 20 in the TAU-EAP trial and 12 in the DIAVEY study in the ≤6 age interval with zero per 1000 patient years in the >6 year age strata for both studies.

The overall incidence of death and SUDEP in the Dravet Syndrome cohort treated with stiripentol is not out of proportion to the observed high mortality rate of Dravet syndrome of approximately 16% in the cohort less than age 18 years, see section 2.1, Analysis of Condition.

The incidence rate of SUDEP in TAU-EAP, DIAVEY and STILON although high, is in the range of candidates for epilepsy surgery identified as 9 events per 1000 patient years. [46] The TAU-EAP study had the largest number of patients and was entirely comprised of Dravet syndrome patients. The SUDEP rate in this study approximates the incidence seen in epilepsy surgical candidates and is not out of proportion to the underlying severity of Dravet syndrome.

Reviewer Comment: The incidence of death and SUDEP observed across the clinical studies in this approval package is not in excess of expectations for Dravet syndrome.

7.4.2. Serious Adverse Events

The definition of a serious adverse event is examined for each study. The category 3 studies, STEV, STILON and DIAVEY have available SAS, xpt transport files included in the NDA package that are from studies that were not performed under IND and span a timeline from 1998 to 2012. The nomenclature differs in some studies, for example in the DIAVEY study the equivalent of an SAE is called a "serious adverse drug reaction" or SADR. The sponsor indicates that adverse events in the STEV study retroactively had the definition of SAE applied as defined in 21 CFR 312.32(a)). Overall the definition of a serious adverse event across the panel of studies presented is adequately in alignment with 21 CFR 312.32(a)) to analyze as would be performed for IND studies, see Table 62.

Table 62 Definition of SAE

STUDY Name	SAE Definition
ATU de COHORTE (TAU-EAP)	An event is considered as serious if it is an event: "which is lethal or may be life-threatening, or results in a disability or incapacity or results in or prolongs hospitalisation". Source: [5.3.5.2; BC.458, Study Protocol section 5.1]
DIAVEY	Serious ADR (SADR) means an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.
STEV 25	The protocol for the STEV study did not provide a definition of an SAE. According to the initial protocol (p48 ISS) "Side effects" were to be classified by intensity as severe, moderate, or mild. For the analyses and datasets submitted in the NDA, the Sponsor retroactively applied the following definition of an SAE (as defined in 21 CFR 312.32(a)). An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to

[46] 11. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurology 2008;7:1021-1031.

STUDY Name	SAE Definition
	conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
STICLO - FRANCE (Called *Serious Intercurrent Event*)	• Fatal outcome or life-threatening • leaving sequelae • requiring hospitalization or its prolongation • involving a congenital abnormality or cancer • requiring the immediate withdrawal of treatment when there is a "reasonable possibility" that the event has been caused by the medicine.
STICLO - ITALY	• a fatal outcome or life-threatening • leaving sequelae • requiring hospitalization or its prolongation • involving a congenital abnormality or cancer • requiring the immediate withdrawal of treatment when there is a “reasonable possibility” that the event has been caused by the medicine.
STILON	• death, • hospitalization or prolonged hospitalization, • life threatening event, • event resulting in permanent disability, • overdose
STIPOP	• Death • Life-threatening event • Required inpatient hospitalization or prolonged existing hospitalization Persistent or significant disability/incapacity • Congenital anomaly • Important medical events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above
STP1	• Leading to death • Life threatening • Hospitalization or extension of hospitalization being required for treatment • Persistent, significant or becoming dysfunctional

STICLO TRIALS

Three were 8 serious adverse events in the STICLO trials from among five patients. 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. All SAEs are identified in STICLO France.

Table 63 reveals that five of eight adverse events were related to seizure occurrence and may be considered to be issues of seizure worsening. These seizure related events occurred in two

placebo arm patients and two STP treatment arm patients. One STP treated patient had an event of allergic dermatitis. The narrative report indicates this dermatitis was an occurrence of giant urticarial that resolved with dechallenge but did not reoccur on rechallenge.

Table 63 Serious Adverse Events in STICLO trials (MedDRA 19)

SUBJECT ID	TREATMENT ARM (50 mg/kg/day)	PREFERRED TERM
STICLO - FRANCE (b) (6)	PLACEBO	Somnolence
STICLO - FRANCE	PLACEBO	Motor dysfunction
STICLO - FRANCE	PLACEBO	Status epilepticus
STICLO - FRANCE	PLACEBO	Epilepsy
STICLO - FRANCE	PLACEBO	Seizure
STICLO - FRANCE	STIRIPENTOL	Seizure (status epilepticus *from narrative*)
STICLO - FRANCE	STIRIPENTOL	Drug eruption
STICLO - FRANCE	STIRIPENTOL	Severe myoclonic epilepsy of infancy

Non-Pivotal Studies of Dravet Syndrome Patients

Examination of SAEs seen in Dravet syndrome patient participants identified as category 2 and 3 (Non-Pivotal Studies) in the study key above (Table 41) reveal that 160 SAEs occurred from among 71 (14.3%) patients. All of these were patients in open label treatment with STP except for a single patient in the STEV study that had a 28 day placebo run in with a subsequent 12 week STP treatment period. All patients were on STP at the time of the adverse event. Death which comprised eleven of the events are discussed above in section on Deaths.

Table 64 shows SAEs in the non-pivotal study, DS patient group, with a frequency of 2 or greater. This examination reveals 20 preferred terms totaling to 123 events that occur from among 59 patients. The top two preferred term events are “seizure” and “decreased appetite”. These 42 “seizure” events are derived from 17 patients. Highest incidence is seen for the preferred terms “seizure”, “decreased appetite”, “status epilepticus” and “death”.

Table 64 DS Patients, Non-Pivotal Studies, SAE ≥2 Events (from 496 patients)

Any SAE*			**14.3%**
Preferred Term (MedDRA 19.0)	**Number of Events**	**Number of unique Patients (a single patient may have more than one adverse event term)**	**Incidence (%)**
Seizure	42	17	3.43
Decreased appetite	13	11	2.22
Status epilepticus	12	8	1.61
Death	7	7	1.41
Pneumonia	5	5	1.01
Pyrexia	5	5	1.01
Somnolence	5	5	1.01

Any SAE*			**14.3%**
Preferred Term (MedDRA 19.0)	**Number of Events**	**Number of unique Patients (a single patient may have more than one adverse event term)**	**Incidence (%)**
Thrombocytopenia	4	4	0.81
Viral infection	4	3	0.60
Bronchitis	3	3	0.60
Dehydration	3	3	0.60
Fatigue	3	3	0.60
General physical health deterioration	3	2	0.40
Cachexia	2	2	0.40
Epilepsy	2	2	0.40
Febrile convulsion	2	2	0.40
Hypoglycaemia	2	2	0.40
Pneumonitis	2	1	0.20
Sudden death	2	1	0.20
Vomiting	2	1	0.20
*DS patients, non-Pivotal (n=496), category 2 & 3 in Table 41 (study key)			

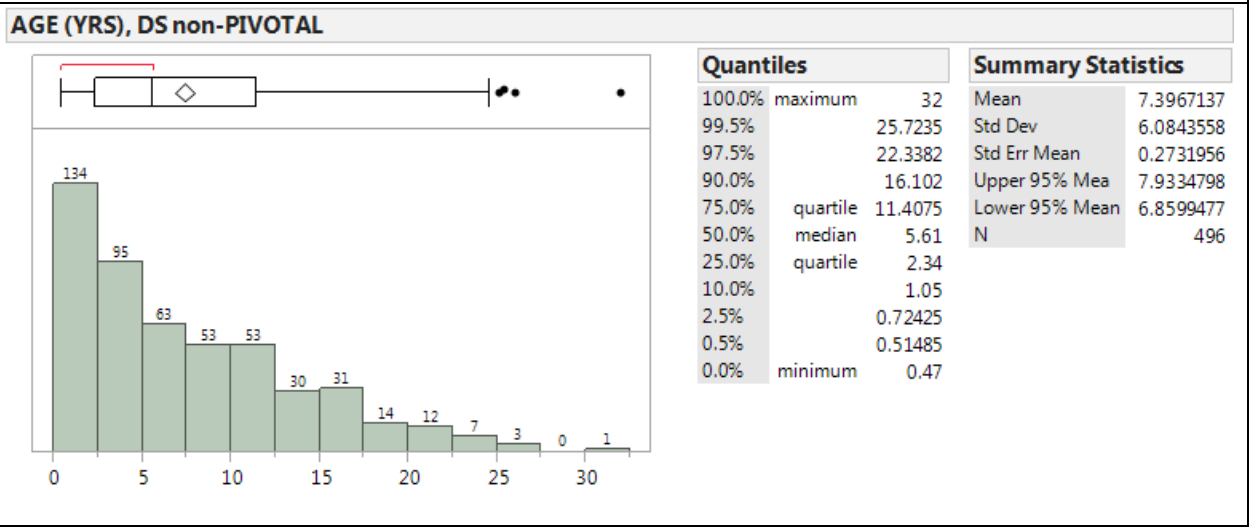
Serious adverse events in DS patients from the non-pivotal studies are examined for difference in SAE profile between the 0 to <10 year and 10 to <20 year age groups. In the younger 0 to <10 year age band there were 13 SAE preferred terms that had an occurrence in 2 or more unique patients in the entire array of SAEs from the 496 non-pivotal DS patients. “Seizure”, “Decreased appetite” and “Status epilepticus” were the top three event terms with an incidence of 3.2%, 2.0% and 2.0% respectively. There were also two HGLT (higher level group terms) “Fatal outcome” terms; these include “Death” and “Sudden Death” with an incidence of 1.7% and 0.6% respectively. In the 0 to <20 year age group there were three terms with an occurrence in 2 or more unique patients in the entire array of SAEs in the 496 non-pivotal DS patients, these were “Seizure”, “Decreased appetite” and “Fatigue”. Similar to the younger age band the two highest incidence preferred terms were “Seizure” and “Decreased appetite” at 4.7% and 2.3% respectively. The smaller array of SAE events in the older 0 - <20 year age group may in part be due to the smaller sample size of this cohort and the occurrence of the “catastrophic” stage of Dravet syndrome in the younger age group, see Table 65.

Table 65 Non-Pivotal DS patient, SAE incidence by Age group, with breakout of individual preferred terms where unique patient events ≥2. (***95.6% of patients in this group are age 20 years or younger***)

AGE GROUPS	**AGE GROUP n**	**INCIDENCE OF SAE BY AGE GROUP**	**SAE and incidence where ≥2 events occurred (based on unique patients)**	
			Preferred term	**Incidence in cohort**

AGE GROUPS	AGE GROUP n	INCIDENCE OF SAE BY AGE GROUP	SAE and incidence where ≥2 events occurred (based on unique patients)	
			Preferred term	Incidence in cohort
0 - <10 yr	346	12.4	Seizure	3.2
			Decreased appetite	2.0
			Status epilepticus	2.0
			Death	1.7
			Somnolence	1.4
			Pneumonia	1.2
			Pyrexia	1.2
			Thrombocytopenia	1.2
			Bronchitis	0.6
			Dehydration	0.6
			Epilepsy	0.6
			Sudden death	0.6
			Viral infection	0.6
10 - <20 yr	128	10.2	Seizure	4.7
			Decreased appetite	2.3
			Fatigue	1.6

*DS patients, non-Pivotal (n=496), category 2 & 3 in Table 13 (study key)



Serious adverse events in DS patients from the non-pivotal studies are examined for difference in SAE profile across the duration of treatment, see Table 66. The incidence of SAE preferred terms by 6 month increments of stiripentol exposure reveals the term “seizure” occurs most consistently as duration of exposure increases. There were seizure event terms in every six month interval with a maximum incidence of 2.73% in the interval between 2.5 and 3 years with the second highest incidence in the first six months with an incidence of 2.46%. Another

epilepsy term, "status epilepticus" has the second most consistent incidence during the first two years of exposure and none thereafter. Outside of a consistent occurrence of seizure across exposure intervals and status epileptics up to two years exposure there was no temporal trend among the adverse event terms. There was also no clear temporal trend for death and sudden death.

Table 66 Non-Pivotal DS patients[†], SAE incidence by time on STP treatment, with breakout of individual preferred terms where unique patient events ≥2.

DURATION OF STP TREATMENT, IN 1 YEAR INCREMENTS	DURATION GROUP n	INCIDENCE OF SAE BY DURATION BAND (unique pts with event / n in cohort)[*]	SAE and incidence where ≥2 events occurred (based on unique patients)	
			Preferred term	Incidence in cohort
0 - <0.5 yr	488	5.3	Seizure	2.46
			Decreased appetite	1.84
			Somnolence	0.82
			Status epilepticus	0.82
			Dehydration	0.61
			Thrombocytopenia	0.61
			Bronchitis	0.41
			General physical health deterioration	0.41
			Pyrexia	0.41
			Cachexia	0.20
			Death	0.20
			Fatigue	0.20
			Vomiting	0.20
0.5 - <1 yr	409	3.9	Pneumonia	0.98
			Seizure	0.98
			Status epilepticus	0.73
			Decreased appetite	0.49
			Bronchitis	0.24
			Death	0.24
			Epilepsy	0.24
			General physical health deterioration	0.24
			Pyrexia	0.24
			Thrombocytopenia	0.24
			Viral infection	0.24

			Vomiting	0.24
1 - <1.5 yr	359	3.1	Seizure	1.39
			Death	1.39
			Status epilepticus	0.84
			Viral infection	0.84
			Pneumonia	0.28
			Pyrexia	0.28
			Somnolence	0.28
1.5 - < 2 yr	292	1.4	Seizure	1.37
			Status epilepticus	0.68
2 - < 2.5 yr	251	1.6	Seizure	1.20
			Decreased appetite	0.40
			Fatigue	0.40
			Sudden death	0.40
2.5 - < 3 yr	220	1.8	Seizure	2.73
			Epilepsy	0.45
			Sudden death	0.45
3 - < 3.5 yr	188	2.1	Seizure	2.13
3.5 - < 4 yr	150	1.3	Seizure	1.33
*Patient may have had an SAE in more than one duration band				
†DS patients, non-Pivotal (n=496), category 2 & 3 in Table 13 (study key)				

Non-DS Patients from DIAVEY AND STILON STUDIES (all STP treatment patients)

In order to extend the safety examination outside of Dravet syndrome the incidence of serious adverse events is examined among the non-DS patients in the DIAVEY and STILON studies. There were 187 patients in this group, 77 patients from DIAVEY and 110 from STILON. Within the STILON study there were 81 patients with partial epilepsy and 29 with “other epilepsies” that are not further characterized. In the DIAVEY study there were 44 patients with partial epilepsy and 33 patients with other epilepsies that include Idiopathic generalized epilepsy, myoclonic epilepsy, LGS, Doose syndrome, and single cases of “others”. Twenty one percent (21%) of the 187 patient non-DS patient cohort of the DIAVEY and STILON studies had an entry for an SAE of any type.

In this cohort, there were SAEs from 2 or more unique patients found under six preferred terms identified in 21% of the patients, Table 67. “Seizure” and “status epilepticus” had an incidence in this group of 5.3% and 2.7% respectively. There were two fatal outcomes as “Death” with an incidence of 1.1%.

Table 67 Non-DS Patients, STILON and DIAVEY Studies, any SAE and SAE ≥2 Events*

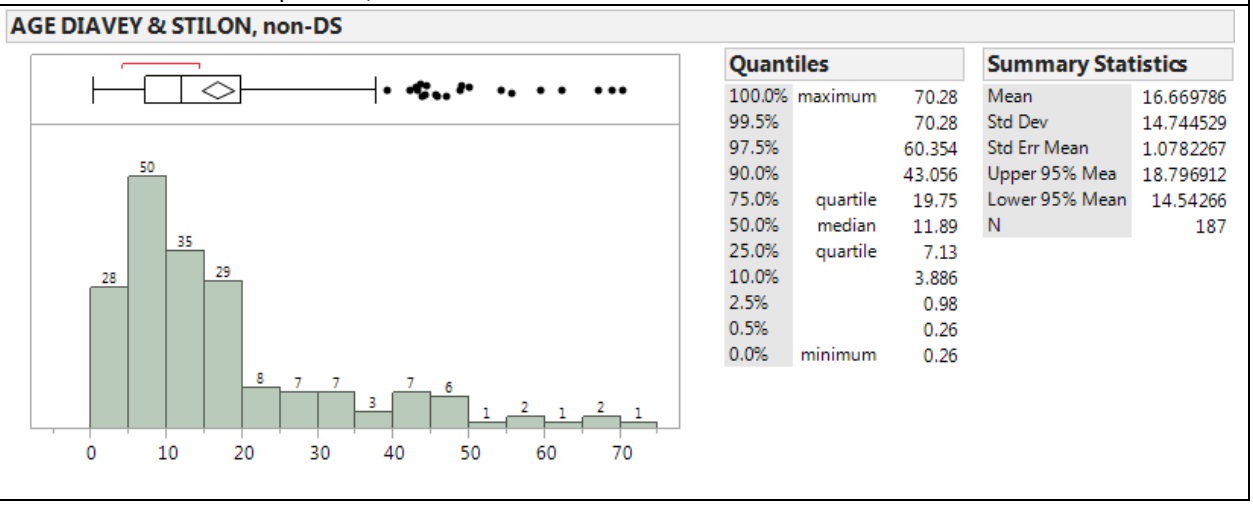
Any SAE			**21%**
Preferred term	**Number of Events**	**Number of Unique Patients**	**Incidence (%)**
Seizure	14	10	5.3
Status epilepticus	5	5	2.7
Arthropathy	2	1	0.53
Death	2	2	1.1
Dizziness	2	1	0.53
Fall	2	2	1.1
*DIAVEY & STILON non-DS patients, n=187			

Serious adverse events in non-DS patients from the DIAVEY and STILON studies are examined for difference in SAE profile across age groups in ten year intervals. There are six resultant intervals with "n" ranging from 78 patients in the 0 to <10 year old age band and 7 patients in the 50< year age band. In the younger 0 to <10 year age band there was a 19.2% incidence of serious adverse events. In this age cohort there were two preferred terms with an occurrence in two or more unique patients, these were "Seizure" and "Status Epilepticus" with an incidence of 3.8% each. In the 10 to <20 year cohort there were 3 preferred terms that appeared as serious adverse events in two or more patients. These were "Seizure", "Arthropathy" and "Status epilepticus" with incidence of 4.7%, 1.6% and 3.1% in this age cohort. The 20 to <30 year age cohort had a 20% incidence of serious adverse events but none in two or more unique patients. In the 30 to <40 year age cohort there was a 30% incidence of serious adverse events where "dizziness" was the only preferred term that occurred as an SAE in two or more patients with an incidence in this cohort of 10%. In the 40 to <50 year age cohort there was a 31% incidence of serious adverse events (from among "n" of 13 patients) where "seizure" occurred in two or more unique patients with an incidence of 27%. The age 50≤ cohort was a small group of 7 patients with 43% incidence of serious adverse events, none in two or more patients.

Table 68 DIAVEY and STILON non-DS patients SAE incidence by Age group*

AGE GROUPS	**AGE GROUP n**	**INCIDENCE OF SAE BY AGE GROUP**	**SAE and incidence where ≥2 events occurred (based on unique patients)**	
			Preferred term	**Incidence in cohort**
0 - <10 yr	78	19.2	Seizure	3.8
			Status epilepticus	3.8
10 - <20 yr	64	17.2	Seizure	4.7
			Arthropathy	1.6
			Status epilepticus	3.1

20 - <30 yr	15	20		
30 - <40 yr	10	30	Dizziness	10.0
40 - <50 yr	13	30.8	seizure	28.6
50<= yrs	7	42.9		
*DIAVEY & STILON non-DS patients, n=187				



Quantiles		
100.0%	maximum	70.28
99.5%		70.28
97.5%		60.354
90.0%		43.056
75.0%	quartile	19.75
50.0%	median	11.89
25.0%	quartile	7.13
10.0%		3.886
2.5%		0.98
0.5%		0.26
0.0%	minimum	0.26

Summary Statistics	
Mean	16.669786
Std Dev	14.744529
Std Err Mean	1.0782267
Upper 95% Mea	18.796912
Lower 95% Mean	14.54266
N	187

Serious adverse events in non-DS patients from the DIAVEY and STILON studies are examined for differences in SAE profile across the duration of treatment, Table 69. The incidence of serious adverse events which occurred across 1 year intervals from the time of STP treatment in each of the studies is examined. In those patients with less than 1 year exposure there was a 9.6% incidence of serious adverse events. Within this panel of adverse events there were three preferred terms in two or more patients that occurred as SAEs. These terms were “Seizure”, “Status epilepticus” and “Arthropathy” with an incidence of 3.7%, 2.1% and 0.5% respectively. In the next cohort of one to <2 year exposure there was an 8.7% incidence of serious adverse events. “Seizure” was the only preferred term that occurred as an SAE in two or more unique patients with an incidence of 1.6%. In the 2 to <3 year exposure cohort there was a 6.5% incidence of serious adverse events. “Dizziness” and “Seizure” appeared as preferred terms in this cohort as serious adverse events in two or more unique patients with an incidence of 1.1% and 2.2% respectively. In the final age cohort of 3 to <4 years exposure there was a 5.7% incidence of serious adverse events with none occurring in two or more unique patients. There were 9 patients in the DIAVEY and STILON non-DS cohort that had no entry for the adverse event start date; therefore, no incidence by duration of exposure could be calculated.

Table 69 DIAVEY and STILON‡ non-DS patients, SAE incidence by time on STP treatment

DURATION OF STP TREATMENT, IN 1 YEAR INCREMENTS	DURATION GROUP n	INCIDENCE OF SAE BY DURATION BAND (unique pts with	SAE and incidence where ≥2 events occurred (based on unique patients)

		event / n in cohort)*	Preferred term	Incidence in cohort
0 - <1 yr	187	9.6	Seizure	3.7
			Status epilepticus	2.1
			Arthropathy	0.5
1 - <2 yr	126	8.7	Seizure	1.6
2 - <3 yr	93	6.5	Dizziness	1.1
			Seizure	2.2
3 - <4 yr	53	5.7		
No AE start date entry†	9			

*Patient may have had an SAE in more than one duration band
† in this group no SAE had more than one entry
‡ patients entered STILON from studies with ongoing stiripentol (STP) exposure, thus the time from beginning STP treatment to onset of SAE does not represent a patient's entire STP exposure prior to the SAE.

SAE Pooled Dravet Syndrome Patients with addition of Non-DS from STILON and DIAVEY

Serious adverse events (SAE) in Pooled Dravet Syndrome Patients from STICLO (STP treatment arm), TAU-EAP, DIAVEY, STILON, STIPOP, STP1 and STEV also including DIAVEY and STILON non-Dravet Syndrome Patients, n=625 STP treated patients.

Serious adverse events from the pool of DS patients in pivotal and non-pivotal studies with the addition of non-DS patients from the DIAVEY and STILON studies are examined. The calculated denominator of this pool by summation of individual (xpt) datasets is 716 patients. The real denominator is less than, n= 716, due to continuation of patients through several clinical studies. The total unique patient in this pool is 625.[47] Any SAE occurred in 112 (17.9%) of patients in this pool. Preferred terms that occurred as an SAE with an incidence greater than 1% were "Seizure", "Status epilepticus", "Decreased appetite", and "Death" with an incidence of 4.5%, 2.1%, 1.8%, and 1.4% respectively. There were 6 patients with "pneumonia" and 6 with "pyrexia" although there is no overlap among these 12 patients. A single "pneumonia" event occurred 6 months after cessation of STP but resulted in death. The extended time from STP treatment to death diminishes a causal relationship between the "death" and "pneumonia" events. There were four patients (0.6%) who experience an SAE of thrombocytopenia; two of

[47] based on all category 1 – 3 Dravet patients plus non-Dravet patients from the STILON and DIAVEY studies in Table 41. However, due to continuation of patients from STEV, STICLO and STILON into TAU-EAP the total of unique patients is lower but cannot be calculated from the individual study datasets (xpt) because patient ID is unique by study. Rather than reviewer calculated, the unique patient total must be taken from the sponsor exposure table 3-8, page 60 in the ISS, 438 patients and is added to the sum of non-DS patients contributed by the STILON and DIAVEY studies, 187 patients to equal a total of 625.

who were withdrawn from STP treatment and 2 (0.3%) patients with an SAE of increased ALT, one of these patients was withdrawn from STP treatment.

Table 70 SAE All Pooled DS Patients (category 1- 3) with non-DS Patients from DIAVEY AND STILON (STP treated patients) ‡

Preferred Term	**Unique Patients per Preferred term*** (drug withdrawn)	**Incidence in total pool (%) n=625†**
Any SAE	112	17.9
Seizure	28 (1)	4.5
Status epilepticus	13 (2)	2.1
Decreased appetite	11 (2)	1.8
Death	9	1.4
Pneumonia	6 (0)	1.0
Pyrexia	6 (0)	1.0
Somnolence	5 (2)	0.8
Thrombocytopenia	4 (2)	0.6
Cachexia	3 (1)	0.5
Dehydration	3 (1) as decreased appetite/cachezia)	0.5
Fall	3 (0)	0.5
Fatigue	3 (2)	0.5
General physical health deterioration	3 (0)	0.5
Viral infection	3 (0)	0.5
Aspartate aminotransferase increased	2 (1)	0.3
Bronchitis	2 (0)	0.3
Dizziness	2 (0)	0.3
Epilepsy	2 (0)	0.3
Lung disorder	2 (0)	0.3
Overdose	2 (0)	0.3
Sudden death	2 (0)	0.3
Vomiting	2 (0)	0.3
*a single unique patient may have an entry into more than one preferred term category †Unique patients less than individual study count due to participation of some patient in more than one study, see footnote. ‡ Note, only PBO controlled group were 31 placebo patients from the STICLO studies, not included in above count, who had 5 serious adverse events from among 3 patients, Table 63		

From among STP treated patients there were 22 preferred terms identified as serious adverse

events from 2 or more unique patients, prior to division into duration of treatment cohorts. In order to determine if duration of treatment is a driver for a safety signal these terms are examined for occurrence in 6 month increments of duration of treatment in Table 71. In order to reduce the table size and retain the most informative data, events with only 1 unique patient in a "DURATION CODE AT EVENT" cohort were removed.

Table 71 SAE Incidence by Treatment Duration Pooled DS Pivotal & Non-Pivotal with non-DS from DIAVEY and STILON Where ≥2 Unique Patients (*per duration group*) Experiences the SAE Term

DURATION CODE AT EVENT*	Preferred Term	Events , Unique Patients (study withdrawal)	Incidence (%) in Cohort at Time of Event†
1	Seizure	13 (1)	1.85
1	Decreased appetite	7	1
1	Status epilepticus	5	0.71
1	Somnolence	4	0.57
1	Dehydration	3	0.43
1	Thrombocytopenia	3	0.43
1	Bronchitis	2	0.28
1	General physical health deterioration	2	0.28
1	Pyrexia	2	0.28
2	Seizure	6	1.07
2	Status epilepticus	6	1.07
2	Pneumonia	3	0.53
2	Death	2	0.36
2	Decreased appetite	2	0.36
3	Death	4	0.82
3	Seizure	4	0.82
3	Status epilepticus	3	0.62
3	Fall	2	0.41
3	Pneumonia	2	0.41
3	Pyrexia	2	0.41
3	Viral infection	2	0.41
4	Seizure	4	0.99
5	Seizure	3	0.87
6	Seizure	4	1.36
7	Seizure	4	1.65
8	Seizure	2	1.11

Duration code = 6 month intervals from start of treatment thus code 8 = 4 years.

† patients per duration code cohort are approximated due to limit of tracking a subset of patients with participation across more than one study. Duration code reflects length of participation of patients uniquely identified in each individual category 1 -3 study.

Significant Adverse Events seen in analysis of Serious Adverse Events from Categories 2 & 3, both DS and non-DS patients.

Decreased Appetite

Decreased appetite was present with a notable frequency in the entire pooled study group with an incidence of 1.54% and discontinuation due to decreased appetite in 3 patients. The narratives of these events are examined to assess the strength of this signal. Table 72 is a list of the decreased appetite patients with a brief extraction from the narrative report. Five of the eleven patients appear to have a causal relationship to STP based on the persistence of the event in parallel with STP treatment, temporal relationship, a partial dechallenge response, or discontinuation of STP treatment.

Table 72 SAE of "Decreased Appetite" from All Pooled patients including DIAVEY and STILON non-DS.

subject ID	AGE	Days of treatment	Verbatim Term	Temporal relationship	Narrative
STP1-(b) (6)	4.3	388	worsening anorexia	no	mild
STP1-(b) (6)	24.6	395	worsening anorexia	no	dose reduced wih improved appetite (+ dechallenge)
STILON-(b) (6)	5.4	1057	anorexia	no	7 yr total STP treatment , did not gain weight in STILON
DIAVEY-(b) (6)	12.9	238	loss of appetite	3 wks	Had endoscopy, anorexia persisted, pt discontinued STP at month 9, positive dechallenge
DIAVEY(b) (6)	7.7	954	anorexia	4 wks	weight gain continued (with loss of appetite)
DIAVEY(b) (6)	2.3	828	anorexia	18 wks (no)	Thrombocytopenia resolved after discontinuation of VPA. Anorexia / dizziness persisted 4 months and resolved
DIAVEY(b) (6)	0.8	955	anorexie	Sometime in 1st 8 weeks (yes)	Reduced VPA and STP with partial improvement. Anorexia and Thrombocytopenia
DIAVEY(b) (6)	12.3	1031	refusal to eat		isolated viral syndrome
DIAVEY(b) (6)	15.6	78	anorexia		Anorexia / coldness persisted on dechallenge . Brief rash after starting STP
ATU de COHORTE - DIACOMIT(b) (6)	3.0	526	anorexia		Dose later increased due to status epilepticus
ATU de COHORTE -	2.8	90	anorexia	4 wks (yes)	Discontinuation, positive dechallenge

subject ID	AGE	Days of treatment	Verbatim Term	Temporal relationship	Narrative
DIACOMIT (b) (6)					

Thrombocytopenia

The narrative reports of thrombocytopenia serious adverse events are examined to evaluate the strength of a potential thrombocytopenia signal. The first thrombocytopenia patient (b) (6) (b) (6) was an 11 month old male with DS in the DIAVEY study who was treated with STP for 40 days before discontinuation due to neutropenia and thrombocytopenia. The patient was also treated with VPA and CLB which remained unchanged at STP discontinuation. The next patient with a thrombocytopenia report is (b) (6) a 9 month old female with DS in the DIAVEY study. Thrombocytopenia was identified after 2 months of STP treatment in addition to failure to thrive, elevated ALT (2 x ULN), and dehydration. The STP dose was reduced to 250mg/day and thrombocytopenia resolved within 2 weeks (positive dechallenge). The third patient with a thrombocytopenia SAE was patient (b) (6) a 13 month old male with DS in the TAU-EAP study. This patient developed thrombocytopenia on day 43 of STP treatment. Stiripentol was subsequently discontinued with resolution of thrombocytopenia in 6 days (positive dechallenge). The final and 4th patient with an SAE of thrombocytopenia was patient (b) (6) a 4 year old male with DS enrolled in the STILON study after participating in the STEV study. Six months after enrolling in STILON, the patient was hospitalized for severe vomiting, which resolved within 2 days. The SAE was judged to be probably related to STP. During the same period of time, the patient was hospitalized for hyperthermia, seizures, and thrombocytopenia with no dechallenge result presented. All of these patients were on VPA and CLB at the time of the thrombocytopenia event.

Table 73 Tabular presentation of thrombocytopenia SAE

USUBJID- age, dur	AGE	DOT YEARS	STP Discontinued	Temporal relationship	Narrative
STILON (b) (6)	4.09	3.4	n	no	Identified in the context of hyperthermia and seizures, no dechallenge data.
DIAVEY (b) (6)	0.77	2.6	n	yes	Count declined to 41,000 /mm3. Positive dechallenge
ATU de COHORTE - DIACOMIT- (b) (6)	1.1	0.12	Y	yes	Withdrawn day 43. Count reached

					43000, Positive dechallenge, thrombocytopenia resolved in 6 days.
DIAVEY (b) (6)	0.95	0.11	Y	yes	Dechallenge on thrombocytopenia not reported, concurrent neutropenia resolved

Neutropenia

There were 2 patients in the total category 1-3 DS and non-DS patients with an SAE of neutropenia. One of the patients DIAVEY (b) (6) is captured in the presentation of thrombocytopenia. This patient also had neutropenia. The report indicates that in patient (b) (6) neutropenia resolved 1 day after discontinuation of STP. The second patient DIAVEY (b) (6), a 2 year 9 month old female who weighted 10kg, had an SAE of sedation, however, review of the report narrative reveals the patient also had mild neutropenia with a count of 1300/mm^3. There is no dechallenge data on this second patient.

Elevated Alanine aminotransferase (ALT)

There was a single patient with an SAE of elevated ALT (not included in Table 70). This patient, (DIAVEY (b) (6)) developed an increase in ALT to 4.8 ULN, from an already elevated baseline of 4.3 x ULN, after approximately 3 weeks of STP treatment at 31mg/kg/day. This (additional) ALT increase occurred concurrently with an elevation of CPK to >10,000 IU/L with ALT of muscle origin as the source of incremental increase over baseline. STP was discontinued.

Reviewer Summary Comment:

Examination of serious adverse events across age groups in increments of ten years reveals a fairly uniform incidence of serious adverse events in the DS patients. The sample size is larger in the younger age cohort with a broader range of preferred terms. The incidence of seizure is similar in the younger and older cohort but death is not reported in the older cohort. This may be due to the window of "catastrophic" Dravet syndrome in the younger DS cohort. The sample size of non-Dravet patients is smaller with a broader range of ages represented. Seizure is seen to be the most consistent serious adverse event across the age groups, similar to the DS cohort.

Examination of serious adverse events by duration of treatment in the DS patient cohort reveals a similar incidence of SAEs across the 6 months increments for the first 1.5 years

followed by a decline in incidence thereafter. The most frequently consistent events across the epochs of treatment are seizure and status epilepticus. Overall there is no signal for a serious adverse event that is related to duration of treatment.

The adverse events with greatest incidence in the category 1,2 and 3 studies are seizure, status epilepticus, decreased appetite and death. The profile of these events and incidence of events is consistent across the subsets of the safety population including DS patients, non-DS patients and the all patient pooled group, thus a selective vulnerability due to disease, age or duration of exposure is not apparent.

The placebo controlled study population is small which reduces signal detection when attempting to differentiate SAEs due to STP treatment from background. A strong temporal relationship, positive dechallenge or both indicate an increasing likelihood of causal relationship between STP and the event. Among the patients who experienced an event of anorexia there were three patients with an onset within one month and three patients with a positive dechallenge response while two patients had both.

From among the patients with thrombocytopenia there were three patients with both a strong temporal relationship and a positive dechallenge. This is consistent with a strong causal signal. There was one patient with an SAE of elevated ALT. This case was causally very weak. The event was an incremental increase over an abnormally elevated baseline measurement in conjunction with an elevation of CPK and was likely of muscle origin.

The preferred terms seizure and status epilepticus were frequent and consistent across diseases, DS and Non-DS, age groups and duration of treatment. Without placebo control these events are best explained by the high frequency of seizure and status epilepticus that occur in the underlying disease process.

Within the 64 patients in the randomized controlled STICLO studies the incidence of seizure and status epilepticus was the same in the placebo and STP treatment arms. There was one drug eruption SAE in the STP treatment group not present in placebo.

Biopharmaceutical and Pharmacokinetic Studies in Healthy Volunteers

Study reports of the healthy volunteer PK studies are examined for serious adverse events. No SAEs are identified in the STIVAL study, while the 6 patients in the Greig study are noted only to have “tolerance good”. The STIUNI study identifies 2 adverse events but no SAE while the Pons study also identifies adverse events of nausea, insomnia, irritability and withdrawal but does not indicate if they are considered an SAE, Table 74.

Table 74 Serious Adverse Events in PK – PD studies

Biopharmaceutical and Pharmacokinetic Studies in Healthy Volunteers						
STUDY identifier (Sponsor Study Number) (Name) (Year)	**category**	**OBJECTIVE**	**DESIGN**	**POPULATION**	**DURATION of Study**	**Analysis for SAE**
BC.481 *STIVAL (2007)*	5	BA	OL- Crossover	Healthy= 24	Single dose	No SAE
BC.287 *Greig (1993)*	5	PK	OL- Crossover	Healthy= 6	Single dose	Only notes "tolerance good"
BC.337 *STIUNI (2002)*	5	Pk	OL- Crossover	Healthy= 12	Single dose	2 AE, rhinitis, pharyngitis
BC.345 *Pons (1995)*	5	cyp	OL	Healthy= 13	14 days	Nausea, insomnia, irritability- withdrawal, not stated if considered SAE

Exploratory Efficacy Studies in non-Dravet Patients

The Lennox-Gastaut study does not declare any SAE but does identify one adverse event of anorexia, vomiting, balance, drowsiness resulting in patient withdrawal. The STICAR study does not include a definition of a serious adverse event but does have four adverse events resulting in patient discontinuation. These adverse events include: 1. esophageal pain, erosive gastritis 2. Status epilepticus 3. Fall, scalp wound (PBO) and 4. Accidental death – cranial injury. The STISEVR study report indicates specifically that no serious adverse events occurred. The WOW study does not define a serious adverse event. There were 10 adverse events leading to withdrawal. These were all central nervous system adverse events not-including seizure and gastrointestinal adverse events. The Martinez- Lage study had no definition of serious adverse events but 4 adverse events leading to patient withdrawal are captured. These include 2 patients with delirious episodes who had a positive dechallenge and one patient each with anorexia and vomiting. The Courjon study (1976) did not define a serious adverse event and had only tolerance scale of "excellent", "moderate" and "poor". The poor tolerance events occurring in 4 patients were all gastrointestinal or common C_{max} related central nervous system events except in one patient there was 4 limb diffuse choreiform movement. In the Loiseau study there is no definition for serious adverse, only a conclusion that with the exception of one psychotic state, stiripentol was in general well tolerated, see Table 75, analysis for SAE column.

Table 75 Serious Adverse Events in non-Dravet Syndrome Exploratory Efficacy Studies

Exploratory Efficacy Studies in non-Dravet Patients						
STUDY identifier	**category**	**OBJECTIVE**	**DESIGN**	**POPULATION**	**DURATIO**	**Analysis for SAE**

(Sponsor Study Number) (Name) (Year)					N of Study	
BC.274 *Lennox- Gastaut* (1994)	4	EFFICACY LGS	SB	Non-DS= 24	2 month	Search: no declared SAE, 1 withdrawal due to anorexia , vomiting , balance, drowsiness
BC.246 *STICAR (1990)*	4	EFFICACY, add on to CBZ	DB	Non-DS= 62	2 month	No SAE defined but AE to withdraw: 1. esophageal pain, erosive gastritis 2. Status epilepticus 3. Fall, scalp wound (PBO), 4. Accidental death – cranial injury
BC.484 *STISEVR (2000)*	4	EFFICACY, ADD CBZ	SB-OL	Non-DS= 32	3 month	No SAE
BC.276 *WOW* (1994)	4	EFFICACY, ADD TO CBZ	OL	Non-DS= 64	70 days	No SAE defined. AE to discontinuation: 1. nausea with shivering, sweating (after first STP tab) 2. nausea /vertigo 3. panic attack, behavioral disorder/hallucination- D33 4. nausea, vomiting, ataxia, instability 5. persistent digestive disorders associated with Lipothymia 6. nausea, cephalea, phonophobia, photobit, lightheaded 7. diplopia, epigastric disorder day 7 8. discomfort accompanied by overexcitement 9. nausea and vomiting 10. nausea, balance disorder, convergence disorder, diplopia, asthenia (D12)
BC.244 *Martinez- Lage* (study report date 1986)	4	EFFICACY	OL	Non-DS= 31	16 week	SAE not defined 2 pts had delirious episodes with positive dechallenge 1 pt anorexia, 1 pt vomiting
BC.109 *Courjon* (study report date 1976)	4	EFFICACY	OL	Non-DS 135	1 month to more than 6 months	SAE not defined, alternative nomenclature is tolerance, defined as “excellent”, “moderate”, “poor”. Moderate events- 7 Poor- 1. diffuse choreiform – 4 limbs 2. GI distress- gastric discomfort, abdominal distension, 3. vomiting 4. vomiting, visual disturbance, psychomotor slowing
BC.243 *Loiseau (study report date 1984)*	4	EFFICACY	OL	Non-DS = 44	16 week maximum	SAE not defined. Conclusion: With the exception of one psychotic state, stiripentol was in general well tolerated.

Reviewer Comment: The PK-PD studies of healthy volunteers and the non-DS exploratory efficacy studies are examined in text narrative and tabular presentations in PDF documents without the utility of SAS transport datasets (xpt). Some studies do not define an SAE or use an alternate system of nomenclature. In these cases the most severe events, such as “poor tolerance” or an adverse event leading to withdrawal are taken as proxy events for an SAE.

The profile of serious adverse events, based on the proxy equivalents, is similar to that seen in the category 1, 2 and 3 studies with the occurrence of central nervous system effects or gastrointestinal intolerance. There is one report of a diffuse choreiform movement disorder, no information is provided on the outcome of the event or if STP was discontinued. The relation to STP treatment is unclear due to insufficient information. Overall there is no signal among these studies of a safety event that is life threatening.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

STICLO Trials (Category 1)

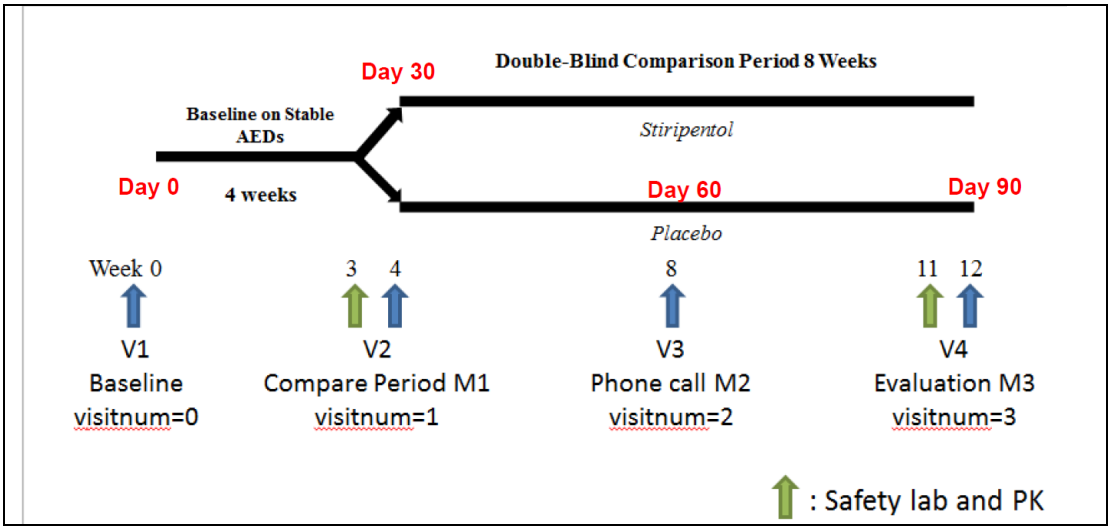
In the pivotal trials there was a higher frequency of discontinuations in the placebo than STP treatment arm with 6 (19%) discontinuations in placebo and 2 (6.1%) in the STP treatment arm. Four of six discontinuations in the placebo arm had a disposition term of "lack of efficacy" while the remaining two had "status epilepticus". In the STP arm one patient had a disposition term of "status epilepticus" and the remaining patient had disposition terms of "Drowsiness, balance impaired, and sialorrhea" consistent with central nervous system adverse effects, see Table 76 and Table 77.

Table 76 STILOC Trials, Discontinuation due to AE

	Placebo	STP
STICLO FRANCE & ITALY	n=31	n=33
Withdrawal	6 (19%)	2 (6.1)

Table 77 STICLO Trials, Reason for Individual Patient discontinuation

SUBJECT ID	TREATMENT ARM	REASON FOR DISCONTINUATION	Days in DB interval
STICLO - FRANCE (b) (6)	PLACEBO	Drowsiness and motor deficit involving the right half of the body	22
STICLO - FRANCE	PLACEBO	STATUS EPILEPTIC	15
STICLO - FRANCE	PLACEBO	LACK OF EFFICACY	33
STICLO - FRANCE	PLACEBO	LACK OF EFFICACY	8
STICLO - ITALY (b) (6)	PLACEBO	LACK OF EFFICACY	24
STICLO - ITALY	PLACEBO	LACK OF EFFICACY	28
STICLO - FRANCE (b) (6)	STIRIPENTOL	STATUS EPILEPTIC	49
STICLO - ITALY (b) (6)	STIRIPENTOL	Drowsiness, balance impaired, and sialorrhea	32



Non-Pivotal Studies Dravet syndrome and non-Dravet (Category 2 and 3)

The discontinuations are examined in the pool of Dravet syndrome patients in the non-pivotal studies and the non-Dravet epilepsy patients in the DIAVEY and STILON studies as well as a pool of this entire group of category 2 and 3 studies of all seizure types. *There is no placebo control in these groupings of discontinuations thus a signal search is directed at discontinuations of special interest in antiepilepsy drugs that include seizure worsening, hepatic toxicity, bone marrow toxicity, and severe behavioral disorders.* There is a pool of 496 patients with Dravet syndrome that may be compared to the pool of non-Dravet subjects to examine differences in reasons for discontinuation. Due to the diversity of study methodology any observation is primarily exploratory.

Table 78 reveals there were a total of 67 discontinuations from the non-pivotal DS patient group while the non-DS, DIAVEY and STILON group had 77 discontinuations. The largest category of discontinuations in both groups was lack of efficacy with the highest percent of discontinuations in this category occurring in the non-DS cohort. The next largest categories of discontinuation were adverse events where there were 19 in the DS patient cohort and 11 in the non-DS cohort. There was one discontinuation in the DS cohort for status epilepticus while the remaining categories of “other”, “recovery”, “lost to follow up” and “non-compliance” present in the two cohorts are not as informative for analysis of safety signals. It is notable that lack of efficacy accounts for a much higher percentage of the discontinuations in the non-DS patient cohort. As noted previously these cohorts are not directly comparable in their duration of treatment.

Table 78 Discontinuations in the Pool DS patients from non-Pivotal Studies and non-DS patients in DIAVEY and STILON studies

DSDECOD (discontinuation category),	Discontinuations, Dravet syndrome, (n = 496)	% of pool (n=496)	Discontinuations, non-Dravet Syndrome n= 187	% of pool (n=187)
LACK OF EFFICACY	33	6.7	41	21.9
ADVERSE EVENT	19	3.8	11	5.9
OTHER	14	2.8	10	5.3
STATUS EPILEPTIC	1	0.2	0	0
RECOVERY	0	0	8	4.3
LOST TO FOLLOW-UP	0	0	6	3.2
NON-COMPLIANCE WITH STUDY DRUG	0	0	1	0.5
Total	67	13.5	77	41.2

A direct comparison of the Dravet and non-Dravet patient discontinuations in the DIAVEY and STILON studies reveals a lower frequency of discontinuations due to "lack of efficacy" in the DS patient cohort while there was a minimally higher frequency of adverse effects in the DS cohort. There were no patients lost to follow up in the DS cohort with a 3.2% frequency in the non-Dravet cohort. This may reflect a higher proportion of adult patients with greater social mobility in the non-DS cohort. The mean and median age for the non-DS cohort of 187 patients was 16.7 and 11.9 years respectively while the mean and median age for the DS cohort of DIAVEY and STILON was 7.5 and 6.7 years respectively. The mean and median ages of the six lost to follow up patients in the non-DS patient cohort was 17.1 and 17.3 years respectively with two patients under the age of 17. These patients were age 8.5 and 14.1 years. These overall older patients may have greater mobility and represent a follow up challenge.

Table 79 Discontinuations in DIAVEY and STILON Studies, DS patients compared to the non-DS patient cohorts

DSDECOD (discontinuation category)	discontinuations, Dravet Syndrome	% of pool, (n=197)	Discontinuations, non-Dravet Syndrome	% of pool (n=187)
LACK OF EFFICACY	26	13.2	41	21.9
ADVERSE EVENT	14	7.1	11	5.9
OTHER	7	3.6	10	5.3
RECOVERY	0	0	8	4.3
LOST TO FOLLOW-UP	0	0	6	3.2
NON-COMPLIANCE WITH STUDY DRUG	0	0	1	0.5
total	47	23.9	77.0	41.2

The adverse event discontinuation category for the Dravet Syndrome patients' non-pivotal

studies and DIAVEY – STILON non-DS patients are examined. There were 19 (3.8%) patients from the overall DS non-pivotal studies with discontinuation due to adverse events. Adverse event terms are grouped into four categories, these include loss of appetite terms, behavior disorder terms, sedation and fatigue terms and laboratory abnormality terms. A single patient may be linked to more than one adverse event term and category. The examination of DS patient non-pivotal studies reveals there were 9 (1.8%) patients with loss of appetite terms, 3 (0.6%) patients with behavior disorder terms, 8 (1.6%) patients with sedation and fatigue terms and 4 (0.8%) patients with laboratory abnormality terms (2 neutropenia, 2 thrombocytopenia and 1 hepatic enzyme abnormality).

There were 11 (5.9%) patients from the DIAVEY – STILON non-DS cohort who discontinued due to adverse events. From among the DIAVEY – STILON non-DS cohort there were 3 (1.6%) patients with loss of appetite terms, 3 (1.6%) patients with behavioral disorder terms, 3 (1.6%) patients with sedation – fatigue terms and 2 (1.1%) patients with laboratory abnormality terms.

Reviewer Comment: There were no features in the profile of discontinuations in the STICLO studies that undermine study integrity. In the STICLO studies there were a higher proportion of discontinuations due to lack of efficacy in the placebo compared to the STP treatment cohort which is in alignment with a positive treatment effect.

When the DS and non-DS cohorts from within the same two open label studies, DIAVEY – STILON are compared there was a higher proportion of discontinuations from all causes in the non-DS cohort and a larger proportion of "lack of efficacy" dropouts in the non-DS cohort. There were a higher proportion of discontinuations due to adverse events in the DS cohort compared to the non-DS cohort by a margin of 7.1% vs 5.9% respectively.

Discontinuations due to adverse events from within all non-pivotal DS patients (496) are compared adverse event discontinuations from within the DIAVEY – STILON non-DS cohort. There were 19 (3.8%) discontinuations due to adverse events in the DS non-pivotal cohort and 11 (5.9) in the DIAVEY – STILON non-DS cohort. Examination of 4 categories of interest reveals a similar proportion of these events in both the DS and non-DS cohorts.

Overall the profile of discontinuations due to adverse events does not indicate any selective vulnerability to adverse events in the DS population compared to the non-DS cohort. The observation of increased discontinuations due to lack of efficacy in the placebo cohort of the pivotal studies and the non-DS cohort of the non-Pivotal studies is in alignment with a selective STP treatment effect for Dravet Syndrome.

7.4.4. Significant Adverse Events

There were no significant adverse events not seen as serious adverse events. From the profile of SAEs and events identified with increased frequency and severity there are a panel of adverse events that will be explored further in section 7.5, "Analysis of Submission-Specific Safety Issues". These will include Thrombocytopenia, Neutropenia, Anorexia, and decreased appetite.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAE) count will include SAEs. Controlled trial treatment adverse events are only available from a relatively small sample of 64 patients from the STICLO France and Italy trials. These will be presented followed by pooled treatment emergent adverse events identified in the larger safety pooled dataset including only DS patients in the category 2 and 3 open label studies (see Table 41). The next group presented will be non-DS patients from category 3 followed by the pool of all available patients in the category 1 STICLO studies, DS and non-DS patients from category 2 and 3. Finally, treatment emergent or adverse events equivalent to treatment emergent adverse events from the category 4 exploratory efficacy studies in non-DS epilepsy patients, with safety data available as PDF tables and narratives in the ISS and individual study reports, will be presented.

Treatment Emergent Adverse Events STICLO Trials

Table 80 STICLO Studies, TEAE frequency by treatment arm

ARM	Patients	%
PLACEBO	17	55
STIRIPENTOL	32	97

The adverse event frequency in the STP treatment group and placebo group for events that occurred in more than a single patient are compared in Table 81. The largest difference between the STP and placebo, > 10%, treatment groups is seen for "somnolence", "decreased appetite", "weight decreased", "dysarthria", and "nausea". These events, most prominent in frequency are in the category of CNS depression and gastrointestinal disorder. Somnolence, an experience of CNS depression is not uncommonly seen in antiepilepsy (AED) drug treatment. Gastrointestinal adverse effect is prominent but may be monitored and is reversible upon discontinuation. Examination of all events that occurred in the STP group does not reveal adverse events related to bone marrow suppression, hepatotoxicity or infection. Infection is noted here as an event of interest because of a high frequency of infection seen in the STP-1 study that will be presented in a subsequent section.

Reviewer Comment: overall the small controlled trial data the identified safety signals that are

manageable by monitoring and discontinuation of treatment if necessary.

Table 81 Adverse Events in Greater than 1 Patient (3.0%), Pooled STICLO (France & Italy) Studies, STP Treatment Compared to Placebo

AEDECOD	Unique PBO Patients	STP Unique patients	STP - PBO	STP % (n=33)	PBO % (n=31)	(STP% - PBO%) diff %
Somnolence	7	22	15	66.7	22.6	44.1
Decreased appetite	3	15	12	45.5	9.7	35.8
Ataxia	7	9	2	27.3	22.6	4.7
Weight decreased	2	9	7	27.3	6.5	20.8
Nervous system disorder	5	8	3	24.2	16.1	8.1
Hypotonia	4	6	2	18.2	12.9	5.3
Tremor	3	5	2	15.2	9.7	5.5
Nausea	1	5	4	15.2	3.2	11.9
Nightmare	2	4	2	12.1	6.5	5.7
Dysarthria	0	4	4	12.1	0.0	12.1
Fatigue	1	3	2	9.1	3.2	5.9
Aggression	0	3	3	9.1	0.0	9.1
Vomiting	0	3	3	9.1	0.0	9.1
Pyrexia	1	2	1	6.1	3.2	2.8
Weight increased	1	2	1	6.1	3.2	2.8
Bronchitis	0	2	2	6.1	0.0	6.1
Nasopharyngitis	0	2	2	6.1	0.0	6.1
Salivary hypersecretion	0	2	2	6.1	0.0	6.1

Treatment Emergent Adverse Events in the DS Populations of Category 2 and 3 Studies

The following discussion is based on an examination of the frequency of adverse events distributed across the study timelines of the DS patients in the category 2 and 3 studies as well as the duration of the studies and frequency of patient contact over time within the studies. These parameters are shown in Table 82, Figure 21, and Figure 22.

The duration of these studies and frequency of patient contact is not homogenous across this group of studies. The adverse events in this group of studies are pooled to increase potential safety signals that may not be seen in the individual studies. The pool does not indicate that study design is homogenous. The ability to capture adverse events is influenced by the frequency of patient contact in each study. The duration of treatment may influence the potential to capture adverse events that are related to cumulative exposure vs events related to more acute toxicity. Table 82 shows the schedule of visits, duration and the number of assessments in the study reflected by the sum of the number of unique patient visit entries for each possible visit field in the vital sign dataset.

The STILON, TAU-EAP and DIAVEY studies were all approximately 4.3 years in duration. This

long duration provides an opportunity to identify adverse events that emerge after cumulative exposure to the study drug. The ability to capture adverse events was not uniform across these studies. The frequency of patient contact was the lowest in the STILON study followed by the DIAVEY study and the highest frequency contact occurred in the TAU-EAP study. The estimation of patient assessments in the STILON, DIAVEY, and TAU-EAP studies was 216, 691 and 1061 respectively. The adverse events in the STILON study are distributed somewhat evenly through the 4 year treatment period while the TAU-EAP study has a cluster of adverse events in the first six months followed by a lower but even distribution of adverse event through the remaining 3.5 years of the study. The DIAVEY study has a cluster of adverse events in the first six months followed by a decreasing frequency through the remaining 3.5 years of the study, see Figure 21.

Although it would be expected, the profile of adverse event frequency and distribution across the study timeline is not predicted by the patient contact frequency, or n size of the study. A factor that is likely influencing the frequency – timeline distribution of adverse events is the number of study patients who are naive to STP treatment or who have been on ongoing STP therapy. This possibility is reflected in the difference seen between the TAU-EAP study and the DIAVEY study. DIAVEY has a cluster of adverse events in the first 4 months and an overall 60% of patients with a recorded adverse event. The larger TAU-EAP population has a small early cluster of adverse events with an overall 26% of patients with an adverse event recorded. This may be explained by the patient population at entry. Most TAU-EAP and STILON patients entered the study on ongoing STP treatment while in DIAVEY all patients have STP newly prescribed at study entry. Exposure could also be an explanatory factor to account for the difference in AE frequency – timeline distribution; however, the TAU-EAP study has the highest proportion of patients on 60 to 100mg/kg/day of STP among the three studies but has the lowest percent of patients with a recorded AE.

In the STP-1 study there is a dense distribution of the 357 adverse events recorded during the 1 year study with 97% of patients showing a recorded AD. This study had the highest average study site contacts per year among all the studies with duration of 3 months or longer. All patients entering the STP-1 study were new to STP treatment. These factors are the likely factors to explain the high proportion of adverse events seen during the course of the study.

The STIPOP study was only 2 weeks in duration and enrolling patients were on ongoing STP treatment. The short duration and adaptation to the STP treatment are likely factors in the low adverse event occurrence.

The STEV study is not shown in Figure 21 because there were no adverse event study dates present in the AE dataset so time from STP treatment onset could not be computed. There were 75 adverse events recorded from among the 24 STEV study patients with DS over the 12 week study as shown in the Figure 22 scatter plot.

Table 82 Schedule of Visits, Duration of Study and Number of Assessments by Study for Category 2 & 3 studies

Study	Schedule of Visits	Duration in years	number of assessments (derived from unique visit entries in vs.xpt dataset)	Average contacts / year	Comment
STILON	Initial visit then every 6 months to 1 year	4.2	216	51	Visit 1 included, ongoing STP treatment possible
TAU-EAP	Initial, day 15 to 30, month 3, month 6, then every 6 months	4.3	1061	247	pre-inclusion included, ongoing STP treatment possible
DIAVEY	All enrolled patients were followed up at least once a year, minimum 1 year, maximum of 5 years participation	4.3	691	161	first visit not included because all patients in this study are newly prescribed STP
STP-1	Assessment weekly during the first 4 week dose adjustment period then every 4 weeks during the 12 week maintenance period, then every three months during the subsequent 9 months of the study.	1	463	463	baseline visit not included, all patients in this study are newly prescribed STP
STEV	Baseline, day 21, day 56, day 77	.23	67	291	baseline visit not included , all patients are new STP treatments
STIPOP	Evaluation only on day 1 of study, 34/35 patients on continuing treatment with STP, two weeks after Day 1 of study patients receive a follow up phone call to assess for AE.	.038 (p 28 protocol)	70	NA	includes study site contact on Day 1 (35 assessments) and phone call at T3 (2 weeks after D1)

Figure 21 Scatterplot of TEAE by Time from Start of STP to Event for Category 2 and 3 Studies, DS patients

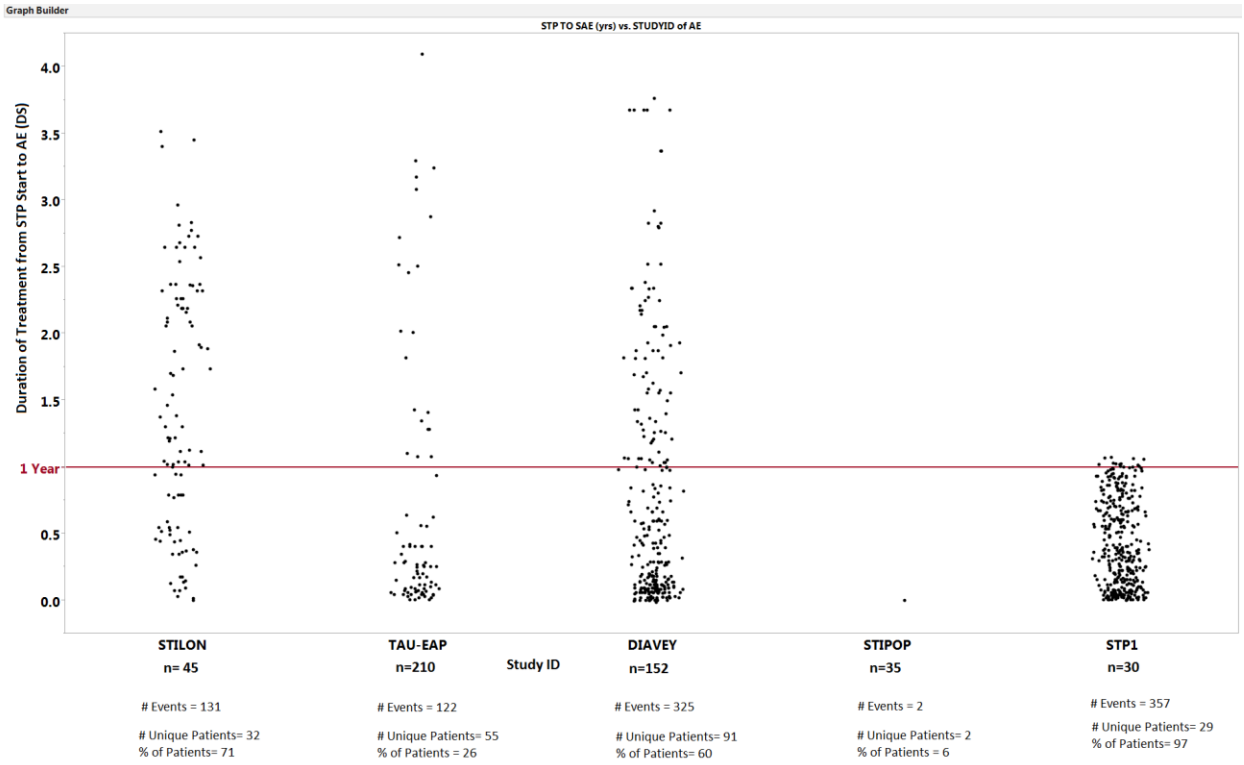
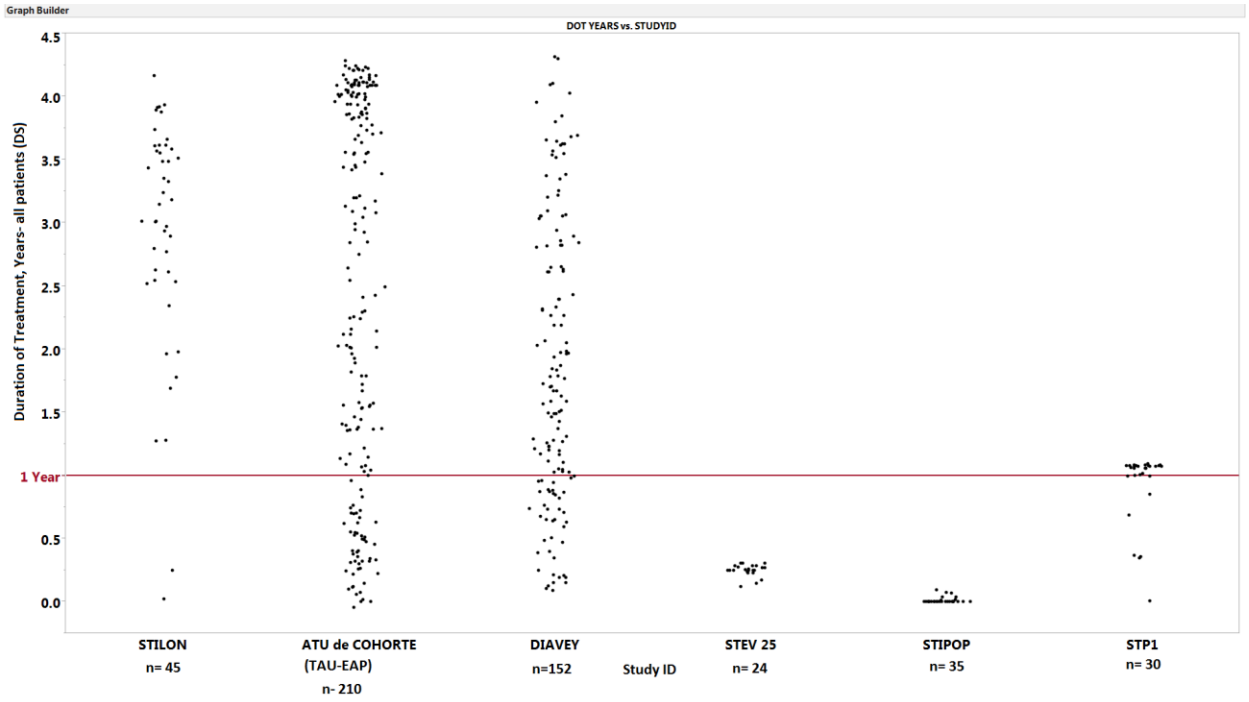


Figure 22 Scatterplot, Duration of Treatment all patients Category 2 and 3 studies, DS patients.



Adverse Event Profile of Individual Category 2 and 3 Studies

Examination of individual studies reveals the percent of patients with an adverse event was 26%, 60%, 93% , 71% 97% and 6% in the TAU-EAP, DIAVEY, STEV, STILON, STP1, and STIPOP studies respectively. As noted in the above discussion of individual study properties the adverse event frequency is likely related to the composition of study patients who are newly prescribed STP compared to patients on ongoing therapy. The study duration and number of participants are secondary factors, see Table 83.

Table 83 Category 2 and 3 Studies, DS Patients, Percent with Adverse Event

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 top ten adverse events identified in the 5 category 2 and 3 studies are shown in Table 84. The most common adverse event across studies is the preferred term “decreased appetite”

that occurs in TAU-EAP, DIAVEY, STILON, and STP1. The related term "weight decreased" also occurs in STILON. The next group of terms appears in three of the studies; these include "somnolence" and "fatigue", "ataxia" and infection related terms then behavioral abnormality related terms. Terms of special interest including bone marrow related laboratory study adverse events and hepatic enzyme adverse events occur in two studies each. Seizure / epilepsy related terms also occur in two studies. There are no clear differences in the profiles of the top 10 adverse events across the studies except for STIPOP where only two adverse events are noted. In subsequent evaluations these studies will be pooled and added to the available non-DS patients from DIAVEY and STILON and STP treated patients from the STICLO studies to help determine if there is a notable safety signal for these adverse events.

From among all the adverse events in the STP1 study there was a high proportion of infection related adverse event terms. From a total of 92 preferred terms identified among study STP-1 adverse events there were 21 that were infection related. This represents 22% of all adverse event preferred terms. The STILON study also had a high proportion of infection related terms where 14 of 50 infection related adverse events (28%).

Table 84 Top 10 Adverse Events (preferred terms) from Individual Category 2 and 3 Studies DS Patients

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	Diarrhoea	
Hypotonia	Aggression	Weight decreased	Gamma-glutamyltransferase increased	
Insomnia	Alanine aminotransferase increased	Abnormal behaviour	Hordeolum	
Seizure	Ataxia	Aggression	Influenza	
Status epilepticus	Thrombocytopenia	Ataxia	Tremor	

Examination of SOC by Study

Examination of SOC by study reveals the most frequent terms with an occurrence in greater than 60% of patients in a study were "infections and infestations" in STP1, "nervous system disorders" in STP1, "metabolism and nutritional disorders" in STEV, "nervous system disorders"

in STEV. The percent of patients with adverse events in these four SOC's are shown in Table 85. In both of these studies patients were naive to STP upon enrollment. Exposure to a new centrally acting drug may explain the high proportion of CNS effects in these studies and also the "decreased appetite" which may be associated with a CNS effect or acute gastrointestinal effect. The frequency of "infections and infestations" in study STP1 is not well explained. Possibilities to account for the unexpectedly high frequency of "infections and infestations" in this study are some characteristics of the study population that confer a selective vulnerability such as age, STP exposure, racial composition, concomitant medication, bone marrow sensitivity (underlying effect on leukocytes or neutrophils). These issues will be further explored in section 7.5 "Analysis of Submission-Specific Safety Issues".

Table 85 SOC where Greater than 60% of Patients had an AE, Category 2 and 3 Studies, DS patients.

STUDY ID	SOC	% of study, unique patients	Comment
STP1	Infections and infestations	83	Most frequent Preferred term "nasopharyngitis" , 19 patients
STP1	Nervous system disorders	83	Most frequent were "somnolence", 21 patients, and "ataxia" 14 patients.
STEV	Metabolism and nutrition disorders	67	All preferred term "decreased appetite"
STEV	Nervous system disorders	67	Most frequent preferred terms were "somnolence" 8 patients and "ataxia" 5 patients.

Treatment Emergent Adverse Effects (TEAE) in Pooled Category 1, 2 and 3 Studies, DS and non-DS Patients

Examination of TEAE events by SOC reveals that among all categories containing greater than 5% of the 625 patient pool the most frequent SOC was "Nervous system disorders" (32.5%) followed by "metabolism and nutritional disorders" (19.2%), "investigations" (16.3%), "psychiatric disorders" (14.9%), "general disorders and administration site conditions" (10.9%), "infections and infestations" (10.4%) , "gastrointestinal disorders" (10.2%), and "blood and lymphatic disorders" (5.9%), see Table 86.

Each SOC is subsequently evaluated by the total number of patients with a treatment emergent adverse effect in that SOC as well as the top two preferred terms contributing to the events in the SOC and the number of serious adverse events (SAEs) that occurred in the top two preferred terms then the number of discontinuations identified from among the SAEs in the two top preferred term contributors.

As noted in the previous paragraph the highest frequency of TEAE was in the SOC "nervous

system disorders" with 203 unique patients recording a TEAE in this SOC. The top two preferred terms from among the TEAEs contributing to the SOC were "somnolence" and "ataxia" while there were 5 SAEs identified from within these two preferred terms. Stiripentol discontinuation is identified as a response to two of the SAEs, Table 86. The high frequency of "nervous system disorders" may be attributed to the central nervous system (GABA receptor) action of STP. It is not unexpected phenomena in AEDs due to their underlying action on the central nervous system.

The SOC "Metabolism and nutrition disorders" had the second highest count of overall TEAEs with 120 unique patients recording a TEAE in this SOC. The top two preferred terms from among the TEAEs contributing to the SOC were "decreased appetite" and "cachexia" while there were 14 SAEs identified from within these two preferred terms. Stiripentol discontinuation is identified as a response to 6 of these SAEs and dose reduction associated with an additional 3 of these SAEs, Table 86. The high frequency of events in the SOC "Metabolism and nutrition disorders" is somewhat unique to STP. These events represent an STP specific safety signal and appear to be severe, based on the observation that SAEs and discontinuations were the most frequently in the "Metabolism and nutrition disorders" SOC.

The SOC "investigations" had a count of 102 unique patients with a TEAE recorded in the SOC. The top two preferred terms from among the TEAEs contributing to the SOC were Gamma-glutamyltransferase (GGT) increased and Aspartate aminotransferase (AST) increased while there were 2 SAEs identified from within these two preferred terms, Table 86. No STP discontinuations are identified from among patients recording a TEAE under these two preferred terms.

The SOC "psychiatric disorders" had a count of 93 unique patients with a TEAE recorded in this SOC. The top two preferred terms from among the TEAEs contributing to the SOC were "aggression" and "insomnia" while there was one SAE identified from within these two preferred terms, Table 86. This patient did not have an STP or dose reduction recorded.

The SOC "General disorders and administration site conditions" may have captured additional central nervous system effects based on the observation that 31 unique patients had "fatigue", a term with similarity to "somnolence" seen in the "Nervous System Disorders" SOC. There were 68 patients with treatment emergent adverse events in the "General disorders and administration site conditions" SOC where 9 events were SAEs. From among the SAEs there were three identified under the "fatigue" preferred term and six were from the "pyrexia" preferred term, Table 86. From among the SAEs there were 2 discontinuations identified within the "fatigue" preferred term group while no STP discontinuations are identified from the "pyrexia" preferred term. Under the "infections and infestations" SOC there were 65 patients with treatment emergent adverse effects. The top two preferred terms from among the TEAEs contributing to the SOC were "nasopharyngitis" and "gastroenteritis" while there were 2 SAEs

identified from within these two preferred terms. There were no discontinuations from among these two SAEs, Table 86. Under the "Gastrointestinal disorders" SOC there were 64 patients with treatment emergent adverse effects. The top two preferred terms from among the TEAEs contributing to this SOC were "diarrhoea" and "vomiting" while there were 2 SAEs identified from within the patient group that had an event under these top two terms. There were no STP discontinuations in response to these SAEs. Under the SOC "Blood and lymphatic system disorders" there were 37 patients with treatment emergent adverse effects. The top two preferred terms from among the TEAEs contributing to this SOC were "neutropenia" and "thrombocytopenia" while there were 4 SAEs identified from within the patient group that had an event under these top two terms, Table 86. Stiripentol discontinuation is identified as a response to 2 of these SAEs. The SOC "Hepatobiliary disorders" is included in the discussion as an event of special interest. There were 4 patients with an entry in this SOC. There was one each of the preferred terms "liver disorder", "hepatocellular injury", "cholestasis" contributing to the events in this SOC, none were recorded as SAEs.

Table 86 SOC Pool, STICLO studies -(STP treatment), Non-Pivotal, DS and non-DS patients. Greater than 5% of Patients, Category 1-3

			Top 2 AE contributors to SOC		Unique pt. SAEs-discontinue in full SOC	
SOC Pool Pivotal (STP treatment), Non-Pivotal, DS and non-DS patients.	**UNIQUE PTS**	**% of 625 pool , unique pts**	**PT (n)**	**PT (n)**	**SAE**	**Discontinuations identified**
Nervous system disorders	203	32.5	Somnolence (85)	Ataxia (43)	62	9
Metabolism and nutrition disorders	120	19.2	Decreased Appetite (110)	Cachexia (5)	14	3
Investigations	102	16.3	GGT increased (50)	AST increased (39)	4	1
Psychiatric disorders	93	14.9	Aggression (26)	Insomnia (18)	3	0
General disorders and administration site conditions	68	10.9	Fatigue (31)	Pyrexia (16)	23	7
Infections and infestations	65	10.4	Nasopharyngitis (24)	Gastroenteritis (11)	16	0
Gastrointestinal disorders	64	10.2	Diarrhoea (15)	Vomiting (14)	6	0
Blood and lymphatic system disorders	37	5.9	Neutropenia (22)	Thrombocytopenia (14)	5	2
Hepatobiliary disorders	4	0.64	Liver disorder (1) Hepatocellular injury (1) Cholestasis (1) Hepatitis (1)	None were SAE	0d	0

* Pt TAU-EAP (b) (6) resolved after reduction of VPA and topiramate dose, pt DIAVEY (b) (6) had marked elevation of CPK, AST and ALT simultaneously. This was likely a muscle source. STP discontinued with partial resolution.	

The preferred terms that had a frequency of ≥ 2% of unique patients in the category 1- 3 pool who were treated with STP, both DS patients and non-DS patients are examined. The frequency and percent of preferred terms in the total patient pool, DS and non-DS patient pools are compared, see Table 87.

There were seven preferred terms where greater than 5% of unique patients in one of the groups had an event under the preferred term. These seven preferred terms were “decreased appetite”, “somnolence”, “Gamma-glutamyltransferase increased”, “ataxia”, “Aspartate aminotransferase increased”, “seizure and “fatigue”. Decreased appetite is seen more frequently in the DS patient compared to the non-DS pool by a margin of 14.3% greater in the DS group. Somnolence is seen more frequently in the DS patient group compared to the non-DS group by a margin of 10%. The preferred term Gamma-glutamyltransferase increased is more frequent in the DS patient group compared to the non-DS group by a margin of 5%. Ataxia is more frequent in the DS patient group compared to the non-DS group by a margin of 6%. The preferred term Aspartate aminotransferase increased is more frequent in the DS patient group compared to the non-DS group by a margin of 4.5%. The preferred term “seizure” is reported more frequently in the non-DS patient group by a margin of 5% over the frequency in the DS patient group.

Of those preferred terms where the occurrence was less than 5% for any of the three groups the largest differences between the DS and non-DS patient cohorts is observed for “nasopharyngitis” where the DS group has an excess of 3.8% over the non-DS group and “status epilepticus” where the non-DS group had an excess of 3.2% over the DS group.

Considerations for the difference seen on appetite and central nervous system adverse effects may be the age of the patient cohorts. The mean and median age of the DS group are 7.5 years and 6 years respectively while the non-DS cohort mean and median ages are 16.7 and 11.9 years respectively. It is possible younger age group is more vulnerable to the CNS and gastrointestinal adverse effects. The adverse effects of “Seizure “and “status epilepticus” had an excess in the non-DS patient cohort that is in alignment with the lesser efficacy for refractory epilepsy treatment seen in the non- Dravet cohort of the STEV study.

The most prominent signal seen in the examination of preferred term adverse effects is “decreased appetite” and the central nervous system adverse effects of “somnolence” and “ataxia”.

Table 87 All Preferred Terms ≥ 2% of Patients in All Category 1- 3 Pool Treated with STP, DS and non-DS

Preferred Term	DS + non-DS, STP Rx, total unique Patients	% of total Pool (n=625)‡	DS Unique pts	% of DS Pool (n=438)* Mean age = 7.4 yrs	non-DS (DIAVEY-STILON) unique pts	% of non-DS Pool (n=187)† Mean age = 16.7 years	Difference in percent of unique patients affected (DS%-nonDS%)
Decreased appetite	110	17.6	101	23.06	9	4.81	18.25
Somnolence	85	13.6	76	17.35	9	4.81	12.54
Gamma-glutamyltransferase increased	50	8	44	10.05	6	3.21	6.84
Ataxia	43	6.88	40	9.13	3	1.6	7.53
Aspartate aminotransferase increased	39	6.24	35	7.99	4	2.14	5.85
Seizure	39	6.24	22	5.02	17	9.09	-4.07
Fatigue	31	4.96	19	4.34	12	6.42	-2.08
Weight decreased	27	4.32	24	5.48	3	1.6	3.88
Aggression	26	4.16	19	4.34	7	3.74	0.60
Nasopharyngitis	24	3.84	23	5.25	1	0.53	4.72
Hypotonia	23	3.68	20	4.57	3	1.6	2.97
Neutropenia	22	3.52	16	3.65	6	3.21	0.44
Insomnia	18	2.88	15	3.42	3	1.6	1.82
Pyrexia	16	2.56	13	2.97	3	1.6	1.37
Diarrhoea	15	2.4	14	3.20	1	0.53	2.67
Tremor	15	2.4	14	3.20	1	0.53	2.67
Status epilepticus	15	2.4	0	0.00	6	3.21	-3.21
Thrombocytopenia	14	2.24	12	2.74	2	1.07	1.67
Vomiting	14	2.24	0	0.00	4	2.14	-2.14
Upper respiratory tract inflammation	0	0	13	2.97	0	0	

*From ISS Table 3-8, page 60
†sum of patients from STILON and DIAVEY non-DS cohort
‡DS pool (438) + non-DS pool (187) = 625

Reviewer Comment: Examination of the frequency of TEAE by SOC and preferred term reveal the most prominent signal is observed for occurrence of decreased appetite and central nervous system adverse effects of somnolence and ataxia. There is also a high frequency of

events under the preferred terms Gamma-glutamyltransferase increased and Aspartate aminotransferase increased however from among these two preferred terms there were only 4 SAEs and one discontinuation. A small excess of seizure related preferred terms were noted in the non-DS patient cohort compared to the DS cohort.

7.4.6. Laboratory Findings

Pivotal Studies (Category 1)

Means, Outliers, Shifts

Chemistry

ALT (Alanine Aminotransferase)

Examination of mean values at baseline and end of study (EOS) visit reveals a small increase in mean ALT value 0.96 IU (5.2%) in the placebo cohort while the STP cohort has a decline in the mean group ALT value -2.3 IU (-12.9%). Low EOS value outliers are not assessed in this analysis.

Examination of outliers reveals only one subject with normal ALT at baseline has an elevated ALT above reference range at end of study where this maximum value is 1.8 X upper limit of normal (ULN).

Examination of shift from baseline to end of study measurements in the placebo cohort reveal 23 patients remain in the normal range with 1 patient each shifting from normal to high and normal to low. One patient high at baseline retains a high out of reference (OORR) range value at EOS. In the STP cohort 23 patients remain in the normal reference range from baseline to end of study, 4 patients normal at baseline have an OORR low value at end of study. No patients are seen to shift from normal at baseline to high at end of study. One patient low at baseline shifts to normal range while two patients low at baseline remain low. One patient high at baseline shifts to normal while one high at baseline remains high.

HY'S There were no bilirubin measurements in this study to allow additional analysis for hepatic dysfunction, however there were no patients at STP end of treatment with ALT > 3 x ULN who would have fulfilled the transaminase criteria for Hy's law.

There is no signal of an increase in the ALT value during STP treatment.

AST (Aspartate Aminotransferase)

Examination of mean values at baseline and end of study (EOS) visit reveals the placebo cohort

had a 4% decrease in mean AST value from baseline while the STP cohort had a 49% increase in mean AST value from baseline to end of study. STP treatment group baseline mean value was 25.4 IU/L with an end of study group mean value of 38 IU/L. As a comparator, the mean of all upper limit of normal reference range vales was obtained and equals 37.5 IU/L (note: there was variation of reference range across patients).

Examination of outliers reveals 10 STP patients with OORR high AST values. Three of these patients had elevated AST at baseline. In each of these three cases there was an additional increase in the AST value from baseline to end of study. The maximum AST value from among all patients with OORR high values was a single patient with an AST value that was 3.3 x ULN. There was an additional patient with a high end of study value equal to 2.8 x ULN but none of the remaining 8 patients had a value that exceeded 2 x (twice) the upper limit of normal

Examination of shift from baseline to EOS measurements in the placebo cohort reveals that 22 patients had normal AST values at baseline and end of study while 2 patients were had normal values at baseline that increased to high OORR at EOS. In the STP treatment cohort there were 21 patients with normal AST values at baseline and EOS while 7 patients with normal baseline value had OORR high values at end of study. One patient had a high out of reference range value at baseline that was normal at end of study while 3 patients were out of reference range high at both baseline and end of study.

Analysis of AST means, outlier and shift values reveal an increase in AST during STP treatment compared to placebo treatment. This increase was not of large magnitude where there was a single AST value as 3.3 x ULN, one of 2.8 x ULN and in the remaining end of study patients none exceeded 2 x ULN. The mechanism of this increase is uncertain. Patients with a shift from normal at baseline to OORR high at end of study or end of study OORR high outliers were examined to identify any concordant elevations in ALT. Only one patient in this group of 10 patients also had a concurrent end of study elevation in ALT, however this patient also had a baseline elevation in ALT of 49 IU/L with a subsequent 22% (60 IU/L) increase at the end of study measurement.

The adverse event profile of the 10 patients with shift to OORR high AST or OORR high outliers was examined. One patient had a TEAE of aspartate aminotransferase increase. Overall these 10 patients had 59 TEAEs, none were SAEs, Seven of the ten patients had TEAEs in the “Gastrointestinal disorders” SOC which were limited to the following five preferred terms; “Abdominal pain”, Diarrhoea”, “nausea”, “salivary hypersecretion”, and “vomiting”. None of the events was in the SOC “hepatobiliary disorders”. There were no bilirubin measurements in this study to allow additional analysis for hepatic dysfunction.

AST signal: This signal of increased AST is not linked to increased ALT or to adverse events in the “hepatobiliary disorders” SOC and on this basis does not appear to be related to hepatic

toxicity.

Hematology

Hemoglobin (Hb)

Examination of group mean placebo and STP treatment hemoglobin values reveal an increase of 0.1 g/L (0.1%) in the mean STP treatment group value between baseline and EOS while there was an increase of 3.0 g/L (2.36%) in the placebo cohort.

Examination of hemoglobin values in the STP treatment cohort reveal 9 patients with a Hb value ≤120 g/L at EOS. 7 of these patients had an OORR low value while two were within the reference range assigned at EOS measurement. Two of these 9 patients had baseline values that were OORR low, including the patient with the lowest EOS Hb value of 99 g/L. The largest decline from baseline was a change from 138 g/L at baseline to 115 g/L (17%) at EOS. From among the remaining 8 patients the largest decline observed was 8% with a mean of -4.5%.

As a comparator, in the placebo cohort, there were 5 patients with a Hb value <120 g/L at EOS. Three of these were OORR low and in two patients there is no entry for reference range value although the most common reference range low value is 120 g/L.

Examination of shift from baseline to end of study measurement reveals 21 placebo patients and 17 STP treated patients had normal Hb values at baseline and EOS. In the placebo cohort there were 2 patients with abnormal baseline values that shifted to within reference range values at EOS. There were 4 patients with OORR low values at baseline that remained low at EOS. In the STP cohort there were 8 patients with normal values at baseline that shifted to OORR low at EOS while 2 patients with low values at baseline shifted to normal range at EOS. One patient had a high value at baseline that remained OORR high at EOS.

In summary, there was no change in mean hemoglobin values in the in the STP treatment cohort. An examination of the number of patients with a decline from baseline reveals 63% of patients in the STP treatment group had a decline from baseline to EOS while 44% of patients in the PBO group had a decline in Hb from baseline to EOS. In the STP group a decline from baseline to EOS was greater than 8% in only 1 patient. The shift analysis reveals more frequent shifts from normal baseline to OORR low at end of study in the STP cohort compared to the placebo cohort. Overall there is a trend to a decline in Hb in the STP cohort compared to placebo although the signal is not prominent. It is unlikely to represent a signal for serious bone marrow suppression, bleeding or hemolysis.

Hematocrit (HCT)

Examination of baseline and EOS, placebo and STP treatment arm group mean HCT values is

performed. In the STP treatment cohort there is a change from a hematocrit of 37.9% to 37.07% equal to a decline of 0.83% representing a 2.25% decline in value form baseline. In the placebo cohort there was change from a hematocrit of 38.03% at baseline to 38.63% at EOS equal to an increase of 0.6% representing a 1.56% increase in hematocrit value over baseline.

Examination for outliers was performed. There were 58 patients with HCT value entries at baseline and all had an entry for reference range. At EOS there were 39 patients with HCT measurement and 23 of these had reference range value entries. Patients with an abnormal low OORR flag (17 patients) or patients with no OORR flag with a hematocrit ≤35.4 % (6 patients) were selected as outliers. The patients with an EOS value who were not flagged but had HCT values below 35.4% had a "normal" lab result flag, apparently due to absence of EOS reference range values in the dataset. A value of ≤35.4 % was selected as a cutoff for abnormal in the patients with no reference range value entries because this is the lower boundary for normal hematocrit in females identified in Harrison's Principles of Internal Medicine, 19e [48]. Fourteen of these 23 patients had abnormal low OORR values or values less than 35.4% at baseline. From among the remaining 9 patients 3 were in the placebo treatment arm. Among the 6 STP treatment patients with low HCT values who were normal at baseline the minimum EOS value was 31.9% with a mean of 34.2 %. From among these 6 STP treatment patients the maximum decline was from 39% at baseline to 31.9% at EOS, a 7.1% total decline. While the median and mean decline of the STP group with abnormal OORR low at EOS were 3.5% and 3.8% respectively. From among the 3 placebo cohort patients with an abnormal EOS hematocrit value and normal baseline the maximum decline was 5.6% with a median and mean decline for the group of 0.6 and 1.9% respectively.

Examination of shift from baseline to end of study measurement reveals 16 placebo patients and 19 STP treated patients had normal hematocrit values at baseline and end of study. Three patients in both the placebo cohort and STP treatment group had normal values at baseline and low OORR values at EOS while 3 patients in each group were OORR low at baseline but returned to normal values at EOS. Five patients in the placebo group and 4 patients in the STP treatment group had OORR low values at both baseline and EOS. One patient in the STP treatment group had an OORR high hematocrit value both at baseline and EOS.

In summary, the outlier examination reveals a small tendency to decline in hematocrit during the STP treatment interval; however, the examination of means and shifts does not reveal a notable signal for decline in hematocrit.

[48] Kratz A, Pesce MA, Basner RC, Einstein AJ. Laboratory Values of Clinical Importance. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79722706. Accessed October 28, 2016.

Erythrocytes

The group mean erythrocyte values had a small increase in both placebo and STP treatment cohorts. The placebo cohort had 1.6% increase in mean erythrocyte value from baseline to EOS while the STP treatment cohort had a 0.24% increase from baseline to EOS.

Outlier values are examined. In order to set an conservative threshold to capture low value erythrocyte count outliers a lower limit reference range of $<4 \times 10^{12}$ /L is selected. This is the most frequent OORR lower limit value in the pivotal trial erythrocyte dataset and is also the OORR lower limit for females identified in the Harrison's Principles of Internal Medicine, 19e[49]. In the placebo treatment cohort there were 3 patients with an EOS erythrocyte count $<4 \times 10^{12}$ /L while in the STP cohort there were 8 patients with an EOS erythrocyte count $<4 \times 10^{12}$ /L. The minimum EOS erythrocyte count in the placebo treatment group is 3.8×10^{12} /L while in the STP cohort the minimum EOS erythrocyte count is 3.5×10^{12} /L identified in two patients.

Percent change from baseline is examined in both treatment arms. The maximum percent decline from baseline to EOS in the placebo treatment arm was 15.2% while in the STP cohort the maximum decline from baseline was 16.2%. The

Examination of shift in erythrocyte values from baseline to end of study reveals the 18 patients in the placebo group and 19 patients in the STP treatment group had normal values at baseline and EOS. In the placebo group there were 2 patients with normal values at baseline with decline to OORR low at EOS. In the STP treatment group there were 4 patients with normal values at baseline that had a decline to OORR low at EOS. In the placebo group three patients had OORR low values at baseline that were normal at EOS while in the STP treatment group there was 1 patient with an OORR low value at baseline that increased to normal at EOS.

In summary, there was no change in group mean STP treatment group erythrocyte value from baseline to EOS while the outlier analysis revealed an excess of STP treatment patients compared to placebo with a >10% decrease in erythrocyte value. The shift analysis also revealed a small excess of 2 patients in the STP treatment group with a shift from normal baseline value to OORR low at EOS. These changes are in alignment with the small decline in values for hemoglobin and hematocrit in the STP treatment group but do not reach a level of evidence for a notable safety signal.

Monocytes

[49] Kratz A, Pesce MA, Basner RC, Einstein AJ. Laboratory Values of Clinical Importance. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79722706. Accessed November 03, 2016.

Only 14 of 63 patients with baseline monocyte measurements had corresponding reference range values for both baseline and EOS values while 36 patients did not have a reference range entry for either baseline or EOS. The absence of reference values for the majority of patients does not allow a shift analysis. The monocytes examination will only be presented for group means and outliers. The Harrisons Principles of Internal Medicine, 19e, Laboratory values of Clinical Importance is uses to provide a rough comparison to the dataset values. Absolute monocyte count range 0.14–0.72 × 10^9/L[50]. The baseline mean of all STICLO patients is 0.58 × 10^9/L with a non-normal distribution.

Examination of the STP treatment cohort monocyte values reveals no change in the group mean monocyte count from baseline to EOS. In the placebo cohort there was a group mean decline in count of 0.05 x 10^9 /L (9.6%).

Examination of minimal and maximal monocyte values at EOS is performed. The threshold for capture of high monocyte counts is set at 125% of the baseline mean with consideration that a 25% increase in the mean value represents a meaningful change; in addition this value, 0.72 × 10^9/L is also the OORR upper limit in the Harrisons Principles of Internal medicine," Laboratory Values of Clinical Importance". In the STP treatment cohort there were 8 patients with an EOS monocyte counts > 0.72× 10^9/L while in the placebo cohort there were 3 patients with an EOS monocyte count > 0.72× 10^9/L. The distribution of EOS monocyte counts has a greater positive skewness in the STP treatment cohort than in the placebo cohort.

From among those in the STP treatment group the maximum percent change from baseline is 261%. The next greatest increase from baseline to EOS is 162%. The mean percent increase over baseline in this STP outlier group is 108% while the 3 placebo patients in the outlier group have a mean percent increase over baseline of 26%.

Using the same metric as above that was used to capture high monocyte OORR outliers, the low OORR outliers are captured using a threshold of EOS value less than 75% of the baseline mean. This value is 0.43 × 10^9/L. At the low end of the distribution of monocyte values there are 23 patients with EOS less than 75% of the baseline mean. There are 13 (42%) patients from the placebo treatment cohort and 10 (30%) patients from the STP cohort in this outlier group. In the placebo group the maximum decline from baseline is -100% with a mean and median percent change from baseline in the placebo group of -11.6% and -22.6% respectively. In the STP treatment, outlier cohort, the maximum decline from baseline is -36% with a mean and

[50] Kratz A, Pesce MA, Basner RC, Einstein AJ. Laboratory Values of Clinical Importance. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79722706. Accessed October 28, 2016.

median percent change from baseline in the STP group of -19% and -21% respectively.

In summary, examination of mean change and the reviewer constructed outlier values for monocyte count at baseline and EOS there is not a notable trend of increase or decline in this hematology metric during STP treatment.

Basophils

Not all patients had reference values for basophils. Thirty six of 58 subjects did not have a reference range value entry for any basophil measurement. A shift from normal to high or low analysis could not be performed due to this missing reference range data. An evaluation of means and change from baseline was performed to assess if activation or suppression of basophils occurred during the STP treatment interval.

Examination of group mean values for the basophil counts reveals a 14.7% decline in the placebo cohort mean from baseline to EOS. The STP treatment group had a decline of 6.5% in mean group basophil count from baseline to EOS.

Examination of outliers reveals a single STP treated patient (STICLO - ITALY (b) (6)) with a 358% increase in basophils from baseline to EOS. This represents an absolute increase from 0.018 x 10^9/L at baseline to 0.0824 x 10^9/L or an increase of 66 million / L. On examination of the complete profile of laboratory studies this patient reveals some increase in leukocytes, percent neutrophils and monocytes but no increase in eosinophils from baseline to EOS. There are five TEAEs, none SAE, with no entries among the TEAEs in the SOCs for “immune system disorders” or “Skin and subcutaneous tissue disorders”. This patient is removed from the outlier examination for additional analysis of the remaining group trend. From the remaining patients the most extreme change from baseline is noted in 7 patients with a 100% decline from baseline, 3 from placebo and 4 from STP treatment and a 105% increase seen in an STP treatment patient.

Examination of the percent change from baseline in the placebo and STP treatment group with patient (STICLO - ITALY (b) (6)) excluded from the analysis reveals the placebo group has a mean and median percent change from baseline of -11.5% and -9.3% respectively. The STP treatment group has a mean and median percent change from baseline of -18.1% and -18.4% respectively. An analysis of patients with a positive and negative percent change from baseline is performed. There were 19 patients in the placebo group and 20 patients in the STP treatment group with both a baseline and EOS basophil measurement. From among the placebo treated patients there were 37% with an increase in basophil count from baseline and 63% with a decrease in basophil count from baseline. In the STP treatment group 50% of patients had an increase in basophil count from baseline while 50% had a decrease in count from baseline.

Overall there is no evidence of a signal for an activation or suppression of basophil production.

Leukocytes (WBC)

Examination of the group mean change in leukocyte count from baseline to EOS in the placebo and STP treatment group reveal a 6.8% and 8.6% decline in leukocyte values respectively.

Values for potential clinical concern (outliers) are not provided by the sponsor for the STICLO studies. An examination of available baseline reference range is performed to set a boundary estimate for significant outliers. The value of change in leukocyte count from baseline to EOS is calculated and a comparison of the number of patients with either a positive and negative change from baseline between placebo and STP treatment patients is performed to determine if there is evidence for a treatment related increase or decrease in leukocyte values across the treatment groups.

Nine patients had no reference range values at baseline and 14 patients had none entered at EOS. These patients are excluded from reference range analysis.

Due to the inconsistent entry of reference range values for leukocyte count in the pivotal trial laboratory dataset a textbook reference range is selected to provide a basis for capture of outliers. The lower and upper boundaries set for capture of leukocyte outlier values are 3.54×10^9/L and 9.06×10^9/L respectively[51]. This strategy is acceptable to identify a starting threshold for the lower or upper boundary of leukocyte count outlier capture and is not being used as an absolute indicator of pathologic abnormality in an individual patient. From among all patients with an EOS leukocyte measurement the maximum value in an STP treated patient was 13.3 x 10^9/L. There were three additional patients with leukocyte values > 10 x 10^9/L. There were three patients with a leukocyte count below 4 x 10^9/L at EOS, the minimum of these was 3.6 x 10^9/L. In one of these three cases the EOS value represents a 51% decline in leukocyte value while in the remaining two the decline does not exceed 12%. These values do not represent extreme outlier values.

Change from baseline: In the placebo group there were 11/27 (41%) patients with positive and 16/27 (59%) patients with negative change from baseline leukocyte value. In the STP treatment group there were 9/31 (29%) patients with a positive and 22/31 (71%) patients with a negative change from baseline leukocyte value. The mean and median values for all Individual patient

[51] Kratz A, Pesce MA, Basner RC, Einstein AJ. Laboratory Values of Clinical Importance. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79722706. Accessed November 03, 2016.

percent change from baseline is calculated for the placebo and STP treatment groups. The placebo and STP mean and median percent change are computed based on the individual baseline to EOS percent change values (as compared to the group mean baseline and EOS leukocyte values noted above). The placebo group mean and median percent changes were 0.67 % and (-3.76%) respectively while the STP treatment group percent change were (-4.8%) and (-10.2%) respectively.

A Shift analysis is performed from the 44 (76%) patients with usable reference range values. Examination of this group reveals the placebo group has 14 patients normal at baseline who remain in normal reference range at EOS while in the STP treatment groups there are 15 patients whose leukocyte values remain in normal range at both baseline and EOS. The placebo group had one patient with a shift from normal to low while the STP treatment group had 5 patients with a shift from within reference range at baseline to low OORR at EOS. There were 2 STP patients with a shift from within reference range at baseline to OORR high at EOS. There was one STP treatment patient with a low OORR value at baseline that remained low at EOS and two STP treatment patients with a high OORR value at baseline that remained high at EOS. There was one STP treatment patient with a high OORR value at baseline that was normal at EOS.

In summary, there is a mild decline trend in leukocyte values over the STP treatment interval based on examination of the mean change from baseline in the treatment compared to placebo arm as well as examination of the number of patients with a negative change in leukocyte count from baseline to EOS in the STP group compared to the placebo group. The evaluable sample size for construction of a shift table is reduced by absent reference range values but among the remaining patients there is a greater shift from normal to low OORR values in the STP treatment group than in the placebo group as well as a greater number of patients within the STP group who shift from normal to low compared to a shift from normal to high. The absolute change in leukocyte counts from baseline to EOS in the STP group does not reveal a notable signal for decline in leukocyte count.

Lymphocytes

Examination of the group mean change in lymphocyte count from baseline to EOS in the placebo and STP treatment group reveal an increase of 0.26% and 1.26% respectively.

The highest and lowest EOS lymphocyte values in the STP treatment group are examined for extreme positions. The maximum three values in the STP group are 7.0, 6.3 and 5.7 x $10^{9/}$L with the 4th highest value 4.3 x $10^{9/}$L. The minimum STP EOS value is 1.3 x $10^{9/}$L with a next lower value of 1.6 x $10^{9/}$L. These upper and lower EOS values are not extreme based on assessment of

the available reference range values in the study dataset and the typical reference range for lymphocytes provided in "Harrison's Principles of Internal Medicine, 19e"[52]

Change from baseline: In the placebo group there were 15/27 (56%) patients with positive and 12/27 (44%) patients with negative change from baseline leukocyte value. In the STP treatment group there were 21/31 (68%) patients with a positive and 10/31 (32%) patients with a negative change from baseline leukocyte value. The values for all Individual patient percent change from baseline is calculated for the placebo and STP treatment groups. The placebo and STP mean and median percent change are computed based on the individual percent change values (as compared to the group mean baseline and EOS leukocyte values noted as the first analysis for each laboratory parameter). The placebo group mean and median percent changes were 9.2 % and 3.3% respectively while the STP treatment group percent change were 5.4 and 6.6% respectively. The largest individual percent decline from baseline in the placebo group was 62% and in the STP treatment group was 70.5%.

There are only 18 evaluable patients for shift analysis who have reference range entries for baseline and EOS therefore shift analysis is not performed.

In summary, there is no signal for decline in lymphocyte count during the STP treatment interval compared to the placebo treatment interval.

Neutrophils

Examination of group mean neutrophil values in the placebo and STP treatment arms at baseline and EOS was performed: The placebo group mean neutrophil counts at baseline and EOS were 3.5 x 10^9/L and 3.2 x 10^9/L respectively. The STP treatment group mean neutrophil counts were 3.3 x 10^9/L and 2.7 x 10^9/L respectively. The percent change in the group means from baseline to EOS in the placebo group was (-9.9%) and in the STP treatment group was (-17.3%).
Examination for severe outlier values is performed. The sponsor has not provided outlier threshold or threshold of potential clinical concern or critical value thresholds for pivotal study hematology or chemistry results. In the case of neutrophils, the typically accepted critical low value is ≤0.5 10^9/L. This value is based on recognized human physiology and should be consistent across laboratories if the physical counting of leukocytes is performed accurately and should not be as dependent on properties of chemistry assays. This value (leukocyte count ≤0.5 10^9/L) rather than individual laboratory derived reference ranges (not provided) will be used as

[52] Kratz A, Pesce MA, Basner RC, Einstein AJ. Laboratory Values of Clinical Importance. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79722706. Accessed October 28, 2016.

the critical low value in this examination[53].

There were no critically low neutrophil values at EOS in the STP treatment or placebo group. The minimum EOS value in the STP treatment group was 1.01 x 10^9 / L. This value was seen in a patient with a baseline value of 1.7 x 10^9 / L and represents a 38% decline. Overall there were 6 patients in the STP treatment group with neutrophil values less than 1.4 x 10^9 / L (Harrisons internal medicine Reference low[54]) and from among these patients the largest percent decline from baseline was 48%. In the placebo arm there were no patients with a value less than 1.4 x 10^9 / L. and the minimum observed neutrophil value at EOS was 1.5 x 10^9 / L which represents a 1.2% increase over baseline.

There are only 16 patients with a complete set of reference range values entered at both baseline and EOS therefore a reference range based shift analysis could not be performed. Shift from baseline by absolute count and percent change is examined.

Examination of patients in the STP treatment group with both baseline and EOS neutrophil measurements reveals that 5 (16.1%) patients had an increase in neutrophil count from baseline to EOS while 26 (83.9%) patients had a decline in count. In the placebo arm there were 11 (40.7%) patients with an increase in neutrophil count and 16 (59.3%) with a decline from baseline to EOS. The mean and median changes in neutrophil count from baseline to EOS in the STP treatment group were 0.57 x 10^9 /L and 0.81 x 10^9 /L respectively. In the placebo group the mean and median change in neutrophil count from baseline to EOS were 0.25 x 10^9 /L and 0.076 x 10^9 /L respectively.

Examination of percent change from baseline to EOS in patients with both baseline and EOS neutrophil counts was performed. In the STP treatment group the maximum percent decline from baseline to EOS was 74% with a mean and median change from baseline of (-4.4%) and (-26.8%) respectively. In the placebo treatment arm the mean and median percent change from baseline to EOS were 18.4% and -4.1% respectively. From among the placebo cohort the maximum percent decline from baseline to EOS was 81.2%. From among the STP cohort the patient with the maximum percent decline in neutrophil count from baseline to EOS had a 73.8% decline (-73.8%) In the STP treatment group the top three largest percent increases from

[53] May Clinic, Mayo Medical Laboratories. Critical Values/Critical Results List. http://www.mayomedicallaboratories.com/test-catalog/appendix/criticalvalues/
DLMP Critical Values/Critical Results List [CL 041647.009] Effective Date: 12/01/2015
[54] Kratz A, Pesce MA, Basner RC, Einstein AJ. Laboratory Values of Clinical Importance. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. *Harrison's Principles of Internal Medicine, 19e.* New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79722706. Accessed November 03, 2016

baseline to EOS were 261%, 188% and 136% while in the placebo arm the largest three percent increases from baseline to EOS were 355%, 238% and 171%.

In summary, a decline in neutrophil count is seen more frequently in the STP treatment group than in the placebo treatment arm. From among patients with a decline in neutrophil count in both STP and placebo treatment arms the magnitude of decline in the STP arm is somewhat greater than in placebo. At EOS in the STP treatment group there are no occurrences of critically low neutrophil counts using a threshold neutrophil count of 0.5 x 10^9 /L and none below 1.0 x 10^9 /L. Overall, in this small placebo controlled dataset, there is a small excess of decline in neutrophil count during STP treatment.

Platelets

Examination of mean values at baseline and end of study visit reveals a 0.3% increase in group mean platelet count in the placebo cohort while the STP cohort has an 8.8% decline in the group mean platelet count. The absolute STP cohort decline in mean platelet count from baseline to EOS was 22 x 10^9 / liter.

Examination of outliers: There were 5 subjects in the STP cohort with an EOS platelet count below a reference value of 150 x 10^9/L. There were no patients in the placebo cohort at EOS with a platelet count below 150 x 10^9/L. One of the 5 STP patients with an OORR low value had a below reference value at baseline, although there was a further decrease. The minimum EOS platelet count at EOS in the STP treated group was 77 x 10^9 /L a patient with no adverse event entry. The range in this group of five patients was 77 to 138 x 10^9/L with a mean of 118 x 10^9/L. No critical value was defined by the sponsor; however as in the discussion of hematologic metrics above, the Mayo Clinic critical values were used as a general benchmark of serious low result. There were no STP cohort EOS platelet counts below a critical value of 40 x 10^9 /L[55]. There were no platelet counts above a reference value of 450 x 10^9 /L values at EOS in the STP cohort.

Examination of shift from baseline to end of study measurement reveals 27 placebo patients and 29 STP patients had both baseline and end of study measurements. In the placebo cohort there were 25 patients with normal baseline platelet counts that remained normal at EOS while in the STP cohort there were 23 patients with normal range platelet counts both at baseline and EOS. In the placebo cohort there was one patient with normal baseline value that was low at EOS and one patient low at baseline that was normal at EOS. In the STP treatment cohort there were 4 patients normal at baseline that transitioned to OORR low values at EOS and 1 patient

[55] May Clinic, Mayo Medical Laboratories. Critical Values/Critical Results List.
http://www.mayomedicallaboratories.com/test-catalog/appendix/criticalvalues/
DLMP Critical Values/Critical Results List [CL 041647.009] Effective Date: 12/01/2015

normal at baseline that was OORR high at EOS. One patient in the STP cohort had an OORR low value at baseline that transitioned to normal at EOS and 1 patient low at baseline remained OORR low at EOS. In the STP cohort there was one patient high at baseline that transitioned to normal within reference range value at EOS.

There is some potential that a decline in platelet count seen in the STP cohort is confounded by concomitant treatment with VPA. When platelet count at end of study was matched to VPA level in ug/ml at the mid treatment period visit (M2 day 60) there was a small trend of declining platelet count as VPA level increased although the slope was -0.86 with a correlation coefficient of only 0.1.

In summary, this analysis reveals a signal for decline in platelet values over the STP treatment period. This is seen in the change in group mean baseline to EOS (end of study) counts, a higher frequency of absolute decline from baseline to EOS in the STP group compared to the placebo cohort, a larger magnitude of negative percent change from baseline in those who had a baseline to EOS decline in platelet count and a greater number of normal to low shifts from baseline to EOS in the STP cohort compared to the placebo cohort. At EOS there were 5 patients in the STP treatment cohort and none in the placebo cohort with a platelet count less than 150 x 10^9/L and from among the 5 STP patients with low values only one was low at baseline. However, there were no declines to critical low values at EOS in the STP group. The minimum EOS count in the STP cohort was 77 x 10^9/L at EOS after a 44% decline from baseline while the maximum percent decline from baseline in the STP group was 57%. In the placebo cohort the minimum EOS count was 150 x 10^9/L after a 2.6% decline from baseline

Reviewer Comment, Pivotal Laboratory Studies: Chemistry studies are limited to AST and ALT. There is no increase in ALT over the STP treatment interval while AST has a clear signal for increase in value over the STP treatment interval. This signal is not linked to hepatic toxicity. The cause of the elevation trend is uncertain. This may be entered into labeling as “seen in clinical trials”.

In the evaluation of hemoglobin there is a small trend to declining values in the STP treatment patients than in the placebo treatment patients. There are more patients with a decline in Hb from baseline to EOS in the STP treatment group (61%) than in the placebo treatment arm (44%), although there was no meaningful change in the STP group mean hemoglobin value from baseline to EOS compared to the PBO arm, difference (0.50 g/L). The maximum percent decline from baseline in an STP treated patient was 16.6%. Small declines in hematocrit and erythrocyte count are in alignment with the findings in hemoglobin values. These observations do not rise to evidence of a significant safety signal.

There was no notable change in total white blood cell count (leukocytes) but there is a modest

signal for decline in neutrophil count during STP treatment supported by the observation of more frequent baseline to EOS shift to lower (*decline but not OORR low*) than baseline neutrophil count in the STP treatment group than in the placebo arm. There were no critical low EOS neutrophil counts in the STP treatment group.

There was a signal for decline in platelets during the STP treatment interval. This is seen in the change in group mean baseline to EOS counts, a higher frequency of absolute decline from baseline to EOS in the STP group compared to the placebo cohort, a larger magnitude of negative percent change from baseline (*in those who had a baseline measurement*) to EOS in those patient with decline in platelet count and finally a greater number of normal to OORR low shifts from baseline to EOS in the STP cohort compared to the placebo cohort. Labeling should reflect thrombocytopenia seen in clinical trials.

Non-Pivotal Trials in Dravet Patients (category 2 & 3)

Acquisition of laboratory studies was not uniform across the non-pivotal studies in addition critical values are not provided, reference range values are inconsistently provided and for some parameters there is a mix of qualitative and quantitative results across patients and treatment intervals. These studies do not have placebo comparators and baseline comparison is inconsistent because some patients enter studies already on STP treatment, for example patients entered the TAU-EAP study from the earlier STILON study[56]. With these limitations common laboratory measurements across studies will be pooled to survey for abnormalities that may emerge over extended exposure intervals.

A limited panel of clinical laboratory parameters was collected in most of the non-pivotal studies except for STP-1. The laboratory parameters collected across the non-pivotal trials is shown in Table 88. Each parameter will be pooled across all studies where the parameter was collected. Patients with an abnormal result at any point on their treatment timeline will have the entire treatment timeline examined to determine the temporal characteristics of the abnormality such as a single isolated event or a progressively worsening trend.

Table 88 Clinical Laboratory Parameters available in Non-Pivotal Studies (category 2 & 3)

	STIPOP	TAU-EAP	DIAVEY	STEV	STILON	STP1
Hematology						X

[56] ISS p37, "Dravet syndrome patients still treated in STILON "rolled over" into the TAU-EAP. A total of 272 Dravet syndrome patients were treated under the TAU-EAP; 124 (46%) of these patients had participated in 1 or more of the clinical trials conducted prior to 2003 and listed in Table 3-1."

	STIPOP	TAU-EAP	DIAVEY	STEV	STILON	STP1
Basophils					X	X
Eosinophils					X	X
Erythrocytes				X	X	X
Hematocrit				X		X
Hemoglobin						X
Leukocytes				X	X	X
Lymphocytes					X	X
Monocytes					X	X
Neutrophils			X		X	X
Platelets					X	X
Chemistry						
Alanine Aminotransferase (n=438)	X	X	X	X	X	X
Alkaline Phosphatase					X	X
Aspartate Aminotransferase	X	X	X	X	X	X
Bilirubin				X		X
Blood Urea Nitrogen						X
Chloride						X
Cholesterol						X
Choriogonadotropin Beta						X
Creatinine					X	X
Gamma Glutamyl Transferase			X			X
Glucose						X
Lactate Dehydrogenase						X
Potassium					X	X
Protein						X
Sodium					X	X
Urobilinogen						X

Chemistry

ALT (Alanine Aminotransferase)

Total Abnormal Results and Type of Result Entry (quantitative or qualitative)

There were 130 entries from 62 patients identified as abnormal ALT values from a total 1621 entries contributed by 438 patients (14%). One patient (DIAVEY (b) (6)) is removed from the abnormal list. Upon conversion of the original units (microkatal) to standard units (IU/L) the patient ALT value was normal. Fifteen patients with 54 abnormal entries are removed from the analysis because the abnormality was found to be low OORR. The analysis is concerned with OORR high ALT values. There are 30 patients with "abnormal" entries from among the TAU-EAP, DIAVEY and STILON studies where the entry is only a character non-quantitative entry. However, these same patients have quantitative entries at other points on their study timeline.

A total of 50 (11.4%) patients are found with at least one abnormal qualitative or quantitative ALT entry. From among the patients in the group with quantitative values the highest ALT measurement was 1.9 x ULN where the next 3 greatest multiples of ULN are 1.8, 1.5 and 1.4 respectively. These events are from first visit entries on study days -70, -2, -102, and -1 respectively. These patients' timelines are excluded from further analysis. From among patients with an ALT value obtained at a non-baseline visit and a measurement taken greater than laboratory day 4, there were five patients with a value > 1.2 x ULN, two of these values were 1.4 x ULN and three were 1.3 x ULN. All remaining patient had either a qualitative entry for ALT or a value 1.2 x ULN or less.

Single Abnormal value Entries

In the remaining patients with any abnormal value entry of ALT over study participation, the timeline of ALT measurements is examined. There were 8 patients from TAU-EAP with only a single entry at "VISIT FROM START OF TREATMENT D0". These patients have only a qualitative "ABNORMAL" entry with no further timeline. There are two additional patients with only a single entry on the timeline. Both of these patients have only a qualitative "abnormal" result. One patient value is from inclusion visit, the second is from visit 2. These patients cannot be further evaluated.

Patients with >1 Entry on Study Timeline and 1 or More Abnormal Values

There are 304 entries that meet the criteria of >1 ALT measurement and represent a patient with one or more abnormal ALT values. Nine entries with visit number "ADDITION" are excluded because these events represent unscheduled study visits and may have occurred at any time along a patient study timeline, these events will be capture in the next analysis by the variable "LBDY", laboratory day. Exclusion of the "ADDITION" visits leave 295 entries from among 40 patients in the STILON (90 entries), DIAVEY (145 entries) and STP1 (60 entries) studies.

ULN by Visit Number

Due to the divergence in study structure noted in the opening discussion of this section each of the three studies are examined separately for an ALT upper limit of normal multiple vs visit number timeline for trend in ALT with cumulative exposure. As an aid to creating a timeline graphic of the ULN multiples for each entry across the pooled study group the qualitative value entries for "NORMAL" and "ABNORMAL" are imputed to 0.5 and 2 respectively to allow a coarse contribution of the qualitative values. This imputation is only needed in the DIAVEY and STILON studies because the 4 patients in the STP1 study who meet criteria for this analysis have quantitative entries at all study visits. Results for this analysis are shown in

Table 89 ALT; Slope, Line of Fit, ULN vs Visit Number for DIAVEY, STILON, STP1

	Line of Fit Slope	
Study	imputed ("NORMAL= 0.5 x ULN, "ABNORMAL"= 2.0 x ULN)	quantitative values only
DIAVEY	-0.021	-0.037
STILON	0.065	-0.006
STP1	N/A	-0.007

Each of the 40 subjects who had one or more entries with an ALT > 1 x ULN had line of fit over visit number examined (not shown) with and without imputed qualitative values and no trend of increasing ALT over cumulative exposure was identified.

ULN by Laboratory Day (LBDY)

There were 40 patients with 231 entries for the variable LBDY (laboratory day) from the DIAVEY, STILON and STP1 studies who had more than one entry on their study timeline and one or more ALT values with a ULN > 1. These studies are individually examined for trend of ALT values over cumulative exposure with the laboratory day as the x axis timeline, see Table 90.

Table 90 ALT; Slope, Line of Fit, ULN vs Laboratory Day for DIAVEY, STILON, STP1

	Slope Line of Fit			
Study	imputed ("NORMAL= 0.5 x ULN, "ABNORMAL"= 2.0 x ULN)	N	quantitative values only	n
DIAVEY	-.0002	20	-.0004	19
STILON	0	16	-.00005781	16
STP1	N/A	4	-.00043	4

An additional analysis is performed on the ALT value in study STP1. This study had complete and systematic collection ALT measurements across the study timeline up to 430 days where 19 of 30 (63%) patients had measurements during the last 45 days of the long term study interval. This analysis reveals line of fit slope of (-.00005208) a slightly negative slope. This result indicates no signal for increased ALT with cumulative exposure.

In summary, there were no ALT entries in the non-pivotal Dravet syndrome studies with quantitative entries with a value greater than 1.4 x ULN at non-baseline measurements. There was no trend of ascending ALT values among quantitative value entries from patients who had an ALT value with ULN >1. There was also no trend of sustained abnormal ALT values over the

treatment timeline inclusive of quantitative and qualitative entries where abnormal was imputed to 2 x ULN for visibility on a graphic timeline. Examination of all STP1 study patients revealed no trend of increased ALT values in examination to laboratory day 250 or 430. There is no signal for abnormal ALT occurrence during sustained open label STP treatment.

AST

Examination of the AST laboratory values from the six category 2 and 3 studies reveals there were 438 patients who contributed 1620 entries to the dataset. It is noted from the DM data that 496 patients entered these studies. From among the 1620 entries 297 were had an ALT value at any time that exceeded the ULN. These 297 entries were contributed by 114 patients. There were 90 patients with an abnormal AST value at any non-baseline measurement that contributed 255 entries. Two hundred and twenty two (222) of these entries were quantitative while 33 were a qualitative entry of "ABNORMAL". The qualitative entries were contributed by 21 patients while the quantitative entries were contributed by 73 patients.

From among patients with quantitative ALT entries and post baseline measurements greater than the upper limit of normal the subset of entries with a value greater than 3 x ULN is identified for analysis of the full timeline of AST values. There were nine entries from seven patients with an ALT value > 3 x ULN. There were three patients from the DIAVEY study with one or more post-baseline abnormal qualitative or quantitative values. There were no abnormal qualitative entries for these three patients and the 16 "NORMAL" qualitative entries were imputed to 0.5 x ULN. From among the three patients there were 6 entries >1 x ULN. Examination of the study timeline for these three patients with study timeline maximum values ranging from 935 to 1342 days reveals **no trend** for increasing values of ALT over the duration of their study participation. There were four patients from the STP1 study with one or more post-baseline abnormal qualitative or quantitative values. All entries were quantitative. The range of maximum laboratory day entries had a minimum of 421 and maximum of 430 days. One of these patients (STP1 (b) (6)) had an elevated baseline ALT value of 1.54 x ULN on laboratory day 1 with a trend toward increasing ALT values during the remaining 406 days of available laboratory measurements. Although there were ALT elevations to 5.6 x ULN and 3.88 x ULN on laboratory days 369 and 370 respectively the final ALT measurement was 0.97 x ULN on laboratory day 407. A second patient (STP1 (b) (6)) had normal baseline ALT with an increasing trend in ALT value over 418 days. In the two remaining patients with an ALT value ≥ 3 x ULN there were sporadic ALT values > 1 x ULN but no trend of increasing values over the timeline of laboratory study days 421 and 430 respectively.

AST values are examined for all entries with a positive value for laboratory day. Negative values are excluded due to the difficulty with interpretation of large negative numbers across the 6 studies of the dataset. The range of negative laboratory day values was from -1 to -2200 with a median of -17 and mean of -82. Ten percent of values had a value of -176 or less. There are

1215 entries from 5 studies (DIAVEY, STEV, STILON, STIPOP and STP1) and 255 patients where all laboratory day values are positive (LBDY). There are 18 entries from the STIPOP study, all but one entry is from day 1, the remaining, "NORMAL" entry is from day 7. These are excluded from further analysis due to the short-term administration. In order to examine for a signal of increase in ALT with long term STP treatment the **slope of the ULN / laboratory day line** of best fit examined. ALT entries with a qualitative normal have a value ***imputed*** to 0.5 x ULN while qualitative abnormal values are imputed to 2.0 X ULN. There are 427 qualitative "NORMAL" entries and 6 qualitative "ABNORMAL" entries in this dataset, thus only 6 entries from six patients are imputed to a value of 2 x ULN. There are 139 patients with 3 or more entries needed for use of fit line method to generate a value for slope. These 139 patients contribute 1047 entries. The slope is evaluated as a simple binary positive or negative and also as positive if there is a rise of ≥ 1 ULN multiple per 1000 laboratory days. The analysis reveals that 29% of evaluable patients had a best fit line with any positive value slope while 9% of evaluable patients had a best fit line with a slope > .001.

AST values by study are examined using best line of fit methodology to generate an equation with a slope coefficient, see Table 91. Entries from the DIAVEY, STILON and STP1 study are utilized for this evaluation. In the DIAVEY study there were 211 entries from 85 patients with a quantitative value. Patients with a first visit laboratory day greater than -30 days or only 1 laboratory value entry were excluded. There were 180 remaining entries contributed by 54 patients. The number of laboratory days that were spanned by these remaining 54 patients ranged from 20 to 1331 days. Forty four patients contributed laboratory day intervals that were greater than 90 days. In the STILON study there were 39 entries from 20 patients that had 2 or more AST measurements during this study. The interval between AST measurements ranged from 86 days to 1126 days with a mean and median of 651 and 716 days respectively. The slope of the ULN vs laboratory day variable has a small negative trend. The STP1 study has a positive slope of 0.247 ULN units over 429 days.

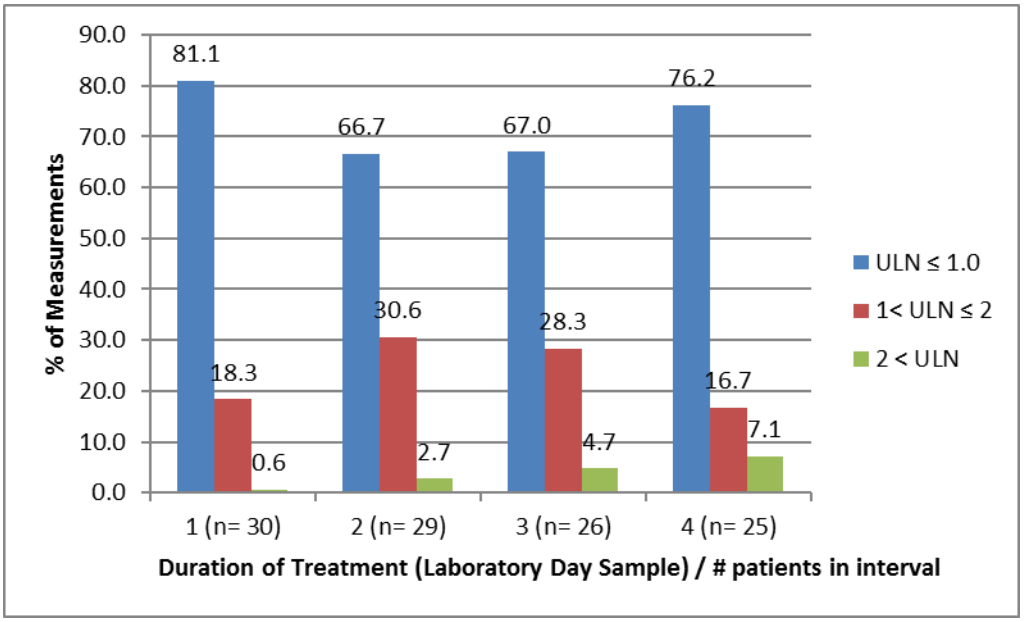
Table 91 Slope of jmp Fit line by laboratory day (LBDY) by Study

Study	slope	n
DIAVEY	+0.000073	54
STILON	-0.00026	20
STP1	+0.000577	30

The STP1 study had the most systematic laboratory study samples with assigned reference range and sampling intervals. The change in AST value by duration of participation is examined. The longest duration AST measurement was taken at laboratory day 429. The laboratory day timeline is divided into 4 epochs of 100 days each with the frequency of measurements in categories identified as ≤ 1 x ULN, ≤ 2 x ULN, and > 2 ULN. This analysis reveals an increase in AST values greater than 2 x ULN rising from 0.6% during the first 100 laboratory days to 7.1% in

the interval from day 300 to day 429, see Figure 23 . However, there were 4 (3.2%) with values > 3 x ULN during this interval while 2 measurements in the interval from 200 days to 300 days were > 3 x ULN and none in the preceding intervals.

Figure 23 STP 1 Percent of Measurements by Upper Limit of Normal (ULN) by 100 day Study Intervals



In summary, there is a trend of increasing AST over a period of long term exposure to STP. In the STP trial the fit line identified an increase of 0.247 ULN units over 429 days. However, from among patients with a quantitative AST value there were 7 patients with 9 entries with an ALT value greater than 3 x ULN with a maximum of 5.7 x ULN. These elevations were primarily sporadic and not part of a systematic increasing trend. Although the pooled analysis of category 2 and 3 studies is limited by frequent qualitative entries for AST measurements the overall evidence does not indicate a notable signal for AST elevation.

Alkaline phosphatase (ALP)

There were only two studies in the category 2 and 3 studies (Dravet patients) where Alkaline Phosphatase measurements. These studies were STILON and STP1. In the STILON study there are 32 entries from 25 patients. Fourteen patients had a visit 1 measurement and 18 patients had a post visit 1 measurement. Seven patients had both a baseline and post baseline measurement. All of these patients were normal at both baseline and follow up. There were 11 patients with only a post baseline measurement and from among these a single patient had an

abnormal value at 1.3 x ULN.

In the STP1 trial there are 488 ALP entries from 30 patients. There were four patients identified who had one or more ALP value greater than 3 x ULN. These patients ULN values are evaluated over the study timeline. None of these patients had normal ALP values at baseline. Two of these patients had a trend of declining values from baseline to last laboratory sample over 350 days later. The remaining two patients had sporadic increase in ALP that did not continue as an upward trend to end of study.

The fit line of laboratory day by ULN multiple of all remaining patients (the 4 patients previously discussed are excluded). From among the remaining 26 patients there were 23 with fit line that had a negative slope. None of the values exceeded 2 x ULN. The remaining 3 patients had a fit line with positive slope with consistent increasing trend from baseline. However, two of these three patients had baseline ALP values >1.5 x ULN. In the third patient the baseline value was 1.26 x ULN. None of the patients that had a fit line with positive slope had a normal baseline ALP value. Twenty two of 26 patients of the group with all values < 2 x ULN had negative slope fit lines.

In summary, only two studies, STP-1 and STILON had alkaline phosphatase measurements. There are no patients with a trend of increasing ALP over the study timeline who had normal baseline ALP (all elevated) in the STP study. There is no signal for elevated ALP associated with increasing STP exposure.

Total Bilirubin

In the category 2 and 3 studies of Dravet syndrome patients there were two that recorded bilirubin. These studies were STP1 and STEV. In the STEV study only 34 measurements are obtained from 20 patients. there were 4 entries from baseline or D0, which are both prior to STP treatment. The remaining 30 entries are captured during the 12 week STP treatment interval. These patients with baseline measurements do not have a subsequent bilirubin value to examine change during STP treatment.

No reference range values are provided for the STEV bilirubin values. Measurements are provided in umol/L. The baseline values for the full STEV study of 227 patients (DS and non-DS patients) are examined to inform expected normal values for bilirubin. The B0 (baseline) median bilirubin value for the group is 8.0 umol/L with a mean of 8.44. The lower and upper quartiles are 5.0 and 10.0 respectively. In addition, standard textbook reference values from Harrison's Principles of Internal Medicine are 5.1 to 22 umol/L. The maximum value entered for those Dravet syndrome patients with post baseline measurement is 12 umol/L. This value appears to be in a normal range. In the small sample of bilirubin measurements from the STEV study there is no signal for elevation of bilirubin.

Examination of bilirubin value from the STP1 study reveals there are no values above upper limit of normal for any entry. Examination of all study bilirubin values reveals the fit line of ULN multiples by laboratory day has a small negative slope. The profile of bilirubin values across the study duration is visually examined for each patient with a best fit line, overall there is no tendency for an increase in bilirubin as STP exposure is prolonged. The bilirubin values were captured approximately monthly over an approximately 14 month interval.

In summary, from the STP-1 study and available measurements in the STEV study there is no signal for increase in bilirubin with increasing STP treatment duration.

Gamma Glutamyl Transferase (GGT)

Two category 2 and 3 studies captured GGT, these studies were DIAVEY and STP1.

DIAVEY

In the DIAVEY study there were 168 entries from 72 patients. Forty-two patients had more than one GGT value recorded while 30 had only one. From among those with one value obtained there were 12 patients with a first visit value only. Two of these had a ULN value greater than 1. These 12 patients are not analyzed further. From among the remaining 18 patients with a single GGT entry the time of entry ranges from follow up visit 1 to 1 year after discontinuation. There were 2 patients with a GGT multiple greater than 1 x ULN in the group with values at follow up visit 1. These values were 1.6 and 2.9 x ULN. From among the remaining patients with only a single GGT entry there was only one patient with a value in the normal range. The remaining value ranged from 1.2 x ULN to 8.5 x ULN. The value of 8.5 x ULN is recorded 1 year after discontinuation of STP and is therefore not related to treatment. The abnormal multiples of ULN occurred at a range of visit from follow up visit 2 to follow up visit 7 with no clear pattern of relationship to STP exposure.

There were 17 patients with only two GGT values captured during their study participation. From among this group there were 6 patients with an increase from normal at initial sample to OORR (out of reference range) high at second sample or high OORR at first sample that increased further at the second sample. There were two patients with a second sample that was greater than 3 x ULN. In case 1 the initial GGT value was .26 x ULN at follow up visit 2 that increased to 5.3 x ULN at follow up visit 4. In the second case the first sample was obtained at first visit and was 1.3 x ULN while the second sample at follow up visit number 1 was 4.3 x ULN. In the remaining 4 patients, the maximum change from first to second sample was from 0.63 x ULN at first visit to 2. 5 x ULN at follow up visit 2. The follow up visit number 2 value was also the highest ULN multiple of these 4 patients.

There were 25 patients with 3 or more entries. The maximum value from these remaining patients was 10.8 x ULN. The fit line for each patient is examined for the presence of a positive slope over increasing treatment time. There were 10 patients with a negative slope and 15 patients with a positive slope where 5 had a correlation coefficient >.6. The narrative reports are examined to determine if any of these 5 patients with a strong trend for an increase in GGT had a related serious adverse event. One of the 5 had an SAE of thrombocytopenia but no content related to hepatic function.

One patient DIAVEY-(b) (6) had a single value at follow up visit 3 (LBDY 380) that reached 36 x ULN. This value was bracketed by a first visit (LBDY -2) value of 1.6 x ULN and a follow up visit 4 (LBDY 449) value of 1.7 x ULN. At visit 3 the high reference range was different than at visit 1 and 4 with a value of 20 while visit 1 and 4 had a value of 65, more typical for the DIAVEY laboratory set. It is uncertain why such a dramatic change would be seen between two modestly elevated values. The change in high normal reference range suggests a possible irregularity of laboratory recording. Alternatively, the patient may have had an exposure from an unidentified agent that caused this sudden spike.

In summary, there is an overall trend for increasing GGT during the prolonged interval of STP treatment but no clear signal for related hepatic dysfunction.

STP1

In the STP1 study there were 504 entries from 30 patients spanning 430 days. Multiples of the upper reference boundaries of normal are calculated for each patient to allow further analysis.

The highest multiple of ULN was 9.0 x ULN at week 12 visit (LBDY 85). All entries for this patient are examined. This exam reveals that following the day 85 sample the GGT values have a decreasing trend to the last measurement on day 365. The first value obtained was 5.4 x ULN.

From remaining GGT measurements the next largest multiple of ULN was observed in patient STP1-(b) (6) with a value of 6.9x ULN. All entries for this patient are examined and an increasing trend for GGT value is observed up to day 146, thereafter value decline to 2.2 x ULN on day 237. The patient had elevation upon enrollment with a value of 1.6 x ULN. Eighteen patients (60%) have an increase in GGT ≥ 40 IU at any sampling point after baseline. One of 24 group 1 and 2 patients has a value > 3 x ULN within the 1st 90 days of the study.

The fit line of all 30 patients is examined for a positive or negative slope. A positive slope is associated with a trend of increasing GGT values over the study interval. This analysis reveals that 27/30 (90%) patients have a positive slope best fit line while 2/30 (7%) have a negative slope fit line and 1 has a slope of zero.

The STP1 study reveals a strong trend for increasing GGT over the study interval that appears to be systematic and sustained for 90 percent of patients. This observation supports a causal relation to STP treatment because patients enrolled in STP1 were not previously treated with STP.

In summary, both analysis of both the DIAVEY and STP1 studies reveal a trend of increasing GGT values associated with increased duration of STP exposure. This trend is especially strong in the STP-1 trial where STP was administered to patients for the first time. The bases of these findings are not clear. Neither the ISS or STP1 study report identifies this trend. Other laboratory parameters associated with hepatic function abnormality including ALT, alkaline phosphatase and bilirubin did not show abnormal trends during the treatment interval in the category 2 and 3 studies nor in the pivotal studies.

Creatinine

In the category 2 and 3 studies creatinine was captured as a laboratory study in the STILON and STP1 study.

STILON

There were 48 entries from 35 patients in the STILON study. Twenty-two patients had only one entry. From among these 22 there were 8 from baseline. In 4 of these patients the value was OORR high. These are not considered further but provide some information on the baseline features of the population. In the remaining 14 patients with post baseline measurements there are three OORR low values for creatinine. These are not considered further.

From among the 13 patients with two or more creatinine measurements there were no abnormal values.

STP1

There were 511 entries for creatinine measurement from 30 patients. There was one entry with a value > 1 x ULN. All values from this patient (STP1-(b) (6)) were examined further. The examination reveals a single OORR high value at day (LBDY) 148, with a cluster of increasing values at days 114, 142 and 148. Thereafter values decline. The overall fit line for this patient in the interval from day 1 to day 425 is negative.

The fit line of all 30 patients is examined for a positive or negative slope. A positive slope is associated with a trend of increasing creatinine. The examination reveals that 25/30 (83%) patients had a decreasing slope of their fit line of creatinine by study day (LBDY) while 5 patients had a positive slope, however these were very shallow changes in 4 of the five

patients. A single patient had a positive slope of 0.1 ULN from baseline to day 421 where the correlation coefficient was 0.439. The maximum value for this patient was 0.7 x ULN.

In summary, there is no signal for an increase in creatinine over increasing time of STP exposure in the STILON or STP1 studies.

Blood urea nitrogen (BUN)

In the category 2 and 3 studies BUN was captured only in the STP1 study. There were 512 entries from 30 patients spanning a maximum interval of 460 days. There were 11 entries from 3 patients with BUN values greater than 1 x ULN. The temporal profile of BUN values over the treatment interval is examined for these three patients. One patient had their only abnormal value at baseline. All values thereafter were within normal limits and had a clear declining trend. From the remaining two patients with BUN values > 1 x ULN both had sporadic values greater than 1 x ULN with a fit line of shallow positive slope.

The fit line of BUN vs study day (LBDY) is examined for the remaining 27 patients where all BUN values are in reference range. There were 17/27 (63%) patients with a positive slope but from among these there were 3 with a correlation coefficient > 0.3. There were 10 (37%) patients with a negative slope.

Overall there were 19 (63%) patients with a positive slope fit line for BUN, ULN multiples by study day (LBDY) while there were 11 (37%) patients with a negative fit line slope.

In summary, although the majority of patients have a trend of increasing BUN during the STP treatment interval there are only 2 patients where the values exceed ULN, and in these two patients the OORR high values are scattered sporadically through the study timeline. Overall, there is no signal for a systematic increase in BUN during the 430 days of STP treatment in the STP1 study.

Potassium

In the category 2 and 3 studies serum potassium is captured in the STILON and STP1 studies.

STILON

There were 50 entries from 35 patients in the STILON study. Examination of the dataset reveals there were two OORR high values occurring in two patients. There were no OORR low values identified. From among the OORR high value one occurred at visit 1 with no further entries. The value was 1.02 x ULN. In the second patient with an OORR high value the entry occurred at visit 11, laboratory day 399. The visit 1 value for this patient was 0.84 x ULN while the OORR high

value at visit 11 was 1.2 x ULN. There are no further entries for this patient.

There were 15 patients with a baseline and post baseline potassium measurement. The post baseline measurements are captured across differing visit numbers ranging from corresponding laboratory days 216 to 1126 (visit number 2 to visit 11). The fit line for the baseline to post baseline visit in these 15 patients has a small negative slope equal to 0.16 mmol/L over the 1126 day measurement interval.

There is no signal for a systematic increase or decrease in serum potassium identified in the available data from the STILON study.

STP1

In the STP1 laboratory dataset there were 510 entries for serum potassium from 30 patients spanning visit numbers 1 to 36 through a maximum duration of 430 days. There were 18 instances of OORR high values that occurred at post baseline values from 9 patients. These patients full profile of potassium value across the study timeline are examined for systematic upward trend.

From among these 9 patients 2 patients ((b) (6)) are identified with a consistent increasing trend of potassium values. The maximum value in the first case is 5.1 mmol/L at day 141 which declines to 4.5 mmol/L at day 369. In the second case the maximum value of 5.0 occurs at the last sampling day 372, rising from a baseline value of 4.2 mmol/L. The adverse event dataset for patient (b) (6) is examined for cardiac, renal or syncope related adverse events and none are present. The ECG dataset is examined and no abnormal interpretation is entered for this patient. From among the remaining 7 patients in this group who had one or more OORR high values there are none with consistent rising or falling trend of potassium values from baseline. The high values are distributed in a sporadic manner.

All entries across the study timeline for the remaining 21 patients are examined for an increasing or decreasing trend of serum potassium. From among these patients there is a single patient (b) (6)) with two OORR low potassium values which occur at day 162 (LBDY) and 302 (LBDY) with an overall positive slope for value from day 1 to 421. These OORR values represent sporadic measurements and are not part of a trend toward hypokalemia. Among the remaining patients there is no consistent upward or downward trend for potassium values.

In summary, the data from the STILON and STP1 studies do not reveal a signal for abnormal alteration of potassium levels during sustained STP treatment.

Sodium

In the category 2 and 3 studies serum sodium is captured in the STILON and STP1 studies.

STILON

In the STILON study there are 50 entries from 35 patients. Fifteen patients have two entries while 20 patients have only one entry. From among the patients with a single measurement there are 8 patients with a baseline only entry. These are not considered further in the analysis. From among the remaining 42 entries there are 4 post baseline value that are OORR low. Three of these patients have a baseline value and from among these the maximum decrease in sodium was 9mmol/L. In the remaining two cases the declines were 5.5mmol/L and 2 mmol/l respectively. The remaining patient of this group of 4 patients had only a single value at visit 5 that was 133 mmol/L.

There were 5 patients with a value that was OORR high but in two of these the high value was from baseline measurement. Three patients had high post baseline OORR values but in only one case had both a baseline and post baseline measurement. This patient had an increase from baseline to post baseline of 2 mmol/L.

In the next analysis all patients with a baseline and post baseline value are grouped for evaluation of the fit line for sodium value across the study timeline. There are 15 patients who meet these criteria. The baseline to post baseline slope has a very small negative slope representing a change of only .0074mmol/L over the study interval with a non-correlated point scatter around the fit line. Overall there is no evidence of a systematic change in serum sodium over the time course of the STILON study with available data.

STP1

The STP1 study had 510 entries from 30 patients spanning a maximum duration of 430 days. There were 31 entries from 14 patients with OORR low values. The lowest sodium value recorded was 133mmol/L in two entries from two patients. In one patient the measurement was a baseline value followed by an increase to 134mmol/L. Overall Five of the low values were baseline measurements. Patient STP1 (b) (6) has a baseline value of 137 mmol/L with 4 additional measurements of 137mmol/L during the study. All patients with OORR low values had individual scatter plots examined with line of fit for the presence of systematic trend to high or low sodium values over the patient study participation. No systematic trend in either direction was observed in this analysis

There were two entries from a single patient with OORR high value. These values were both 145mmol/L which was only 1mmol/L greater than baseline value of 144mmol/L.

Individual scatterplots with lease square regression lines are generated for the remaining 15

patients with no values outside of the low and high reference range values. These are examined for evidence of a systematic trend of increasing or decreasing sodium values within and across patients over their period of study participation. This analysis reveals no trend of increasing or decreasing sodium values during the STP1 study interval.

In summary, the data from the STILON and STP1 studies do not reveal a signal for abnormal alteration of sodium levels during sustained STP treatment.

Chloride

From among the category 2 and 3 studies serum chloride was captured in STP1. There were 510 entries from 30 patients spanning maximum study duration of 430 days. Examination of all entries reveals that 209 entries were OORR high. The individual scatterplots with least square regression lines are examined from all patients individually. This analysis reveals all values, including baseline, from 12 patients were above the reference range high of 110mmol/L. From among these 12 patients there were 9 with a positive slope regression line and 3 with negative slope regression line. Three (STP1-(b) (6), STP1(b) (6), STP1(b) (6)) of the 9 positive regression line patients had a consistent upward trend in chloride value with correlation coefficients >0.1. The adverse event dataset for these patients is examined. Patient (b) (6) had episodes of fever and impaired appetite that may have been related to a serious adverse event of "general physical health deterioration". Patient (b) (6) had multiple entries for impaired appetite. If the impaired appetite involved poor hydration then hyperchloremia may result. Patient (b) (6) did not have any adverse events that are associated with hyperchloremia.

There were 18 patients with a mix of chloride values less than 110 mmol/L. Individual scatterplots with regression lines are examined for these patients. This analysis reveals there were 9 patients with positive slope regression lines and 9 patients with negative slope regression lines. There was a single patient ((b) (6)) with a positive slope regression line that had a correlation coefficient of 0.6. The adverse event dataset for this patient is examined. The patient had an even of norovirus gastroenteritis at day 31 and fever at day 118. The fever is entered as a serious adverse event. It is possible that an interval of diarrhea and a fever both with free water loss could cause elevated serum chloride but this is not certain.

Overall change from baseline chloride values are examined. There are approximately equal numbers and magnitudes of declines and increases in chloride values. Examination of percent change in serum chloride from baseline at selected timepoints is performed, these include week # 3 dose adjustment period, month 2 of maintenance STP treatment, month 3 of maintenance STP treatment, week 20 of post dose titration period (8 weeks post maintenance) and week 28 of post titration period (16 wks. post maintenance). This analysis reveals that percent change in chloride measurements across patients at each timepoint have

approximately equal magnitude of shift to greater than and less than baseline value.

In summary, 41% of 510 entries for serum chloride in the STP1 dataset were above reference range. This may be due in part to 12 (40%) of patients where all chloride values including baseline were above reference. Within this subset a majority (9:3) of patients had a trend of increasing chloride values with increasing time in the study. There were three patients in this subset that had more positive regression line slopes and somewhat stronger correlation coefficients than the remaining 6 patients in the cohorts. Two of these patients had adverse effects that may account for an increase in chloride.

In the subset of patients with majority of values within reference range there were an equal number of patients with positive and negative slope chloride value vs study day (LBDY) regression lines. One patient with a positive slope and notable correlation coefficient had a viral gastroenteritis and fever which may account for an elevation in chloride if the gastroenteritis was diarrheal.

On analysis of mmol/L of chloride increase there were 7 patients with an increase of > 5mmol/L at any post baseline measurement. From among these 7 patients there were 2 who accounted for all values of 10 mmol/L or more. One of these two patients, (b) (6) had the largest increase and also accounted for 11 of the 32 instances of any measurement with an increase more than 5 mmol/L. This patient had an SAE of malnutrition and bronchitis (based on narrative) but continued STP treatment.

Examination of shifts in chloride values and percent change reveals no overall trend of chloride increase. Subset increases seen may be due to patients with gastrointestinal adverse events.

In summary, there is no overall signal for change in chloride values over the course of the STP-1 study.

Urine Glucose

Only the STP1 study captured glucose measurements as urinalysis in the category 2 and 3 studies. There were 235 entries from 19 patients obtained during the 12 week STP1 maintenance and up to 52 weeks in the STP1 long term follow up period. There were four entries from 2 patients ((b) (6)) where abnormal glucose in urine was detected. The remaining 231 entries were normal.

Vital signs and adverse event profile of these two patients are examined. Patient (b) (6) is a 25 yo female who weighs 50kg. There was one serious adverse event of decreased appetite. There were a total of 21 adverse events entered with one “upper respiratory tract inflammation”. A stress response might account for increased glucose with some output in the

urine however the infection would only correlate with one instance of positive urine glucose.

Patient (b) (6) is a 23 year old male who weighs approximately 50kg. Patient (b) (6) had a single positive urine glucose entry on day (LBDY) 225. This patient has 13 adverse events entered, one serious, identified as pneumonia on day 246. There is a possibility of correlation with infection stress if the patient had ongoing illness prior to the entry of the pneumonia adverse event on day 246. Otherwise this is a sporadic event of uncertain significance.

In summary, there is no evidence for a signal of urine glucose in the STP1 laboratory dataset.

Protein (STP-1 study)

In the category 2 and 3 studies protein values for serum chemistry and urinalysis were only captured in the STP1 study

Serum

There were 510 entries from 30 patients spanning maximum study duration of 430 days. There were 19 patients with 96 entries with an OORR low serum protein value. In six of these patients the value was low OORR at baseline measurement. This results in 13 patients or 43% of patients who had a shift from normal to OORR low serum protein during STP treatment. There were 5 entries from 2 patients with OORR high serum protein measurements. One of these two patients had a single entry at baseline.

Patients were separated into two groups, those with an OORR low protein value at any study timepoint and those with no low OORR values. A scatterplot with regression line was generated for each individual patient. These were examined for directional trend over the study timeline. A count of patients in each group with positive and negative regression line slopes was performed to assess directional trend across patients. Patients with strong decreasing directional trends were further examined for adverse events that may be related to decreasing serum protein, primarily terms “decreased appetite” or “anorexia”.

In the subset with OORR range low protein at any timepoint there were 19 patients. 8 patients had a positive slope while 11 had a negative slope. There were six patients with a stronger negative slope with a correlation coefficient >0.1. Examination of the adverse event dataset for these six patients reveals that 5 patients had a preferred term entry of “decreased appetite”. One of the six patients also had a preferred term for “malnutrition” and 2 patients in the cohort had a preferred term entry of “weight decreased”. One patient had no appetite or weigh related terms.

In the subset with no low OORR serum protein entries there were 11 patients. Seven patients in

this subset had a positive slope for protein value over study timeline and 4 patients had a negative slope. The adverse event profile from 3 of the 4 negative slope patients with the strongest correlation coefficient was examined. Two of these patients had a preferred term entry for “decreased appetite” while all three had an entry for “diarrhea”. One of these patients had an entry for vomiting.

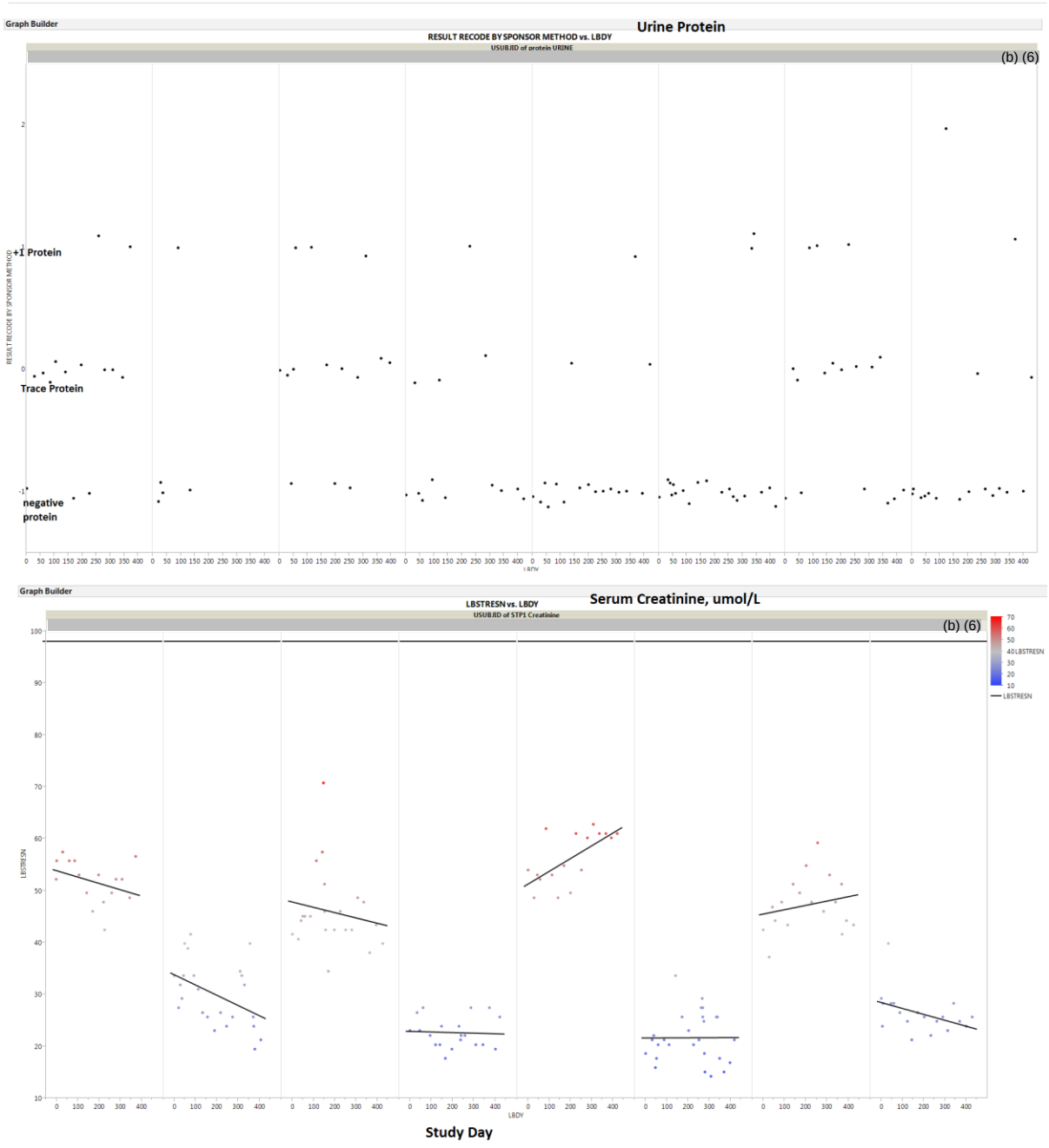
In summary, there is no discussion entry for protein in the STP1 study report or ISS; however decreased appetite was seen as an adverse event term in the STP treatment arm of the STICLO studies more frequently than in the placebo arm. There was also a notable higher frequency of this term across the non-pivotal trials noted in the ISS. It is a plausible hypothesis that decreased appetite is playing a role in the low OORR protein values seen with high frequency in this chemistry dataset.

Urine Protein

In the STP1 urine protein dataset there are 235 entries from 19 patients spanning 428 days. Fifteen of these patients have an abnormal urine protein value at one or more timepoints during the study. There are 84 entries with trace or greater urine protein and 20 entries with +2 or greater urine protein. 19 of these latter values are derived from one patient (STP1 (b) (6) (b) (6)) who has +2 and +3 urine protein throughout their 428 day participation in the study. The remaining entry is from a patient where 4 of 17 measurements during the study are abnormal.

There are 14 entries with a +1 protein value from 14 patients. The urine protein values form the study timeline of each of these patients will be evaluated for any trending of elevated urine protein as STP exposure progresses. The examination of these 8 patients reveals a mix of protein negative, trace and +1 protein. No clear pattern is present that relates the occurrence of trace or +1 protein to duration of STP treatment. For example, an increased frequency of the qualitative entry for +1 protein toward end of study. The scatterplot of serum creatinine during the study timeline is examined for these 8 patients. There are no OORR high creatinine values among these 8 patients and no consistent trend of increasing creatinine value with increasing duration of STP exposure, Figure 24.

Figure 24 Distribution of Urine Protein Measurements, Negative, trace, +1 in Patients with Max of +1, with Corresponding Plot of Serum Creatinine over STP1 Study Duration



In summary, 201 of 235 entries are negative for protein or are trace protein presence. Trace protein may be normal. The scatterplots of qualitative urine protein values over study timeline does not reveal a pattern consistent with increasing protein associated with increasing duration of STP exposure. Comparison of corresponding serum creatinine scatterplots in the patients

with +1 urine protein does not reveal any abnormal creatinine values or trend of increasing creatinine over time. There are sporadic abnormal urine protein measurements in the STP1 study cohort but there is no overall evidence for a signal of renal injury.

Lactate Dehydrogenase

From among the category 2 and 3 studies only study STP1 captures lactate dehydrogenase (LDH) an enzyme that is elevated in a variety of tissue injuries such as liver injury or myocardial infarction. There are 511 entries from 30 patients spanning a maximum of 430 days. Examination of the LDH values reveals that 158 entries from 20 patients are OORR high. Baseline LDH values are found to be OORR high in 14 patients. The maximum LDH value observed in the study is 2.45 x ULN.

Scatterplots with least square regression lines are generated all 30 patients. Examination of the regression lines reveals that 23 of 30 patients have a negative slope regression line while 7 are positive. Elevated values appear sporadically across multiple patients.

In summary, there is no evidence of an increase in LDH values with increasing duration of STP treatment.

Cholesterol

From among the category 2 and 3 studies only study STP1 captures serum cholesterol. In the STP1 study there are 482 entries from 30 patients spanning a maximum study interval of 430 days. There are 17 entries from 4 patients with value that are OORR high while there are 102 entries from 17 patients where the cholesterol value is OORR low.

Scatterplots of cholesterol values with least square regression lines are generated for all patients and examined for systematic trend of increasing or decreasing cholesterol associated with duration of STP treatment. Examination of the 30 scatterplots reveals that 17 patients have a positive slope for cholesterol value by study day (LBDY) and 13 patients have a negative slope. Although there are more frequent OORR low entries in the dataset there is a trend across patients for a positive change in cholesterol value as duration of STP treatment increases. Examination of the entries that are OORR low reveals a positive slope associated with study duration.

In summary, there is a trend of increasing cholesterol associated with increase in the duration of STP exposure. There are few values that cross into OORR high levels. There is no clear signal for a safety risk for OORR high cholesterol.

Urobilinogen

Urine urobilinogen was captured in the STP1 trial. No abnormal values were identified.

Hematology

Hemoglobin (Hb)

From among the category 2 and 3 studies hemoglobin was only captured in the STP1 study. There were 515 entries from 30 patients spanning a maximum of 430 days.

Hb is examined in 24 patients who have an entry for 1st day study enrollment (MEC patients) or 1st day study drug administration (MEF patients), these will be considered study drug treatment day 1 entries. The change in HB is examined for patients with these day 1 entries who remain in the study to Visit number 30 (LONG-TERM ADMINISTRATION PERIOD - WEEK 36). There are 19 patients who have entries at both these time points. These patients have a mean and median exposure of 341 and 364 days respectively. This subset of patients has a mean and median change in hemoglobin value of -6.1g/L (0.61g/dL) and -6.5g/L (0.65g/dL) respectively where 16 patients have a decline in Hb value, 2 patients have no change and 6 patients have an increase in Hb values. The slope of a line connecting day 1 value to V30 value is calculated for each patient as the change from day 1 to V30 / elapsed treatment days to V30. These slopes range from 0.044 to -0.075. A threshold slope of concern is derived from the rate of negative Hb change needed to cause a decline from median normal Hb value to median low reference value over 400 study days (concern = 20 g/L/400days = 0.05). Median normal is the midpoint between median OORR high and median OORR low for all STP-1 study entries while median low OORR value is derived from the OORR low value for all STP Hb entries. This analysis reveals there are 5 patients with a negative slope of concern at V30 while patients with a decline in Hb exceed the number of patients with an increase in Hb by 2.7:1.

Change in Hb is examined in 24 patients with an entry for 1st day study drug administration (V2) and maintenance period stage 3 (V9). These 24 patients have a mean and median exposure of 111.6 and 112 days respectively. This subset of patients has a mean and median change in Hb of of -0.92g/L (0.092g/dL) and -1.0g/L (0.1g/dL) respectively with a range of -20g/L to 36g/L. There are 12 (50%) patients with a decline in Hb value, 3 (12.5%) patients with no change and 9 (37.5%) patients with an increase in Hb value. The slope of a line connecting day 1 value to V9 is calculated for each patient as the change from day 1 to V9/ # days elapsed from day1 to V9. A threshold slope of concern is applied with the same criteria noted in the paragraph above. The analysis reveals there are 9 patients with a negative slope of concern.

The preceding two analyses include 29 of 30 patients in study STP1.

A scatterplot is generated for each all patients in STP1 using hemoglobin value as the y axis and

laboratory day (LBDY) as the x axis. A least squares line of fit is also generated for each patient. Laboratory day is approximately 30 days greater than actual STP treatment exposure for 24 patients but equal to STP exposure days for six patients whose entry points in the dataset is designated "LONG-TERM ADMINISTRATION PERIOD ENROLLMENT). The least fit line is examined for positive or negative slope. The analysis reveals there are 17 (56%) patients with negative slope, 12 (40%) patients with positive slope and one patient with no change in Hb with a slope of zero. From among the patients with a least squares line of fit showing an overall decline in Hb over the course of STP treatment there are two patients ((b) (6) with a slope of concern (0.05). Patient (b) (6) has no adverse event preferred term entries from the "blood and lymphatic system disorders" SOC. Patient (b) (6) has a preferred term entry for "thrombocytopenia" and "Platelets decreased" but no other "blood and lymphatic system disorders" SOC entries. Both patients have entries for "anorexia"

In summary, there is a trend of decreasing Hb values during the course of STP treatment in study STP-1. In this study 24 patients were newly treated with STP, therefore the change in Hb from baseline to V9 and V30 are associated with the addition of STP. This condition (new STP exposure) strengthens the association but does not reach a level of evidence to conclude causality.

Hematocrit (HCT)

From among the category 2 & 3 studies of DS patients only STP1 and the STEV study captured hematocrit.

The STP1 study had 515 entries from 30 patients spanning a maximum of 430 study days. A scatterplot with least square fit line is generated for each patient. A count of fit line slope is performed to examine the hematocrit trend across patients. Slope of the least fit line is positive in 9 (30%) patients and negative in 21 (70%) patients. Analysis of HCT trend reveals a higher frequency of negative slope then in the Hb analysis. These findings are in agreement with the findings of the Hb analysis.

The STEV study has 36 entries from 21 patients spanning laboratory sampling days -10 to a maximum of 109 days. Thus, hematocrit values are captured in 84% of DS patients in the STEV study. One of these patients has 4 measurements obtained, 12 patients have two measurements. There is no placebo comparator group. From among the patients with 2 or more measurements obtained there were two patients with a day 0 and post baseline entry while in the remaining 10 patients a measurement was captured on D28 of STP treatment and day 84 of treatment. From among the two patients with a pre-STP treatment both had a decline in hematocrit value. Patient STEV (b) (6) had a decline of 1.5% from D0 to D 84 while the second patient, STEV (b) (6) had a decline of 2.9% from D0 to D56 to a value of 34.3%. Among the remaining 11 patients with two hematocrit measurements the first entry is D28 and

the second entry is day 84. From among this subset there were 7 patients with an increase in hematocrit from D28 to D84 while there were 3 patients with a decrease hematocrit value and one patient had no change. None of the 3 patients with a decline in value had a measurement below 35%. There were 8 patients with only single value obtained. One of these patients had only a baseline value and is not considered further. The remaining 7 patients had a D28 measurement. The mean and median HCT for the group are 37.3% and 37.6% respectively. The available dataset from the STEV study is limited by infrequent sampling, absent baseline values, and absent placebo comparator. There is no clear signal for decline in hematocrit associated with STP treatment duration.

In summary, the STP1 study reveals a signal for a decline in hematocrit that is congruent with the hemoglobin findings of the STP1 study. The STEV study has an overall trend for an increase in HCT, however this study is more limited in baseline comparators and frequency of sampling.

Leukocytes (WBC)

From among the category 2 and 3 studies leukocyte measurements were taken in the STILON, STEV, and STP1 study. These will be considered separately.

The STILON study had 69 entries from 41 patients (91 percent of DS participants in STILON), where 28 patients had values obtained at V1, study enrollment and 1 subsequent follow up visit. Follow up visits occurred every six months. Thirteen patients had only a single WBC measurement where 8 had only a V1 sample, these patients are not considered further. Five patients had a single measurement at V2, V3, V4, and two at VF (FINAL). The mean and median of these samples will be provided (6.01, 6.4).

The difference between baseline and follow up visit is calculated for the 28 STILON patients with two WBC measurements. This analysis reveals a near normal distribution of the 28 patient differences. The follow up measurements do not occur at the same point in time which confounds the attempt to determine if there is a trend for declining WBC count with increasing STP treatment duration. Elapsed days between V1 and the next follow up measurement range from 177 days to 1149 days with a mean of 712 days and median of 760 days respectively. An examination of least squares fit line for the V1 to subsequent WBC measurement day reveals a trend toward declining WBC count as X axis value (laboratory day) increases. Slope of the least squares line of all 28 patients examined together is equal to a group decline of 1.04×10^9 WBC/L over the 972 day interval.

The difference from V1 to subsequent measurement is examined for all 28 patients with two measurements. There were 14 patients with an increase from baseline and 13 with a decline from baseline, thus advancers approximately equal decliners. The group (28 patient) mean and median change from baseline were 0.15×10^9 WBC/L and 0.17×10^9 WBC/L .The mean and

median value for the 13 patient with a single mid study measurement were 6.01 x 10^9 and 6.4 x 10^9 WBC/L. These are in the normal range.

In summary, the STILON laboratory data does not reveal a signal for change in WBC count during sustained treatment with STP.

STEV study

The STEV study has 36 entries from 21 patients spanning a maximum of 110 days. Twelve patients had 2 WBC measurements; one patient had 4 measurements while the remaining 8 had only one measurement. Where patients had 2 measurements the difference is calculated. Nine of 12 patients had an increase from baseline to follow up while 2 patients had a decline and in one patient a result could not be determined because units were unclear. The patient with four measurements had a fit line with a negative slope but a 0.1 x 10^9 WBC/L increase from baseline to final measurement. The STEV data does not reveal a signal for a decline in WBC during sustained treatment with STP

STP-1 Study

The STP1 study had 515 entries from 30 patients spanning a maximum of 430 days. Four patients had a value below 4.0 x 10^9 WBC/L at baseline, these were STP1 (b) (6) STP1- (b) (6), STP1 (b) (6), and STP1 (b) (6). These four patient least square fit lines are examined for trend to determine if beginning at a low leukocyte count presents a special vulnerability for further decline. The trend for patients (b) (6) remains level with little change across 400 study days. The trend for patient (b) (6) continues to decline through the 400 study days. The trend for (b) (6) shows an increasing WBC count until approximately day 300 and the trend for patient (b) (6) declines. Overall, there is no systematic outcome for the patients who begin the study with OORR low WBC counts.

In this open label study, the approach used to search for a signal of elevation or decline in WBC count will be to examine the trend in WBC count over time from the introduction of study drug STP. The first analysis will be examination of the change in count in the between baseline (1st day of study drug treatment, test before drug administration), early follow up visits and late follow up visit. It is expected a more compelling signal will be identified in a time locked manner to the beginning of STP treatment that shows a temporal relationship. The mean and median change from V2 – 1st day study drug treatment to V6 – approximately 30 days from start of treatment are found to be -0.1 x 10^9 WBC/L and -0.2 x 10^9 WBC/L respectively where 13 (54%) of 24 measurements have a negative value. The mean and median change from V2 to V9 (approximately 101 days after initiation of study drug treatment) are -0.1 x 10^9 WBC/L and +0.1 x 10^9 WBC/L where 11 (46%) of 24 measurements have a negative value. This analysis does not reveal a notable change in the frequency of declining values of WBC count between an early, 30

day, and later, 100 day measurement. The frequency of patients with decline compared to those with an increase in WBC value at each of these timepoint is approximately equal although the magnitude of negative changes is somewhat greater as reflected in the negative mean change.

Analysis of the 6 patients who start STP treatment after maintenance period reveals one patient with only two measurements before discontinuation. This patient has a decline of 1.48 x 10^9 WBC/L but remains within reference range. From among the remaining 5 patients there are two with a positive slope of least squares fit line vs 3 with a negative slope. In two of these latter patients the trend is very shallow. There is no evidence from this analysis of a systematic decline in WBC count that has temporal relationship to initiation of STP treatment.

An additional examination of the scatterplot profile and least squares fit line for each of the 30 patients is performed. There were 20 patients with a negative trendline and 10 with a positive trendline. There was no trend of a temporal relationship between initiation of STP treatment and decline in WBC count.

Overall examination of WBC count across the study timeline in the patient cohort from the STP-1 study does not reveal a signal for a decline in WBC count that is temporally related to initiation of STP treatment. A majority of patients are seen to have a declining WBC trend over the full course of the STP-1 long term treatment interval, however evidence from this interval is confounded by concomitant treatment with valproic acid and clobazam and is not supported by a temporal relationship to the initiation of STP treatments.

In summary, examination of leukocyte counts from studies STP1, STILON and STEV does not reveal a signal for a decline or increase in WBC count associated with STP treatment.

Lymphocytes

From among the category 2 and 3 studies leukocyte measurements were taken in the STILON, and STP1 studies. These studies will be considered separately.

STILON

The STILON study had 69 entries for lymphocyte measurements from 41 patients. From among the 69 entries there are 17 entries from 13 patients are in 10^9/L format while the remainder are in percent. These will not be analyzed further.

STP1

In the STP-1 lymphocyte dataset there were 510 entries from 30 patients with measurements

spanning a maximum of 430 days. Twenty-four of These patients are naive to STP prior to study drug initiation and were followed for change from baseline during a 12 week observation period after initiation of STP treatment. A subsequent 6 patients on prior STP treatment were entered into long term maintenance after the observation period.

One patient had an OORR low values during the course of the study. This patient entered the study with a normal value of 1.72 x 10^9/L but declined to a value of 1.1 x 10^9/L at day 28. The patient subsequently had 6 measurements in reference range and 7 OORR low over the study timeline. No other patients were identified with OORR low values.

A scatterplot is generated for all 30 patients with the values of lymphocyte count as y values and laboratory day as x value (laboratory day – 30 days approximately equals STP treatment duration). The point distributions and least fit regression line are examined for trend of lymphocyte count over study duration. The analysis reveals there were 10 patients with a trend of declining lymphocyte count in the first 75 days while all recovered thereafter. A slope analysis reveals there were 20 patients with a least square fit line that had a negative slope while 10 patients had a positive slope.

The percent change from baseline lymphocyte value of the 24 patients in group 1 & 2 of STP-1 who entered the study without previous history of STP treatment is examined. The patients are followed to week 36 of treatment. There are 24 patients participating to week 16 when at end of maintenance observation 3 patient's withdrawal due to lack of efficacy. The disposition of one patient not accounted for is not provided in the study report. There are 20 patients remaining to follow up to week 36. During this interval the group mean and median % change from baseline are examined. The values are found to be negative through the entire interval but remain at a fairly constant percent delta from baseline.

These values are shown in Figure 25 and Figure 26.

Figure 25 STP-1 Lymphocytes, Median % Decline from Baseline at Study Week

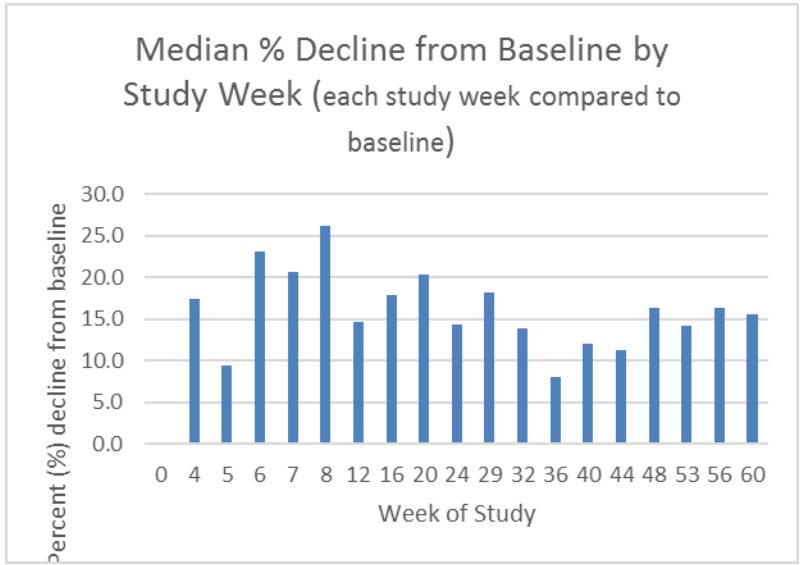
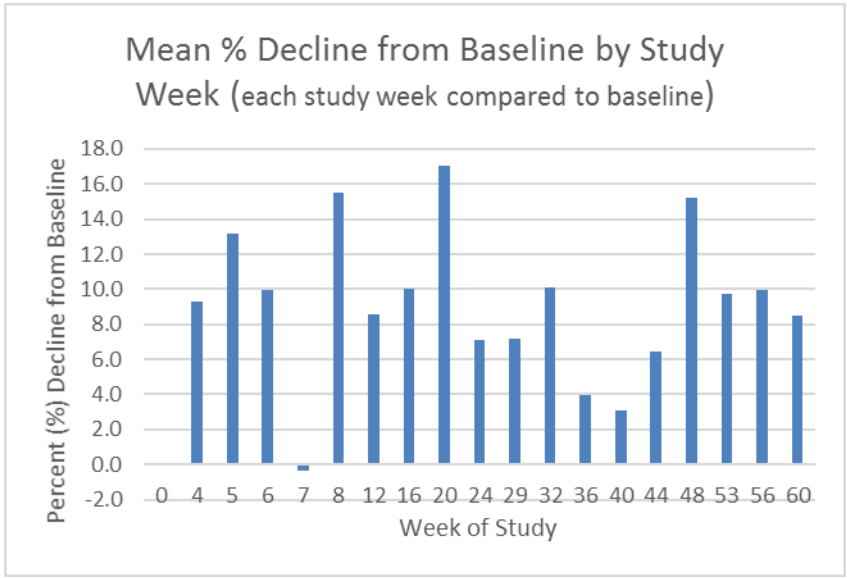


Figure 26 STP-1 Mean % Decline from Baseline at Study Week



Overall

In summary, there is a shift to lower lymphocyte counts after initiation of STP treatment. About one third of patients have an upward trendline through the course of the study while two thirds have a negative trend but among those with negative trend only one patient has values that enter the OORR low range.

Neutrophils

In the category 2 and 3 studies in DS, patient neutrophil measurements were obtained in the DIAVEY, STILON and STP1 trial.

DIAVEY
In the DIAVEY study there were 718 entries from 142 patients. From among these entries there were 103 quantitative entries and 615 qualitative entries. The 103 quantitative neutrophil entries are derived from 60 patients. Forty-two (42) of these patients had an initial visit baseline value. From among these 42 patients there were 16 with greater than a single measurement. Only the remaining 16 patients could have evaluation of the neutrophil values over time based on quantitative results.[57]

From these 16 patients there were 13 entries from 7 patients with ANC values < 1500. Three of these were initial baseline values leaving 3 patients with a shift from normal baseline to less than 1500 ANC. These remaining 4 patients had one baseline and one follow up entry each. One patient (b) (6)) had a 42-day interval between baseline and follow up value where there was an 88% decline from 7160 to 850 neutrophils. The second patient had a 366 day interval from baseline to 2nd measurement. During this interval, there was a 13% decline form 1134 neutrophils to 987. The third patient had an 808 day interval between first and second measurement with a 66% decline from 3042 to 1038 neutrophils while the final patient had a 982 day interval between measurement 1 and 2 where there was a 39% decline from 2340 to 1440 neutrophils. There may have been additional neutrophil samples in these patients but entries were qualitative “normal”.

The adverse event dataset for patient (b) (6) was examined. This patient was an 11 month old male who was discontinued from the study at day 40 for SAEs of neutropenia and thrombocytopenia.

[57] An information request for all entry of all quantitative values to replace qualitative normal / abnormal entries was sent to sponsor. On 4/18/17 a submission containing version 2 of the DIAVEY laboratory dataset was received. The neutrophil dataset did not contain any additional quantitative measurements.

One additional patient in this group (DIAVEY (b) (6)) with 1 critical low quantitative entry present. This patient was followed for 935 days and had 8 additional neutrophil entries, all qualitative "normal" The patient was 9 month old female found to have a value of 0.368 x 10^9/L at follow up visit number 1. The adverse event dataset is examined for this patient and there are two related preferred term entries of "leukopenia" and "thrombocytopenia" that are identified on study day 72 and 67 respectively. The "leukopenia" event is not coded as a serious adverse event but the "thrombocytopenia" event is coded as a serious adverse event (SAE). The measurement is below a critical value ANC of 500/mm^3 no baseline measurement is available. This corresponds to laboratory day 72 in the lb.xpt dataset. The STP was not discontinued and at 39 months an adverse event of failure to thrive had resolved.

In summary, quantitative assessment of the DIAVEY dataset is difficult due to the high proportion of patients with qualitative entries. From the few patients where the dataset allows, there was a single patient with a rapid decline in neutrophil count during the first 40 days of treatment that resulted in an SAE for "neutropenia" but no dechallenge data is provided. A second patient with a critical low value at 1st follow up visit on day 72 had no SAE for neutropenia and remained in the study on STP treatment until day 935.

STILON

The STILON study had 168 entries from 41 patients spanning laboratory days (LBDY variable) -111 to 1126. From among these entries there were 69 entries from 41 patients that had a quantitative value while there were 99 entries from 33 patients with only qualitative "NORMAL "or "ABNORMAL" entries. There were 34 patients with both quantitative and qualitative entries. Ninety-eight (98) of the 168 entries in the STILON neutrophil dataset do not have laboratory day entries (LBDY). These entries correspond to all but two of the qualitative only result entries and are not useful for plotting a trend of neutrophil count over the duration of the study. Those 69 entries with quantitative results will be the basis for analysis.

As noted in the above paragraph the span of the STILON neutrophil measurements is up to 3.4 years. A causal inference based on temporal relationship is confounded by such a long duration. The difference between baseline (V1) visits and subsequent measurements from those entries with quantitative measurements will be examined to determine if there is a strong systematic decline of neutrophil values over the course of STP treatment. From the quantitative result cohort there were 28 of 41 patients with 2 entries, a V1 baseline entry and subsequent entries from V2 to V8 as well as final visits designated VF. The laboratory study day (LBDY) for these post V1 visit spanned 178 to 1126 with a mean and median of 716 and 749 days respectively. The percent change from V1 neutrophil value to the single subsequent visit entry for each patient is calculated. Ten (10) patients had a decline in neutrophil count and 18 had an increase in neutrophil count. The maximum decline was 49% while the maximum increase was 201% with a mean and median percent change of 35% and 17% respectively.

There are 13 patients remaining in the quantitative STILON subset with only a single entry for neutrophil count. Eight of these entries are V1 entries, all within a normal range. There are remaining five entries are from visits 2, 3, 4 and 2 from VF (final visit). The minimum value occurred at the V4 entry at 1.4 x 10^9/L . This value is below the posted reference range of 1.5 x 10^9/L for this entry. The remaining 4 entries are normal.

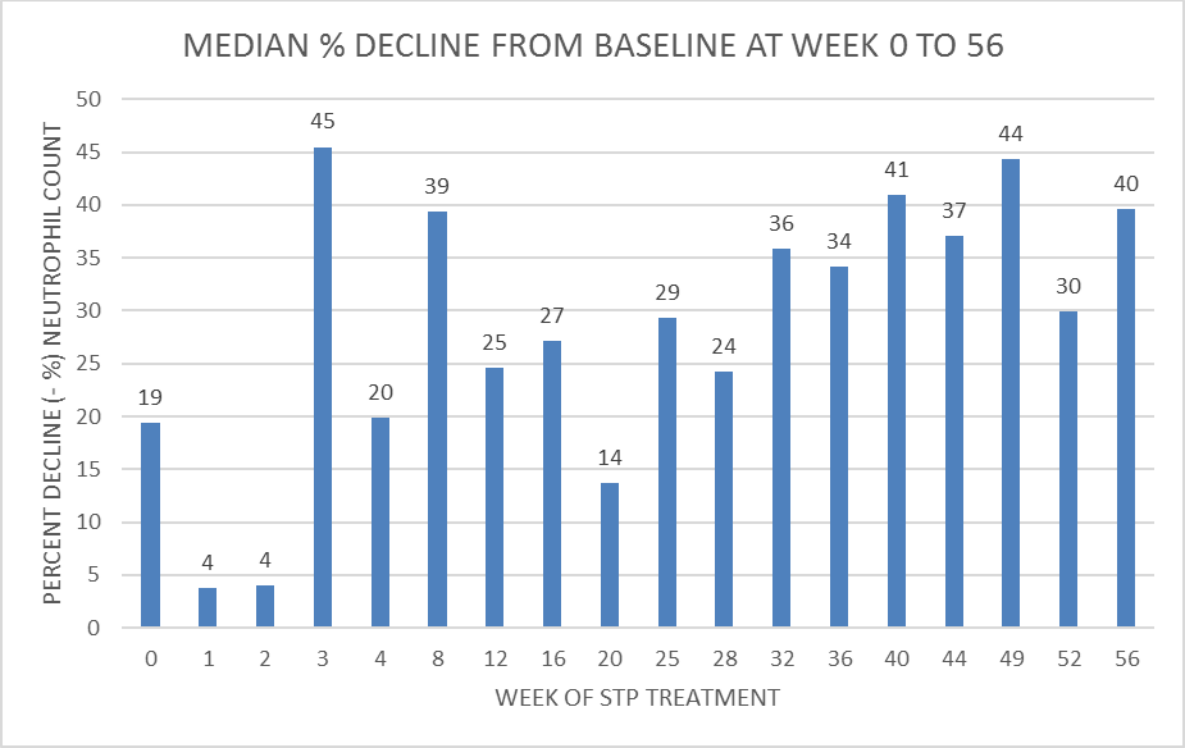
Overall the analysis of neutrophil counts for this subset of STILON entries with a quantitative value does not reveal a systematic decline over the course of STP treatment. The maximum decline in value between baseline and subsequent visit is less than increases that are observed. There is very limited ability to draw conclusions on the effect of STP on neutrophils in this study due to the long interval between study entry and subsequent neutrophil measurement in most cases, the irregular occurrence of measurements along the extended timeline and the uncertainty of actual STP exposure because these patients entered STILON from prior treatment with STP.

STP-1

The STP-1 study had 509 entries from 30 patients spanning a maximum of 430 days. The Group (1 & 2) patients are examined separately from group 3 patients because group 3 patients enter the study after the maintenance observation period with ongoing STP treatment.

There were 24 group 1 & 2 patients. Twenty-three (23) of these patients had baseline neutrophil values greater than 1500 ANC. These are analyzed further. This subset had a mean and median percent shift from baseline at week 4 of STP treatment of -10% and -20% respectively. Nine (39%) of these patients had a shift to ANC < 1000 at one or more subsequent measurements. The group median percent decline from baseline at 18 sampling times over 56 weeks of treatment reveal a ranged from 3.7% during STP dose titration to 46% during maintenance and extension phase at target dose of 50mg/kg/day. The group overall retains a median percent decline from baseline of near (minus) -30% during the 56 week treatment interval, see Figure 27. The sample size change from 24 to 20 after week 16 due to 3 discontinuations for lack of efficacy and 1 patient discontinuation where the reason could not be determined.

Figure 27 STP-1, Groups 1 & 3 (new STP treatment), Median Group % Decline by Treatment Week. (n= 24 to week 16, n=20 to week 36 , n=19 to week 52, then n=18))



The minimum ANC identified was 528 in patient (b) (6) and represented a 69% decline from baseline. The mean and median decline from baseline at any post baseline values in this subset with any value < 1000 ANC were 62% and 60% respectively. The scatterplot of ANC values for this patient over the course of the study reveals variability of values in the near critical range, see Figure 28. The adverse event dataset for this patient is reviewed for neutropenia related terms. The preferred term "neutropenia" was not present but here were 5 adverse events in the SOC "Infections and infestations" including preferred terms "nasopharyngitis", "influenza", "pharyngitis", and "viral infection". The "viral infection" was entered as an SAE. The patient remained in the study on STP treatment.

Figure 28 STP-1 Patient (b) (6) Scatterplot of Neutrophil Measurements over the Course of Study (to day 430)

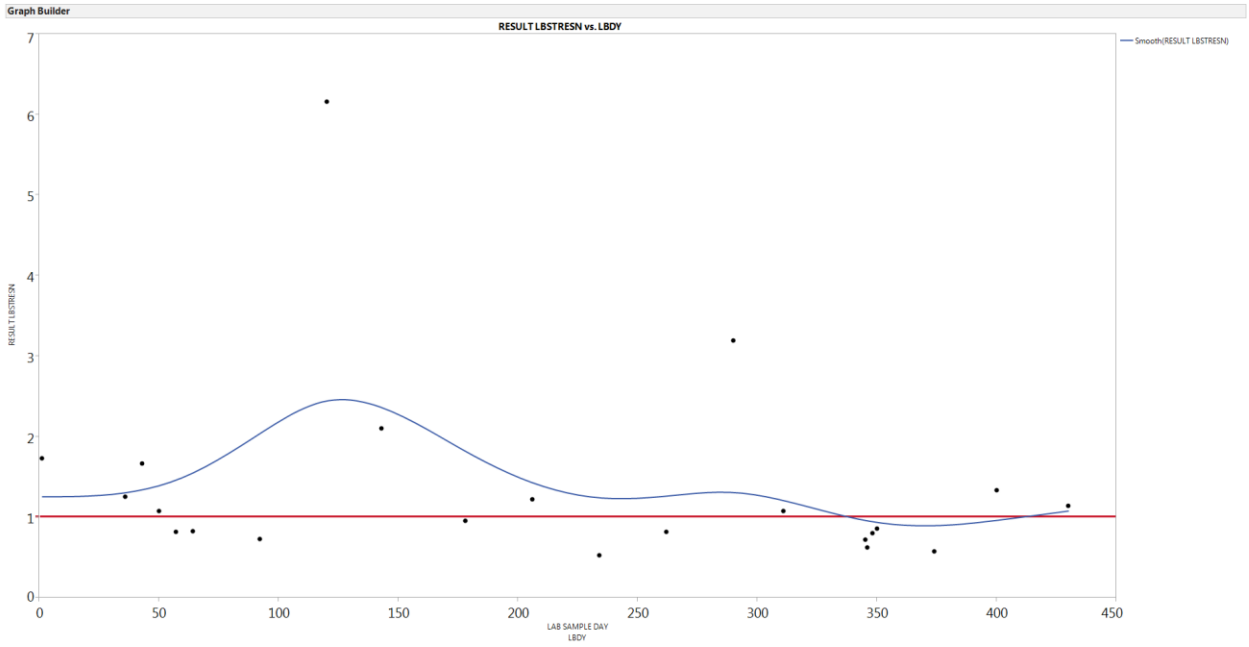


Figure 29 STP-1 Neutrophil Scatterplot of Values over Study Interval for 4 of 9 Patients with Any ANC Value < 1000 (1 x 10^9 /L), (Patients STP1 (b) (6), STP1 (b) (6), STP1 (b) (6), STP1- (b) (6)**)**

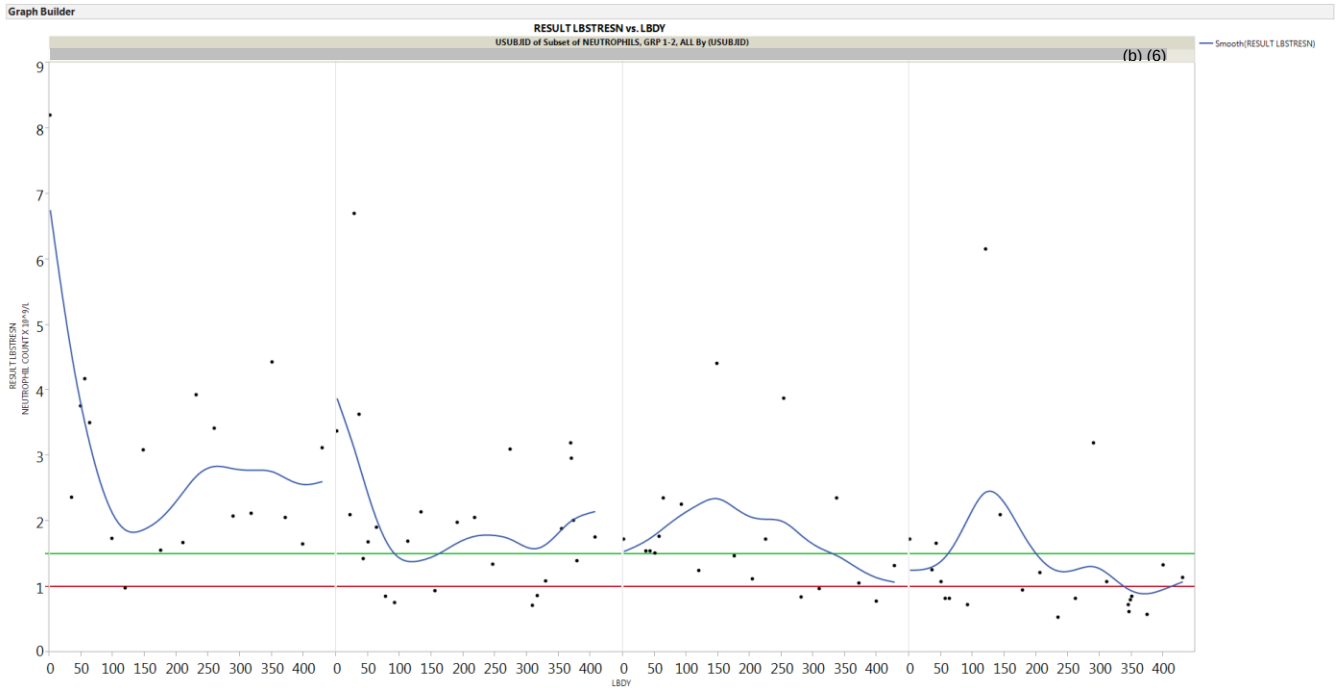
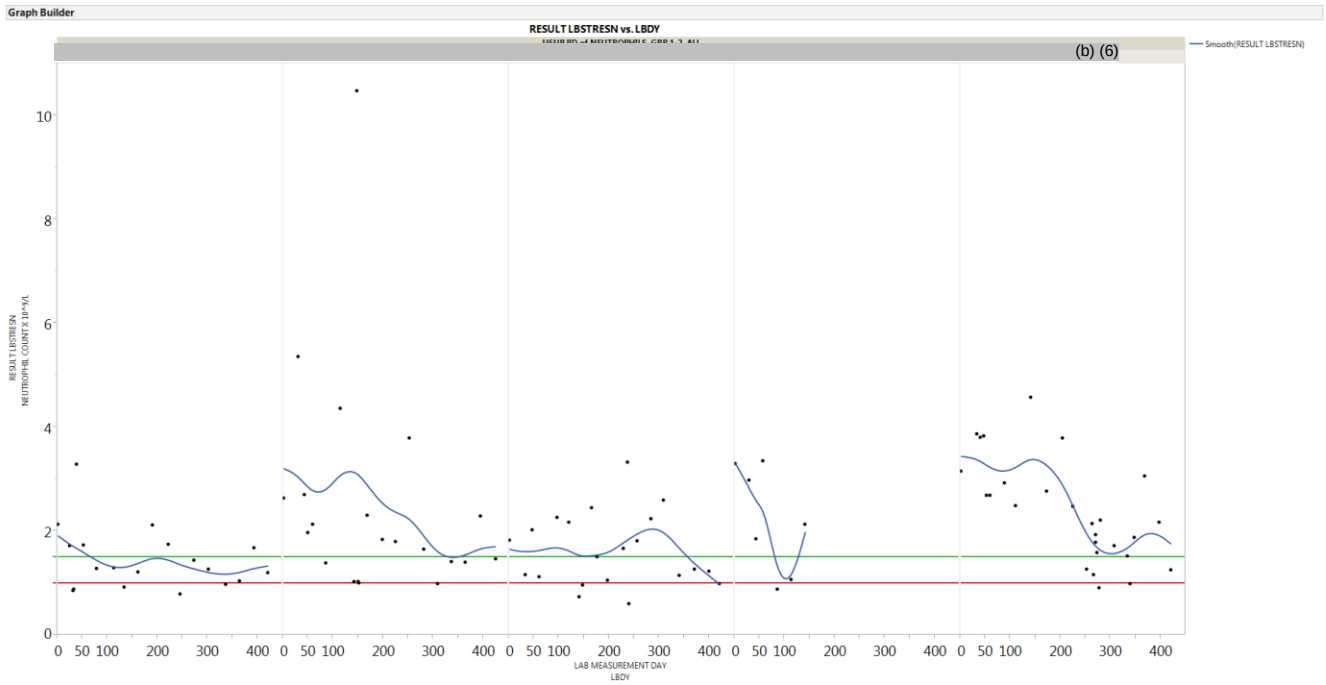

Graph Builder
RESULT LBSTRESN vs. LBDY
USUBJID of Subset of NEUTROPHILS, GRP 1-2, ALL By (USUBJID)
(b) (6)
Smooth(RESULT LBSTRESN)
RESULT LBSTRESN
NEUTROPHIL COUNT X 10**9/L
LBDY

Figure 30 STP-1 Neutrophil Scatterplot of Values over Study Interval for 5 of 9 Patients with Any ANC Value < 1000 (1 x 10^9 /L), (Patients STP1 (b) (6), STP1 (b) (6), STP1 (b) (6), STP1 (b) (6) (b) (6) STP1 (b) (6))



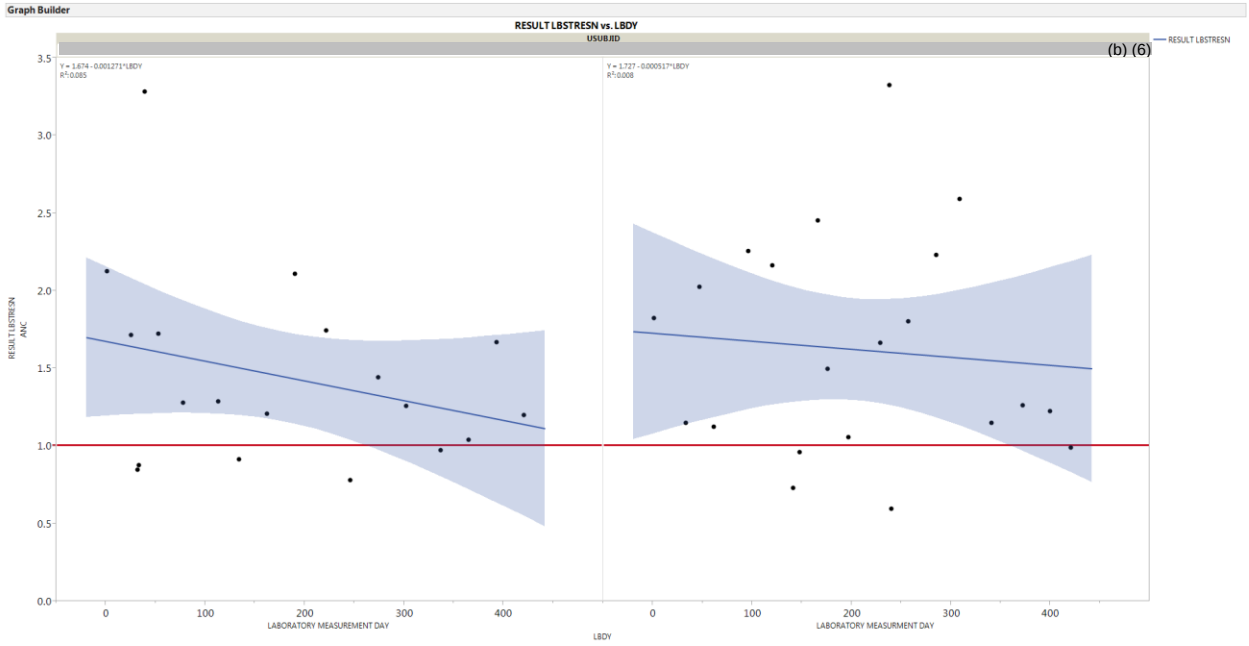
Patients STP1 (b) (6) and Patient (b) (6)

Two patients from the set of nine who had shift to < 1000 ANC were found to have adverse events of "neutrophil count decreased", none of these were entered as serious adverse events (SAEs). STP1 (b) (6) (study days 32, 134, and 246) STP1 (b) (6), (study days 141, 421). Patient (b) (6) had a dose reduction on study day 235 but neither patient was discontinued from the study. Both patients also had adverse event entries for "decreased appetite" where in patient (b) (6) the event was coded as an SAE. Scatterplots of the neutrophil counts over the STP-1 study timeline of patients (b) (6) and (b) (6) are presented in Figure 31.

From among the nine patients with shift to <1000 ANC the scatterplot of neutrophil values is examined. The distribution of values trends to lower values but generally retain a broad distribution over time from minimum to maximum values, see Figure 29 and Figure 30.

Examination of the group 3 patients from the STP-1 study reveals that mean and median percent change from baseline to all study days +3% and -16% respectively while 1 patient (16%) had a decline from baseline above 1500 ANC to < 1000 ANC. None of these patients had an adverse event of "neutrophil count decreased".

Figure 31 STP-1 Patients ((b) (6)) with Shift to ANC < 1000 at Any Time During the Study and an Adverse event of "neutrophil count decreased". (*red line, ANC = 1000, X axis is laboratory day, Y axis , absolute neutrophil count***)**



The serious adverse event (SAE) dataset of the nine patients with ANC < 1000 at any time is examined. Seven patients had 11 SAEs that may be related to the depressed neutrophil counts. Five patients had events in the SOC "Infections and infestations" that included "acute bronchitis", Acute bronchitis due to undernutrition", "acute pneumonia due to undernutrition", "viral infection", "infection" and "pneumonia". Three patients had events in the SOC "Metabolism and nutrition disorders", including "malnutrition" and "decreased appetite". The occurrence of infection related events may be causally related to the depressed neutrophil counts while there is a possibility that depleted nutritional status contributes to the depressed neutrophil count and infection.

Overall examination of neutrophil counts in the two STP-1 subsets reveals that in the 24 patients new to STP exposure (group 1 & 2) there was a trend toward declining counts through the course of the study. The trend was much more attenuated in the group 3 patients who entered the study with established STP treatment. There were 9 patients in group 1 &2 who had a decline from baseline > 1500 ANC to < 1000 ANC. The group median percent decline from baseline at 18 sampling times over 56 weeks of treatment reveal a ranged from 3.7% during STP dose titration to 46% during maintenance and extension phase at target dose of 50mg/kg/day. There were two patients with adverse event entries for "neutrophil count decreased" neither coded as an SAE, both patients remained on STP therapy while both also had adverse events

related to decreased weight or nutritional status.

Neutrophils Summary

In summary, examination of STP-1 and DIAVEY studies support a signal for neutropenia. The STP-1 study reveals a declining trend in neutrophil counts in a notable proportion of patient. Thirty-eight (38%) of patients with baseline neutrophil values within reference range had a decline to ANC < 1000. One additional patient (9th from discussion above) who had a decline to ANC < 1000 at any point during study participation had a baseline OORR low neutrophil value. Two patients with ANC < 1000 had non-serious AE entries of "neutrophil count decreased" and 7 of the (ANC < 1000) patients had SAEs related to infection and / or depleted nutritional status. All of these patients continued STP treatment. Examination of the STILON study suggest neutrophil count may remain stable in patients on long established STP treatment.

Platelets

In the category 2 and 3 studies platelets were measured in the STILON and STP1 study.

STILON

In the STILON study there were 69 entries from 41 patients. Twenty-eight patients had 2 measurements, one each at visit 1 (baseline). The second measurement was not uniform across patients. The follow up measurement (second) were taken at visits 2 through 8 spanning laboratory days (variable LBDY) 178 to 1126. The large interval from study entry to second measurement reduces inference of causal changes by temporal association. Three patients had second platelet measurements at less than 216 days, the remaining 25 patients all had second (follow up) measurements at intervals greater than LBDY 358.

Three patients (10% of those with two are identified with platelet count below 150/ mm^3 at second measurements where baseline measurement was in normal range. The maximum decline is 122 x 10^9/L from day – 52 to day 644, a span of 1.9 years. The remaining two patients show a decline of 63 x 10^9/L and 38 x 10^9/L over a span of 510 and 376 days respectively. The long intervals from initial to final (low) value make causality unlikely.

Examination of the change from initial to second measurement in all patients with two entries is performed. The maximum increase in platelet count is 47%, to a value of 315 x 10^9/L, 1053 days from baseline. The maximum percent decline is 55% to a value of 100 x 10^9/L, 696 days from baseline value. The minimum and maximum values for platelet counts at follow up are 94 x 10^9/L and 430 x 10^9/L respectively. There were 5 patients with a decline > 10%, in only 2 of these patients was the measurement interval less than one year. For these two patients the measurement intervals were 191 and 216 days.

From among the 13 patients with only a single measurement 8 were taken at baseline. The remaining patients had values from visit 2 through visit final and all were within reference range.

Overall there were 3 patients with a decline from baseline normal to OORR low; however, this decline occurred over an interval that does not support a temporal relationship. There were five patients with >10% decline from baseline to follow up, while three of these resulted in an OORR low value, again only two of these changes occurred inside of 216 days while in two of the remaining three cases were captured in the analysis of patients that declined to low OORR values. These observations do not support a systematic decline in platelet count associated with increasing STP treatment duration. The long time between measurements in the STILON study obscure causal inference. In addition, 41 of 45 Dravet syndrome patients participating in the STILON study had ongoing treatment with STP prior to entry.

STP1

There were 515 entries from 30 patients spanning a maximum of 430 days. Twenty-four patients enrolled prior to maintenance period while 6 patients enrolled at long term study interval.

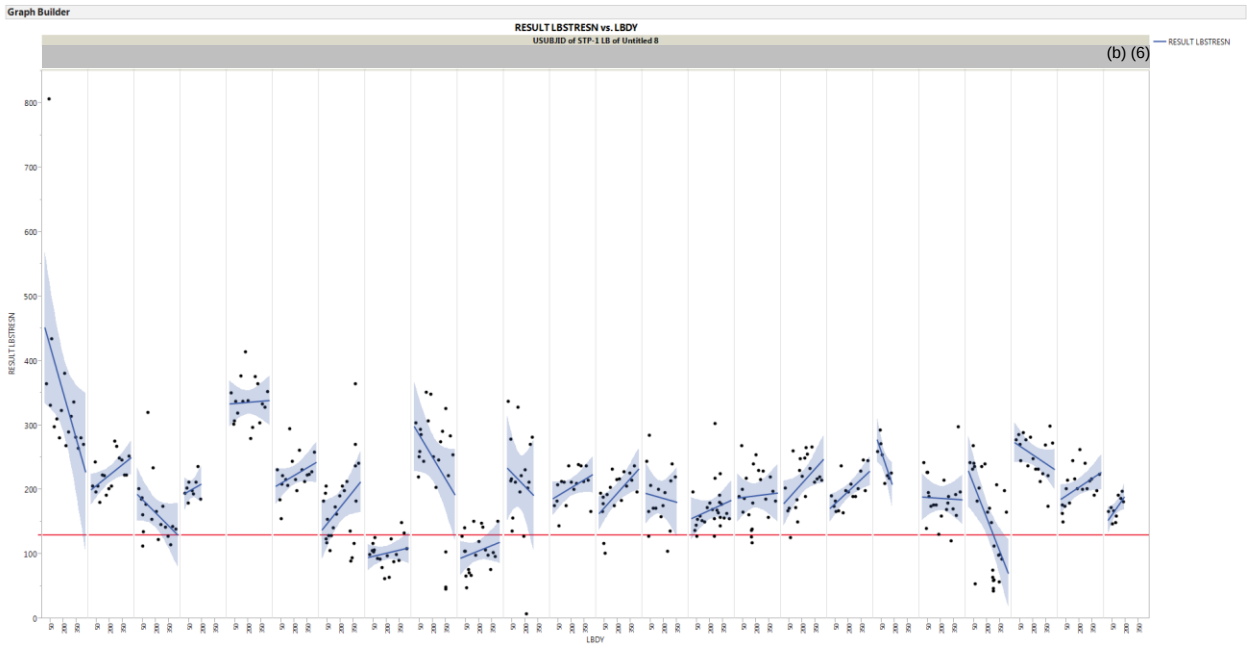
Percent change in platelet count is examined from baseline to approximately day 30 and day 100. The intervals are approximate because actual blood sampling day could take place a few days on either side of the 30 or 100 day mark.

From baseline to day 30 the mean and median percent change in platelet counts were -5.7% and -4.6% respectively. There are 17 patients with a decline in platelet count with a maximum percent change of -78%. This patient (STP1 (b) (6)) had a baseline value of 232 x 10^9/L with a decline to 54 x 10^9/L after 28 days of STP treatment. The next largest percent decline of 45% occurred in patient (STP1 (b) (6)) who had an OORR low baseline platelet count of 104 x 10^9/L that further declined to 48 x 10^9/L. There was one additional patient (STP1 (b) (6)) with a 23% decline from OORR low at 116 x 10^9/L to 89 x 10^9/L. Two patients had a decline from within reference range to OORR low (STP1 (b) (6), STP1 (b) (6)) with declines of 39% and 25% respectively.

From baseline to day 100 the mean and median percent change from baseline were 3.0% and 1.7%. There are 14 patients with a decline in platelet count and 15 with an increase in platelet count. The patient with the maximum percent decline in platelet count of 65% had a baseline value of 806 x 10^9/L that declined to 280 x 10^9/L at day 100. There were two patients with a 100 day OORR low value; however, these patients had baseline values that were OORR low.

All patients have a scatterplot of values generated from platelet count and laboratory day. A least squares line of fit is calculated and examined for overall trend of platelet count through the duration of the study. Examination of these plots reveal there were 20 patients with a positive slope least square line and 10 patients with a negative slope least square line. From visual examination, slope and correlation coefficient there were two patients with scatterplots of concern. These patients were (b) (6) who had some consistent decline in points with a slope of -0.226 and R2 of 0.143, and a nadir of 46 x 10^9/L and initial value of 304 x 10^9/L. This patient has no entries in the adverse event dataset for thrombocytopenia. The second patient of concern (b) (6) had consistent decline in platelet counts with a slope of -0.35 and correlation coefficient of 0.32 and a platelet count nadir of 43 x 10^9/L and baseline value of 242 x 10^9/L. This patient had an entry in the adverse event dataset for "Platelet count decreased" and "thrombocytopenia".

Figure 32 STP-1, Group 1 and 2 (n= 24) Scatterplot of Platelet Count



In addition to the two patients noted above with consistent decline in platelet count to OORR low, there are two additional patients with consistent decline in platelet count but no values were OORR low. The first patient was (b) (6) whose fit line slope was -.48 with a correlation coefficient of 0.26. The second patient with a consistent decline over time was (b) (6) whose fit line slope was - 0.4 with a correlation coefficient of 0.58. This latter patient had the most compelling decline over time.

Platelet Count Summary
In summary, the STILON study is unrevealing for determination of a signal for decreasing

platelet count. The STP1 study identifies four patients with decline in platelet count that is plausibly related to STP based on consistency of the decreasing count. Examination of the profile of all patient platelet count vs time scatter plots reveals that 66% of patients have a trend of increasing platelet count. There does not appear to be systematic decline in platelet count across patients but there are sporadic patients with a notable decline in count associated with STP treatment.

Eosinophils

In the category 2 and 3 studies eosinophil measurements were obtained in the STILON and STP1 studies.

STILON

The STILON study had 69 entries from 41 patients where 28 patients had measurements at baseline and a subsequent follow up visit. STILON patients were all in long term follow up of previously initiated STP therapy, therefore inclusion visit is not the initiation of STP therapy and subsequent laboratory values are not representative of STP effect from date of STILON inclusion but rather are part of a longer continuum of STP treatment. The available follow up visits were not uniform across patients but some patient follow up was closer to baseline than others. Three patients had a visit 2 follow up, 2 had a V3 follow up, 3 had V4 follow up, 4 had V5 follow up 1 had v6 follow up, 5 had V7 follow up, 1 had V8 follow up while 9 had a VF or final visit follow up. The inclusion visit is V1 while subsequent visits are spaced six months apart.

The patient subset with inclusion and follow up visit is examined for upper boundary OORR values. Examination of highest eosinophil count will use typical upper reference range value as a filter for detection of an eosinophilia signal. The value to be used is 0.54 x 109/L although in the dataset the upper reference range (available for only 48% of all 69 STILON entries) spans from 0.25 x 10^9/L to 0.8 x 10^9/L.

In the subset of patients with two visits there were 3 patients with an eosinophil count higher than is 0.54 x 10^9/L. Two of these are found as inclusion visits while the third is at visit 4. The patient with a value of 1.0 x 10^9/L at V4 has an inclusion visit value of .067 x 10^9/L. Patients with an inclusion and follow up visit are also examined for the direction of change from inclusion to follow up visit. Fourteen patients had an increase from inclusion to follow up but in only one case did the follow up value exceed 0.54 x 10^9/L. This case was patient STILON (b) (6) captured in the discussion above.

From among the patients with only a single entry 8 of 13 were inclusion visits. In this group one patient had a value of 4.1 x 10^9/L but the same row indicates this entry has an upper reference value of 4.0 x 10^9/L which is out of line with all other entries with an upper reference value. The

validity of this entry is in question. From among the 5 single visit entries that were non-inclusion visits the maximum value observed is 0.17 x 10^9/L.

Overall there is no signal for an increasing trend of eosinophil values during continuing treatment with STP in the STILON dataset.

STP-1

The STP-1 study has 510 entries from 30 patients spanning a maximum duration of treatment of 430 days. Patients in the STP1 study are new to STP treatment at inclusion. There are 24 patients who enter in a dose adjustment phase followed by a 3 month fixed dose maintenance period while six patients enter only into long term treatment phase where STP dose may be adjusted after the 3 month maintenance period.

Examination of the STP1 eosinophil entries reveals one patient with OORR high values. This patient has a high normal within reference range 1st day of treatment value that decline in the initial 100 days of STP treatment then rises to approximately 2 x ULN at day 113 then has a decline trend to day 368 with a subsequent sharp rise to 2.8 x ULN at day 393. The adverse event dataset for this patient is examined. There are no entries related to hypersensitivity; however, there are 7 entries for “nasopharyngitis”.

A scatterplot of eosinophil values by laboratory day (STP treatment = LBDY -30) is generated. From the scatterplot, a least square fit line is calculated. The trend of each fit line is examined across the thirty patients. There were 16 patients with a negative fit line slope and 14 patients with a positive fit line slope. Among the patients with a positive slope line only (b) (6) exceeded their ULN. This case is discussed in the 2nd paragraph above. One additional patient (b) (6) with a steep line of increase is identified, although without exceeded the ULN. The maximum eosinophil vale for this patient is reached on LBDY 312 with a value 0.62 x ULN. There is no clear rise until approximately day 200 with an increase to day 312 then a decline. The adverse event dataset for this patient is examined. An entry for “stomatitis” is found on study day 362. It is uncertain if the stomatitis is related to hypersensitivity. The event is not an SAE.

In summary, the STILON and STP1 eosinophil data do not reveal evidence of a systematic increase in eosinophil count associated with continuing STP treatment. Only one patient exceeds the ULN for eosinophils but has no hypersensitivity related adverse events. Another patient has an increasing trend but remains in reference range but has an event of stomatitis.

Non DS Patients in the DIAVEY and STILON Studies, Category 2 & 3

DIAVEY

In the DIAVEY study neutrophils, Alanine Aminotransferase, Aspartate Aminotransferase and Gamma Glutamyl Transferase were measured.

Only the AST values were examined from. xpt datasets. The remaining assessment of non-DS laboratory studies was obtained from the ISS, p275.

AST (Aspartate aminotransferase increased)

In this cohort there were 16 patients with both a first visit and a follow up sample. The difference in value for each of 16 patients is examined. There is one patient with a notable abnormal laboratory response. The remaining 15 patients with quantitative entries with both a first visit and follow up AST measurement have no notable increase in ALT value.

DIAVEY Patient (b) (6)
The patient with a notable increase is DIAVEY (b) (6), who had a first visit AST of 65 IU (1.4 x (b) (6) that increased to 361 IU on day 19 of STP treatment in DIAVEY. ALT was also seen to increase from 78 IU (1.3 x ULN) to 288 (4.8 x ULN) by day 19. Bilirubin was not sampled in this study. This event was entered as an SAE and STP treatment was discontinued. Examination of the narrative report reveals the patient was a 6 year old female. STP treatment was added to VPA 550 mg/day, CLB 7.5 mg/day, levetiracetam 700 mg/day, ethosuximide 400 mg/d.

Table 92 Patient with Maximum Elevation of ALT and AST, DIAVEY Patient (b) (6)

DIAVEY (b) (6)	Date (b) (6) (Baseline)			Date (b) (6)			D/C (b) (6)	1 year later		
	ULN	value	Multiple	ULN	value	Multiple		ULN	value	Multiple
ALT	18	78	4.3	60	288	4.8		60	144	2.4
AST	20	65	3.3	45	361	8.0		45	97	2.2
CPK					10000<					

ISS Report:

Neutropenia

> The sponsor reports two patients had neutrophil values in neutropenic range. One patient ((b) (6) a 7-year-old male) was reported with an AE of neutropenia. This patient, who had a baseline neutrophil count of 1,400/mm3, was reported with an abnormal neutrophil count of 1,100/mm3
>
> A second patient ((b) (6) a 14-year old female) was reported with an AE of neutropenia at follow-up visit 2, possibly related to STP. This event had stopped at visit 4 and did not reoccur despite STP continuation.

Thrombocytopenia

One patient ([(b) (6)] a 10-year-old female) was reported with an AE of thrombocytopenia. Platelet counts are not available.

Elevated transaminases

Five patients were identified with increases of a transaminase during treatment with STP. These are presented in Table 93. This table includes patient DIAVEY [(b) (6)] discussed above. This latter patient had the most serious and rapid elevation in values.

Table 93 Elevated transaminases in DIAVEY, non-DS patients

Country	Patient #	Relatedness to STP	Measurement points	AST (IU/L)	ALT (IU/L)
France	[(b) (6)]	Possible	Baseline	Normal	Normal
			V1	76 (ULN=60)	27 (ULN=40)
Germany		Improbable	Baseline	Normal	Normal
			V1	37 (ULN=35)	
Germany		Improbable	Baseline	45	Normal
			V4	233 (ULN=58)	59 (ULN=41)
Germany		Possible	Baseline	Normal	
			V2	104 (ULN=38)	
Italy		Possible	Baseline (day 1)	65 (ULN= 45)	78 (ULN = 60)
			V1 (day 19)	361 (8 x ULN)	288 4.8 x ULN)
			FINAL (day 380) (discontinued)	97	144

In summary, data from the DIAVEY non-DS population reveal findings in alignment with laboratory abnormalities seen in the DS populations. There were two patients with neutropenia, although in the first patient the decline was not below 1000/mm^3 and in the second patient (without values provided) the neutropenia resolved without change in STP treatment. Thrombocytopenia was seen in a single patient. From among the 5 patients with transaminase elevation three were mild while in one patient the AST value alone exceeded 4 x ULN.

In the fifth and most serious case elevations in both AST and ALT occurred in 19 days with ALT reaching 4.8 x ULN. This patient had elevation of baseline ALT and AST to 4.3 and 3.3 X ULN respectively. The further increase over baseline was associated with a concurrent elevation of CPK to > 10000 IU/L. Although no bilirubin measurement is available for this patient the

elevated values of AST and ALT seen 19 days after initiation of STP treatment are likely of skeletal muscle origin on already abnormally elevated baseline values, see Table 92.

STILON

ISS Report:

The ISS identifies only abnormal hematology findings in the STILON non-DS patient group as stated in section 5.10.1. There are no abnormal laboratory values identified in the ISS aside from the hematology values presented in Figure 33.

Figure 33 Sponsor Table 5-24, STILON Non-Dravet Patient Abnormal Laboratory Values from ISS Section 5.10 "Abnormal Laboratory Values in STILON (n=110)"

Table 5-24. Abnormal Hematology Values in 110 Non-Dravet Syndrome Patients in the Lon Term, Open-Label STILON Trial

Patient No.	Abnormal Item	Laboratory Value		Comment
Partial Epilepsy (N=81)				
(b) (6)	Neutropenia	Neutrophils Baseline: Vf (b) (6):	 1,224/mm^3 (NCI Grade 2) 1,365/mm^3 (NCI Grade 2)	Concomitant treatment: CBZ
	Neutropenia	Neutrophils Baseline: V3 (b) (6) Vf :	 1,001/mm^3 (NCI Grade 2) 1,220/mm^3 (NCI Grade 2) 1,295/mm^3 (NCI Grade 2)	
	Neutropenia	Neutrophils Baseline: V2 (b) (6) V3 : Last assessment (b) (6):	 1,428/mm^3 (NCI Grade 2) 1,271/mm^3 (NCI Grade 2) 1,156/mm^3 (NCI Grade 2) 2,132/mm^3 (NCI Grade 2)	
	Leucopenia	Neutrophils Baseline: V2 (b) (6) Last assessment (b) (6):	 1,449/mm^3 (NCI Grade 2) 749/mm^3 (NCI Grade 3) 3,300/mm^3 (NCI Grade 1)	Concomitant treatment: CBZ, VPA, diazepam
Other Types of Epilepsy (N=29)				
(b) (6)	Leuconeutropenia	Neutrophils Baseline: V4 (b) (6) Last assessment (b) (6) Leucocytes V4 (b) (6) Last assessment (b) (6)	 1,116/mm^3 (NCI Grade 2) 536/mm^3 (NCI Grade 3) 1,644/mm^3 (NCI Grade 1) 3,150/mm^3 (NCI Grade 1) 4,110/mm^3 (NCI Grade 1)	Concomitant treatment: VPA, CLB, LTG

STILON lb.xpt dataset ALT, AST and neutrophil screen

ALT Screen

The quantitative and qualitative entries from the STILON ALT results are screened for notable elevations. From among 30 quantitative results the maximum is 34 IU/L. No normal range is posted for this entry but the textbook upper limit of normal for ALT is 41 IU/L[58]. Therefore, all quantitative values entered are below the upper limit of normal; however there 356 entries for ALT in the STILON non-DS dataset and from among these there are 88 qualitative entries of "ABNORMAL". It is therefore uncertain there are ALT results of concern among the 106 patients where an ALT result is posted.

AST Screen

There are 356 entries for AST from 106 patients. From among these there are 31 quantitative results and 205 qualitative entries of "normal" or "abnormal". From among these qualitative entries there 75 are identified as "abnormal" and 130 identified as "normal". Examination of the available quantitative results reveals 3 values higher than an ULN of 38 derived from the Harrisons laboratory normal values referenced above. These values are 41, 42 and 62. The value of 62 represents 1.6 x ULN and originates from visit 1 with a baseline flag. The values of "abnormal" qualitative entries are unknown leaving uncertainty about the severity of AST elevations among those entered as "abnormal".

Neutrophil Screen

There are 361 entries for neutrophil values where 190 are qualitative with "normal" or "abnormal" entries and 162 are quantitative entries. From among quantitative entries there is inconsistent presence of a posted reference range. Due to this deficiency in the ability to identify a cut off for low reference the textbook OORR low from Harrisions, cited above is again used. This value is 1.42 x 10^9 cells/ liter. From among the 162 quantitative entries there are original units identified as percent values among other original units of (value) x 10^6/L. These mixed entries where present are all converted to SI units of (value) x 10^9/L. where the percent entries have been converted to SI units there is no reference range posted and the associated value for variable "LBRIND (=Reference Range Indicator) is set to "normal". The reviewer scans these 162 derived SI units for abnormal value below a uniform OORR low of 1.42 x 10^9 cells/ liter. There are 53 entries with a value <1.42 x 10^9 cells/ liter. From among these there are 27 that are posted as baseline entries. These are not considered further unless they act as initial values for follow up entries that are also OORR low.

[58] Kratz A, Pesce MA, Basner RC, Einstein AJ. Laboratory Values of Clinical Importance. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79722706. Accessed December 15, 2016

There are 26 entries <1.42 x 10^9 cells/ liter. The minimum value posted in patient STILON (b) (6) (b) (6) at visit 3 (LBDY 373) is 0.00338 x 10^9/L. This is equivalent to an ANC of 3.4 cells. There are additional post baseline entries with values less than 100 cells/mm^3. It is uncertain if these are in error due to faulty unit conversion or represent serious neutropenia. This screen of the lb.xpt dataset neutrophils is divergent from sponsor table 5-24 seen in Figure 33.

Reviewer Comment: Examination of the non-DS patients in the DIAVEY and STILON studies is primarily limited to the sponsor report in the ISS. The lb.xpt dataset is difficult to interpret due to the high proportion of qualitative entries and the mix of apparently typical values for laboratory parameters and values that may be implausible, possibly due to unit conversion error as seen in the neutrophil values of patient STILON (b) (6). The entries for patient STILON (b) (6) in ISS table 5-24, page 273 indicate there are appropriate values that have not been entered into the. xpt dataset, as seen for the V4 entry of ANC 536 cells/mm^3 and the entry for final visit on (b) (6) was 1644 cell/mm^3 but the only entries in the dataset are baseline and final where both show an ANC below 100 cells/mm^3. If the fidelity of the ISS is accepted then the findings in the non-DS patient of these two studies are in alignment with findings in the STICLO trials and Dravet syndrome category 2 and 3 patients where there is a signal for neutropenia.

Category 4, Exploratory studies in non-Dravet patients. (No .xpt datasets are available for analysis. Date of studies range from years 1976 to 2000)

Table 94 Clinical Laboratory Measurements and Abnormal Values across Exploratory Studies in Non-Dravet Syndrome Patients[59]

Trial (Year Started)	Number of Patients on STP	Safety Assessments	Results
Exploratory Studies in Mainly Children with Epilepsy			
STEV [5.3.5.1; BC.288]	202	Laboratory safety tests	1 patient (b) (6)) experienced an SAE of neutropenia that resolved under continued STP treatment.
Lennox-Gastaut [5.3.5.1; BC.274]	24	Laboratory safety tests	Grade 1 thrombocytopenia: 1 patient (b) (6)
Farwell et al., 1993 [5.4]	10	Laboratory safety tests	No abnormal laboratory values were reported.
STISEVR [5.3.5.1; BC.484]	67	Laboratory safety	Grade 1 neutropenia: 5 patients (b) (6) (b) (6) Grade 2 neutropenia: 3 patients (b) (6)

[59] Sponsor Table 5-25, ISS page 274

Trial (Year Started)	Number of Patients on STP	Safety Assessments	Results
		tests	
Exploratory Studies in Children and Adults with Epilepsy			
STICAR [5.3.5.1; BC.246]	STP+CBZ: 62 CBZ: 69	Laboratory safety tests	Minor not clinically relevant increases in mean GGT in STP group
WOW [5.3.5.2; BC.276]	64	Laboratory safety tests	Mild leucopenia (5 patients), mild increases in AST (1 patient), fluctuating mild increases in γ-GT
Courjon [5.3.5.1; BC.109]	135	N/A	Not applicable as no laboratory safety tests were performed.
Exploratory Studies in Mainly Adults with Epilepsy			
Loiseau [5.3.5.2; BC.243]	44	Laboratory safety tests	No laboratory abnormalities were mentioned in the study report.
Martinez-Lage [5.3.5.1; BC.244]	31	Laboratory safety tests	Mild fluctuations in γ-GT
Loiseau et al., 1988 [5.4]	11	N/A	Not applicable as no laboratory safety tests were performed.
Rascol et al., 1989 [5.4]	7	Laboratory safety tests	No change in routine biological tests was observed at any time.

Reviewer Comment: category studies in non-DS patients reveal findings similar to those seen in Dravet syndrome open label studies where more extensive analysis of datasets was performed. There was a single patient with and SAE of neutropenia that was reversible upon discontinuation, mild neutropenia in 5 patients and moderate in 3 patients but no follow up information or indication if and of the moderate were entered as an SAE. There was mild increase in GGT, AST and mild leukopenia reported in 5 patients. This profile does not change the safety conclusions of the Dravet syndrome safety assessment.

7.4.7. Vital Signs

Pivotal Studies (category 1)

Blood pressure and heart rate were not measured in the STICLO trials, see Table 53. The dataset includes baseline Height, weight and BMI. Subsequent weight is measured at the start of double blind STP treatment interval and at the end of the 8 week double blind period.

In the pooled STICLO studies change in weight in the 8 week interval between start of STP double blind treatment and end of DB STP treatment was calculated. The mean and median changes in the placebo group were 0 and 2.6% respectively. In the STP group the mean and median percent change from baseline were 0% and -0.31% respectively. The STP group had a higher frequency of values less than zero compared to the placebo group, Figure 34.

There were 12 patients with weight loss in the STP treatment group during the study interval and 6 patients in the placebo group. The maximum percent weight loss in the STP treatment group was 16% compared to a maximum of 3.6% in the placebo group. From among patients with weight loss in the STP treatment group the mean change was -7.4% while in the placebo group the mean change was -2.7%. The adverse event profile of all patients in the STP group with weigh loss was examined. Ten of these 12 patients had 24 instances of preferred term entries for “decreased appetite” and/or “weight decreased”, none were serious adverse events (SAE). From among the placebo cohort patients with weigh decrease there were entries of one instance each for the preferred terms “decreased appetite” and “weight decreased”. These two entries arose from one of the six patients. Neither was an SAE.

Patients were grouped by age quartile and the change in weight over the 8 week STP treatment interval compared by quartile, Table 95. The largest difference between the placebo and treatment groups is observed in the 3rd quartile with the next largest in the 1st quartile. The sample interval of 2 months is fairly short however no weight loss is expected during these age quartiles where weight change is expected to be positive.

Figure 34 Distribution of Percent Change in Weight at the end of 8 Week STP Study Interval, Placebo and STP treatment groups, Pooled STICLO studies.

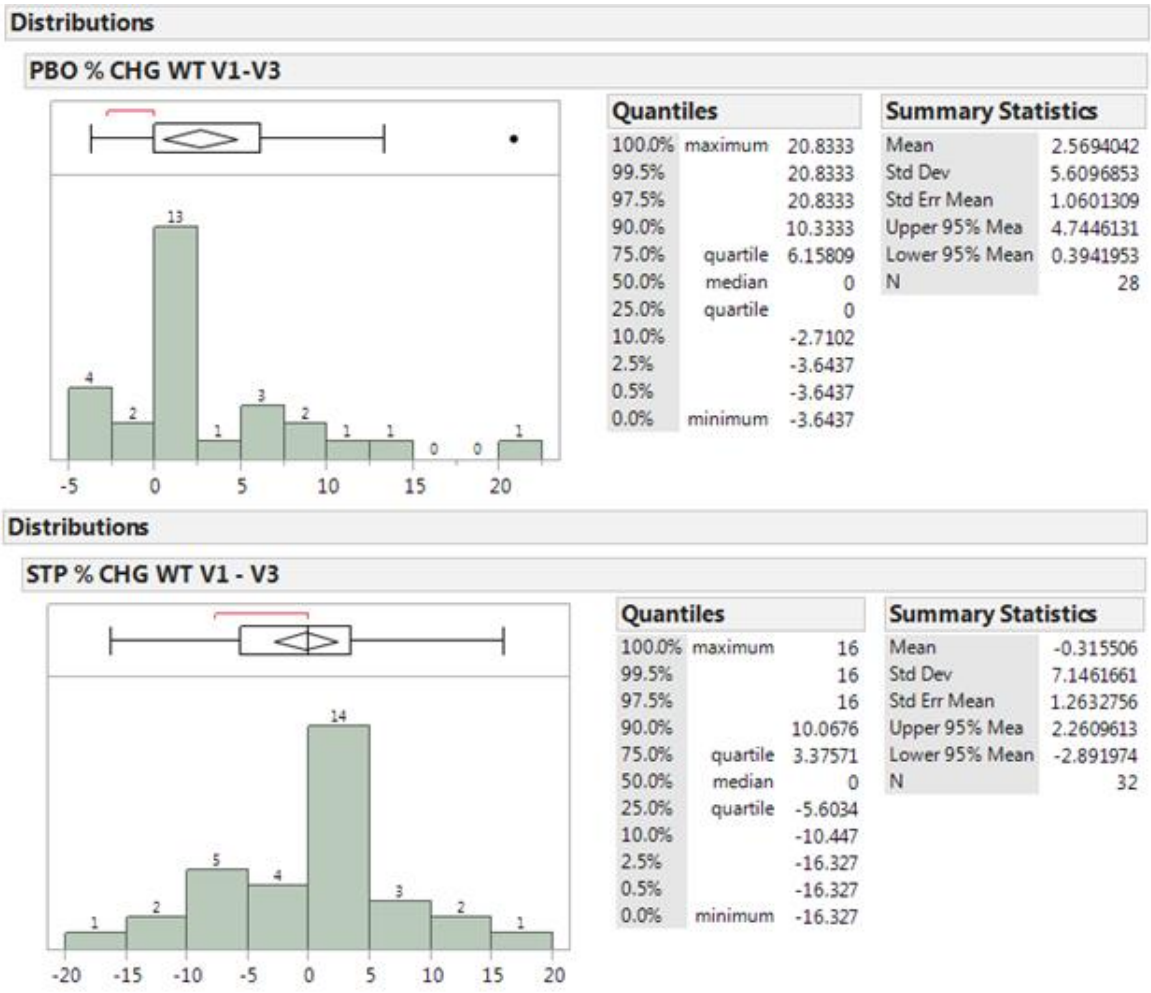
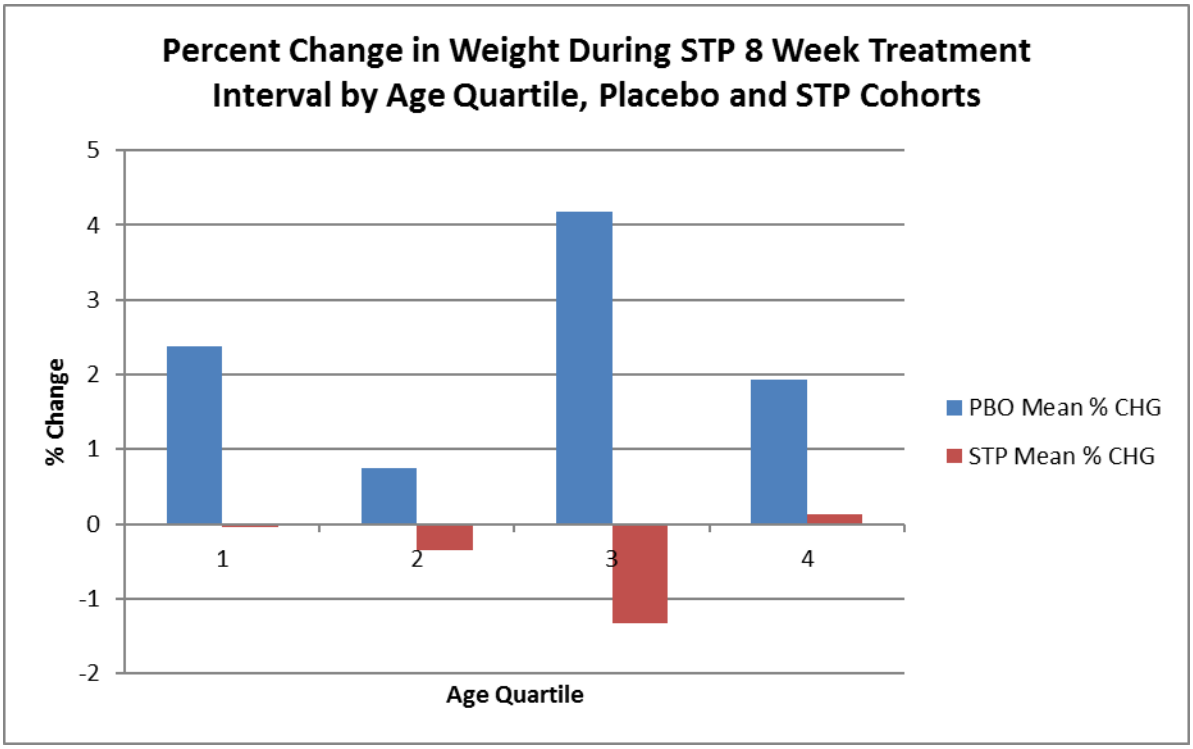


Table 95 Percent change in weight by pooled STICLO age quartile, Placebo and STP treatment Groups.

PBO AGE QUARTILE	Quartile content, range in years	Total Patients in Quartile	Patients with Weight loss in Quartile	PBO Mean % CHG	Std Dev(% CHG WT V1-V3)	Median(% CHG WT V1-V3)
1	3.2 - 5.6	9	1	2.37	4.1	0.37
2	5.6-8.8	6	1	0.75	3.3	0
3	8.8-10.5	10	3	4.18	8.3	0

PBO AGE QUARTILE	Quartile content, range in years	Total Patients in Quartile	Patients with Weight loss in Quartile	PBO Mean % CHG	Std Dev(% CHG WT V1-V3)	Median(% CHG WT V1-V3)
4	10.5-20.7	6	1	1.93	4.3	1.02
STP AGE QUARTILE		# patients		STP Mean % CHG	Std Dev(% CHG WT V1 - V3)	Median(% CHG WT V1 - V3)
1	3-6.3	7	3	0.0	4.9	0
2	6.3-8.6	10	4	-0.4	9.9	0
3	8.6-12.8	6	2	-1.3	4.2	0
4	12.8-16.7	10	3	0.1	7.8	1.5

Figure 35 Percent Change in Weight during 8 Week STICLO Treatment Interval by Age Quartile, Placebo and STP Cohorts



Reviewer Comment: this placebo controlled data reveals a differential in weight loss between the placebo and STP treatment groups. The frequency of weight loss is greater in the STP group and of larger magnitude. There is a signal for weight loss due to STP treatment that should be placed in section 5 of labeling. The sponsor currently proposes language for this section of labeling. (b) (4)

(b) (4)

Non- Pivotal Trials in DS Patients (Category 2 and 3 studies), see Table 53

Weight

Weight data for non-pivotal studies DIAVEY, STILON, and TAU-EAP is examined by generating scatterplot of weight by visit day (STILON, DIAVEY) visit number (V1 to V9- every 6 months following V3) in TAU-EAP study. In all studies the long interval of observation is associated with an upward sloping least square regression line. No notable trend of weight loss is discernible with this method. There is also a superimposed positive growth curve expected for patients up to age 20 however this interaction is not assessed. Overall there is no apparent signal of long term attenuation of weight trajectory on inspection of these long term studies.

For these three studies, the sponsor examines Z scores across the span of follow up visits. This method does not identify a trend of deviation away from a z score of zero for DIAVEY, STILON, and TAU-EAP.

The 25 DS patients in the STEV study have weight data for a shorter interval than the aforementioned DIAVEY, STILON, and TAU-EAP studies. In the STEV study there are baseline, D0, D28 and D84 weight measurements. Weight will be examined across the intervals of D0 (start of study drug treatment) to D84. The maximum percent decline in weight from D0 is 12% with a mean and median of 0.7% and 1.8%, both a positive percentage, respectively. The maximum percent increase was 13%. There were 8 patients with a zero or negative percent change in weight from D0. The adverse event profile for these patients is examined and all are found to have preferred term entries of “decreased appetite” or “weight decreased”. None are entered as serious adverse events.

STP-1 Study

The STP-1 study had 516 entries from 30 patients spanning a maximum of 430 days. Percent change in weight from first day of STP treatment to 3 and 6 months is examined. At the 3 month measurement the maximum percent decline is 20% with a maximum increase of 12%. The mean and median percent changes in weight from first treatment to 3 months are 0.43% and 0.6% respectively. At six months the maximum percent decline from baseline weight is 14% with a maximum percent increase in weight of 13%. The mean and median percent changes from start of STP treatment are 0.8% and 1.8% respectively.

A scatterplot of weight by visit day is generated for each patient and a least square regression line is fitted. These plots are examined for trend in weight change over the study interval. The

most notable trend for decline in weight is observed in patients (b) (6) (b) (6). All of these patients have preferred term entries for "decreased appetite" and "weight decreased". Patient (b) (6) has an entry for decreased appetite that is an SAE. Patient (b) (6) had an SAE for "bronchitis" and patient (b) (6) had an SAE for "pneumonia", the verbatim term for this "pneumonia" entry is "acute pneumonia due to under nutrition" while patient (b) (6) has an SAE for "pyrexia".

Reviewer Comment: examination of weight trends in the STP1 study reveals a signal for "decreased appetite" and "weight decreased". The associated serious adverse events indicate this is a signal of significant magnitude. The long term DIAVEY, STILON, and TAU-EAP studies do not reveal a clear signal but it is difficult to assess the interaction of expected weight gain with the trajectory of observed weight change across the diversity of ages and underlying disease severity in these studies. This sponsor uses a method of z score assessment over time which does not reveal notable deviation from expected trend lines. The weight / appetite effect is best seen in the interval of 1 year in the STP1 trial that also had frequent weight documentation. This observation supports the differential in weight loss between the placebo and STP treatment groups seen in the pivotal studies.

Blood Pressure

From among the category 2 and 3 studies only STILON and STP-1 study captured systolic and diastolic blood pressure, see Table 53.

STILON

The STILON study will be examined for long term blood pressure trend based on group difference between baseline and six months study intervals to 24 months.

There are 49 entries for systolic and diastolic blood pressure that include visits up to V4 (approximately 18 months). These entries are contributed by 19 patients. Thus 42% of DS syndrome patients contribute to this data. Examination of percent change across visits 1 to four reveal no systematic change associated with duration of STP treatment. Examination of scatterplots for each patient systolic and diastolic blood pressure by study day from V1 to VF reveals no consistent trend in blood pressure associated with STP treatment.

STP-1

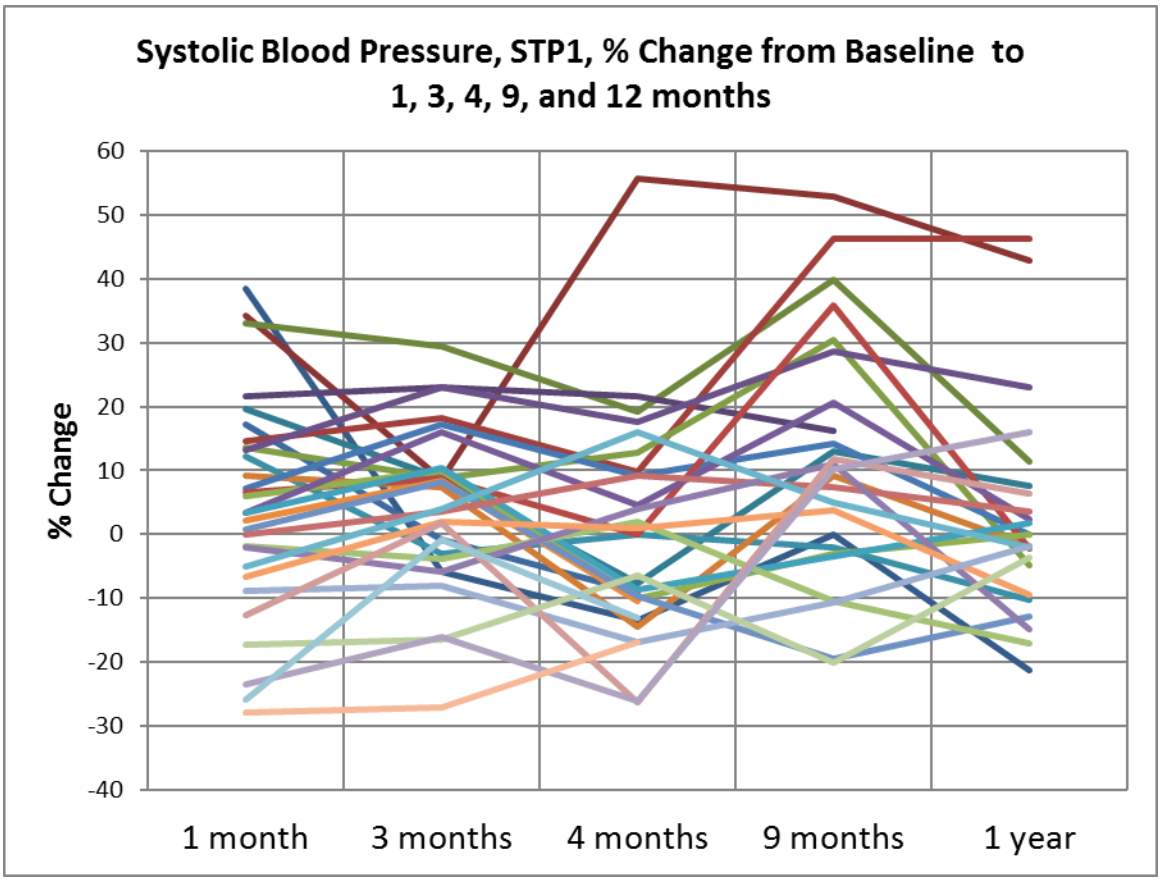
There are 511 entries from 30 patients spanning 430 days. The systolic blood pressure trend is examined by calculating percent change from first day of treatment interval to the 1st month, 3rd month, 4th month, 9th month and 1 year time point. No clear trend of blood pressure change is observed across these time intervals. The group mean systolic blood pressure values

increase at all follow up periods except 4 months where there is a small decline of -0.2%. at all intervals the number of patients with a blood pressure higher than baseline is greater than the subset with a decline in blood pressure. The mean and median systolic blood pressures may be seen in Table 96 . A line graph of patient systolic blood pressures is provided in Figure 36 and this also does not show a clear trend in movement of systolic blood pressure over the test intervals. The adverse event profile of the 3 patients with greatest % positive and negative change from baseline is examined. From among these patients there were no adverse events from the SOC "Vascular disorders".

Table 96 Systolic Blood Pressure, STP-1, mean and median % Change from Baseline to 1, 3, 4, 9, and 12 months with number of patients and % of patients with decline.

Interval from Baseline (1st day STP treatment, measurement prior to drug administration)	1 month (n=30)	3 months (n=29)	4 months (n=29)	9 months (n= 25)	1 year (n= 24)
Mean % Change	4.8	4.5	-0.2	11.5	2.5
Median % change	4.7	7.3	0	10.1	-0.9
# patients with decline from baseline	10	10	14	7	12
% of patients with decline	33.3	34.5	48.3	28.0	50.0

Figure 36 Line Plot of % Change from Baseline Systolic Blood Pressure, STP-1 patients, n=30



Reviewer Comment: there is no signal for consistent alteration of blood pressure during sustained STP treatment.

Heart Rate

From among the category 2 and 3 studies heart rate was measured in the STP1 study, in 17 patients from the STILON study and a single patient in the STEV study.

STEV study

A single patient in the STEV study had entries for heart rate at baseline, D28 and D56. There was no notable change across these study intervals.

STILON
The heart rate profile over the study interval was visually inspected for sustained alteration to a higher or lower rate. Two patients (STILON- (b) (6), STILON (b) (6)) with a cluster of increased

rate late in the study interval were identified and a single patient had only one value of 133 entered (STILON (b) (6)). The adverse event profile for these three patients was examined. Patient STILON (b) (6) had no adverse events entered, while patient STILON (b) (6) had adverse event entries but none related to heart rate from the "cardiac disorders" or "infections or infestations" SOC. Patient STILON (b) (6) did have an entry for "Parotitis" but the study day was not entered. The event was not entered as an SAE. Overall there was no trend of increased or decreased heart rate.

STP-1

The STP1 study had 540 entries from 30 patients spanning a maximum of 430 study days.

The heart rate profile across study entries for each patient was examined for systematic change. No trend of heart rate change is identified. A single patient STP1 (b) (6) was identified who had a cluster of elevated heart rate measurements that were more rapid than baseline. These were seen all near day 150. Examination of the adverse event dataset reveals a preferred term entry for an adverse event of "pneumonia" at study days 246. The entry indicates a serious adverse event.

In summary, examination of heart rate in the STILON and STP1 study does not reveal a systematic increase or decrease in heart rate associated with sustained STP treatment.

Temperature

STP1

Only the STP1 study included temperature measurements from among the category 2 and 3 studies. The maximum temperature identified was 39.8 from patient STP1 (b) (6). The full profile of temperatures across the study timeline revealed 25 entries for body temperature. Twenty-two of these entries are >37.5^{o} C while three is greater than this threshold. The highest temperature of 39.8 occurs on day 147 which corresponds to an adverse event preferred term entry of "Upper respiratory tract inflammation". Two additional temperature entries >37.5^{o} C occur on days 177 and 312 which correspond to preferred term adverse event entries of "influenza" and "streptococcal infection" respectively.

The temperature dataset is examined for temperature >37.5^{o} C (99.5^{o}F). There were 35 entries from 13 patients with temperature higher than this threshold at 33 post baseline measurements (pre STP treatment). There was a small predominance of these elevated measurements in patients less than 8 years old. The temperature profile across all measurements for each patient was examined. There was no consistent change in temperature trend identified. Short spikes of temperature elevation were associated with preferred term

adverse event entries from within the "infections and infestations" SOC.

7.4.8. **Electrocardiograms (ECGs)**

Pivotal Studies

ECG recordings were not made during the pivotal STICLO studies.

Non-Pivotal Studies (category 2 & 3)

From among the category 2 and 3 studies in DS patients only the STP1 study had ECG recordings performed. Twelve lead recordings were performed before initial administration of STP and at completion of the dose maintenance (3rd period) interval. 9/30 had abnormal entries at baseline while 10/30 had an abnormal entry post baseline. The dataset entries do not characterize the nature of the abnormality.

ECG parameter results are examined in the STP-1 sponsor study report section 12.6, page 294. Mean, median, quartile, minimum and maximum changes are provided for ECG parameters in sponsor table 12.6.1 . ECGs in this table are available from 24 subjects who entered the study and had a dose adjustment period followed by a 12 week maintenance period at a target dose of 50mg/kg or upper limit of 2500mg/day. ECG was obtained before commencement of STP and at the end of the 12 week fixed dose maintenance. The sponsor tested the differences using a paired t test and Wilcoxon test for RR interval, QRS, and heart rate. No pre to post treatment significance was identified.

7.4.9. **QT**

A thorough QT study was not performed prior to NDA submission. ECG was not measured in the pivotal study as noted above. ECG was recorded in the STP1 study with analysis of QT interval but this was not in the format of a thorough QT study. Recording were obtained prior to initiation of STP in 24 patients then repeated 16 weeks later after completion of a 4 week dose adjustment interval and 3 month maintenance interval. Across this comparison interval the mean and median were similar with no difference between treatment periods as assessed by a paired t test and Wilcoxon test. In addition, a formal analysis of this data performed by the sponsor's agent, (b) (6), was performed. This analysis concluded "Therefore, there was no significant difference in the changes of parameters related QT interval due to ME2080 administration, no ECG effect with blood concentration dependency and a small impact on ECG parameters, as there was also no adverse event report related to QT interval."

<u>STP-1 QT assessment</u>

Summary of QTc assessments in Study STP-1

Design: Phase III trial in Japanese Dravet patients. This was an open-label study (not randomized trial). There was no concurrent placebo group or positive control group.

ECG methodology: Sponsor conducted an ECG central reading evaluation in addition to the site reading.

- 12-lead ECG data collected from sites were converted to digital.
- ECGs were measured on three consecutive beats by trained cardiologists using the QT analyze system (b) (4).
- The ECG interval duration measurements were performed in Lead II.
- This QT analyze system was developed and validated by (b) (4) to meet ICH E14 guidance requirement; (1) digital data, (2) central reading by trained cardiologists, (3) blind patient information in the system, (4) same reader reads all ECGs per patient, (5) provide the information of the morphological change of T-U wave, and (6) validated system accuracy and detectability of QT measurement.

Sample size: A total of 24 stiripentol (STP) (ME2080)-naïve Dravet syndrome patients (Groups 1 and 2) were enrolled in the STP-1 trial. ECGs were analyzed in patients 1 to 18 years of age (Group 1; N=20) and in patients 19 to 30 years of age (Group 2; N=4). Patients were analyzed in 3 groups:

- Group 1 (N=20): STP-naïve patients, 1 to 18 years of age (mean ± SD = 5.7 ± 4.3 years, range: 1 – 18 years)
- Group 2 (N=4): STP-naïve patients, 19 to 30 years of age (mean ± SD = 22.8 ± 1.3 years, range: 21 – 24 years)
- Group 3 (N=6): patients previously treated with STP, 1 to 30 years of age (mean ± SD = 15.0 ± 5.6 years, range: 10 – 24 years).

Table 97 Study STP-1 ECG Time points

Group	Cardiac Report	Description
Groups 1 and 2	Baseline	Baseline (prior to STP treatment)/ Before ME2080 dosing on Day 1 of dose adjustment period
	At the end of 3rd phase	End of week 16 / At the end of dose maintenance period
	At the end of long term administration period	At the end of long term administration period
Group 3	At the end of 3rd phase	At the entry of long term administration period
	At the end of long -term administration period	At the end of long term administration period

STP-1 ECG Study Results

- No subject had an absolute value for either QTcF or QTcB that exceeded 450 ms.
- Four subjects had a 30 to 41 ms prolongation of QTcF and/or QTcB between baseline and end of Week 16, but no subject had a prolongation that exceeded 60 ms.
- Similar to the results obtained during the short-term administration portion of the trial (baseline to end of Week 16), there was no difference in mean QTcF and QTcB at end of trial.
- No subject had a prolongation of QTcF or QTcB >60 ms.
- No subject in any analysis group had an absolute value for QTcF and/or QTcB >450 ms, except for one subject ((b) (6) 24 years old, Group 3). This subject had QTcB values of 469 ms at baseline and 466.2 ms at the end of the long-term administration period).
- Data collected in Dravet syndrome patients receiving STP in combination with various AEDs did not detect any impact of STP on QTc, both in short- and long-term treatment.
- In addition, there was no correlation between QTcF or QTcB and STP (ME2080) plasma concentration (Cmin).
- There was no adverse event related to QT prolongation in this study.

Table 98 QTcF Study STP1 QTcF mean, median, Quartile, Difference from Pre-STP treatment to Completion of 3rd Period Dose Maintenance. *

	Before start of Administration	At completion of 3rd period in dose maintenance period
Subjects, QTcF	**24**	**24**
mean ± SD	349.68 ± 24.72	348.58 ± 24.79
min - max	309.2 - 412.6	307.1 - 400.6
25% point, median, 75% point	332.3, 349.1, 359.8	332.7, 346.1, 372.3
95% CI (lower limit - upper limit)	-7.55 - 5.36	
p value(paired-t)	-	0.7296
p value(Wilcoxon)		0.4607
* From Sponsor table 12.6.1, page 294 study report		

Reviewer Comment: Although there appears to be no signal for QT prolongation identified from the ECG data provided in the STP-1 study it is insufficient to support a waiver for a TQT study. The QT-IRT has provided the following comments on the deficiencies of this study:

- The clinical study STP-1, in which ECGs were collected following oral dosing of up to 50 mg/kg/day of stiripentol in patient population, cannot be used as a substitute for a TQT

study. The study lacks a placebo control and the exposures may not cover the highest clinically relevant scenario of exposures with therapeutic dosing (e.g. when stiripentol is given to patients with hepatic impairment; the drug is eliminated by hepatic metabolism and that impact of hepatic impairment on exposures has not been studied yet).

- Furthermore, in this study the post-treatment ECGs were collected only at Ctrough at Week 16 and Ctrough at Week 52. Thus, these ECGs are not adequate to quantify the effect of stiripentol on the QTc interval.

7.4.10. Immunogenicity

N/A Stiripentol is a small molecule.

7.5. Analysis of Submission-Specific Safety Issues

See Section 7.11.8 "Summary" of Integrated Assessment of Safety.

7.6. Safety Analyses by Demographic Subgroups

Data on racial composition is absent, age is limited to less than 18 years. Effects in age subsets is examined in individual analyses above.

Patient Using (b) (4) Formulation

The sponsor treated the formulations as interchangeable. There were no formulation flags in the AE dataset or identification of dose form in the pp.xpt datasets. Overall independent differential safety analysis based on formulation could not be performed. The ISS is silent on any relationship between safety and formulation. There is one explicit statement that addressed safety by formulation, this was present in the STIVAL bioavailability study (health volunteers) where the sponsor states "*Overall, it was concluded that single oral administration of 2x500 mg stiripentol was safe and very well tolerated, regardless of the study formulation*." The reviewer surveyed the core individual study reports and did not find specific statements concerning safety by formulation. Two of the long-term studies, TAU-EAP and DIAVEY had a large proportion of patients on (b) (4), approximately 50% each. A differential safety effect would most likely occur on initiation of STP as the (b) (4) formulation, perhaps with initial CNS adverse effect such as somnolence or ataxia at Cmax until there is time for patient adaptation. These adverse events were very common with no means to differentiate by formulation.

Reviewer Comment: A differential effect of formulation due to the larger Cmax associated with the (b) (4) formulation would be most apparent in healthy volunteers of the STIVAL study who are not adapted to the CNS effects of any antiepilepsy drug. Overall, since the healthy volunteers did not have a differential tolerance, the safety reports did not have identify a difference based on formulation and a

large proportion of long term study patients were on (b) (4) without note of a differential effect there does not appear to be a safety signal selectively due to the (b) (4) formulation.

7.7. Specific Safety Studies/Clinical Trials

Not Applicable

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

See non-clinical review, not posted at time this writing.

7.8.2. Human Reproduction and Pregnancy

Clinical data on exposure during pregnancy is very limited. The ISS did not identify any reports of exposure during pregnancy. There were no entries in the category 1, 2 or 3 AE datasets of fetal exposure. The sponsor states there were no reports of pregnant or lactating women in Biocodex-sponsored studies and in the published literature the sponsor did report a search in the Biocodex pharmacovigilance database up to June 2016 for any event related pregnancy recorded with DIACOMIT either during the clinical development of the drug or during the commercialization of the drug identified 3 cases. All 3 cases were non-Dravet patients in which DIACOMIT was added on to carbamazepine cases, birth was uneventful and the child was judged to be normal at birth. Outcome is unknown in the third case.

7.8.3. Pediatrics and Assessment of Effects on Growth

No study contained a prospective study of growth and development with targeted tools. The occurrence of decreased appetite and weight loss does raise the concern that growth and development may be affected. Examination of the category 1-3 adverse event dataset (for Dravet and non-Dravet patients) reveals 2 reports of failure to thrive in the DIAVEY study and 1 report of growth retardation in the STILON study.

One report of failure to thrive was entered as an SAE. This patient was a 12 year old Norwegian male with Dravet syndrome on concomitant VPA and CLB. The patient remained on STP for an additional 6 months while medication adjustments were initiated in response to the adverse event. However, STP was discontinued after 6 months of attempted remediation.

A formal systematic study of STP effects on growth could not be performed. The standard assessment of adverse events and weight does reveal a signal for weight loss and diminished appetite that could be predicted to effect growth in the long term. This risk is currently

presented in the proposed label in section 5.2 "(b) (4) (b) (4)" where it is stated that "Given the frequency of these (b) (4), the growth of (b) (4) treated with DIACOMIT should be carefully monitored".

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The sponsor reports no reports of overdose with STP in Dravet syndrome patients enrolled in the pivotal and non-pivotal clinical trials. No Rebound effect or withdrawal syndrome terms. There were 3 reports of overdose 2 non-Dravet patients in the STILON study and 1 in the TAU-EAP study. One report from each of the studies is entered as an SAE. Examination of the report summaries reveals that patient STILON-(b) (6) had an overdose of carbamazepine rather than STP while the TAU-EAP serious adverse event in patient ATU de COHORTE - DIACOMIT-(b) (4) had an overdose of VPA.

Reviewer Comment: overall there is no signal for STP withdrawal effect, rebound or overdose.

7.9. Safety in the Postmarket Setting

7.9.1. Safety Concerns Identified Through Postmarket Experience

There is no US post-marketing experience. Post marketing experience in the EU has been captured in the DIAVEY study that has been included in the safety analysis.

7.9.2. Expectations on Safety in the Postmarket Setting

The clinical data for efficacy assessment STP was used as adjunctive treatment with established background therapy with VPA and CLB. There is no evidence to support use of STP as monotherapy. In the event prescribers initiate STP as monotherapy in the post marketing setting there may be therapeutic failure. Labeling should reflect the basis for establishing STP effectiveness as studied with VPA and CLB.

7.10. Additional Safety Issues From Other Disciplines

Only the IRT consult available at time of completion, see above

7.11. Integrated Assessment of Safety

7.11.1. Deaths (STICLO, Category 2 & 3 -DS and non-DS, Category 4)

In the multidose studies presented in the application there were a total of 21 deaths that occurred from among a total of 1409 Dravet syndrome and non-Dravet patients included. 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 Dravet cohort of the DIAVEY and STILON studies then in the non-Dravet cohort. The SUDEP rate is similar in DIAVEY for both the Dravet and non-Dravet cohort while in STILON it is higher in the non Dravet cohort. The overall incidence of death and SUDEP in the Dravet Syndrome cohort treated with stiripentol is not out of proportion to the observed high mortality rate of Dravet syndrome.

The incidence rate of SUDEP in TAU-EAP, DIAVEY and STILON although high, is in the range of candidates for epilepsy surgery identified as 9 events per 1000 patient years. The TAU-EAP study had the largest number of patients and was entirely comprised of Dravet syndrome patients. The SUDEP rate in this study approximates the incidence seen in epilepsy surgical candidates and is not out of proportion to the underlying severity of Dravet syndrome. The incidence of death and SUDEP observed across the clinical studies in this approval package does not appear to be in excess of expectations for Dravet syndrome.

7.11.2. **SAE**

Pivotal

The highest frequency with 2 patients each in the STP and PBO treatment arms had seizure related events with 1 drug eruption in the STP group and 1 patient in the PBO group having experienced CNS adverse effect of motor dysfunction and somnolence. Due to the small size of each treatment arm and even distribution of the seizure events there is no clear differentiation in SAEs between treatment arms.

Non-pivotal

DS Patients

DS patients: the top three preferred terms associated with serious adverse events in the non-pivotal (non-STICLO) Dravet patient cohort were “Seizure”, “Decreased appetite” and “status epileptics” in 3.4%, 2.2%, and 1.6% of patients respectively. There was no difference in the frequency of “decreased appetite” between the 0 to 10 year age cohort and the 10 to 20 year group.

Non-DS Patients

Non-DS Patients: the most frequent preferred terms associated with serious adverse events in the non-DS cohort are “Seizure” and “Status epilepticus” at 5.3% and 2.7% respectively. The preferred term in third position was “arthropathy” at a frequency of 0.53% in the cohort where

n= 187. Examination by age reveals that “seizure” and “status epileptics” retained the number one and two positions in both the 0 to 10 year old and 10 to < 20 year old cohorts where 75% of patients were 19.75 years or younger. The terms “thrombocytopenia” and “cachexia” occur with a frequency of 0.81% (4 reports) and 0.4% (2 reports) respectively.

DS and non-DS Pooled

All pooled DS and non-DS patients: examination of the total pool of STP treated patients in both the DS and non-DS cohorts the frequency of any SAE was 18% while the SAE preferred terms with a frequency greater than 1% were “seizure”, “status epilepticus”, “decreased appetite” and “death” at 4.5%, 2.1%, 1.8% and 1.4% respectively. The terms “thrombocytopenia” and “cachexia” occur with a frequency of 0.6% (4 reports) and 0.5% (3 reports) respectively where 2 patients were withdrawn from study due to “thrombocytopenia” and 1 patient due to “cachexia”.

From among the patients with thrombocytopenia there were three patients with both a strong temporal relationship and a positive dechallenge. This is consistent with a strong causal signal. There was one patient with an SAE of elevated ALT. This case was causally very weak. The event occurred in conjunction with an elevation of CPK and was likely of muscle origin.

The adverse events with greatest incidence in the category 1,2 and 3 studies are seizure, status epilepticus, decreased appetite and death. The profile of these events and incidence of events is consistent across the subsets of the safety population including DS patients, non-DS patients and the all patient pooled group, thus a selective vulnerability due to disease, age or duration of exposure is not apparent.

The preferred terms seizure and status epilepticus were frequent and consistent across diseases, DS and Non-DS, age groups and duration of treatment. Without placebo control these events are best explained by the high frequency of seizure and status epilepticus that occur in the underlying disease process.

7.11.3. **Discontinuations**

Pivotal Studies (STICLO)

There were 6 discontinuations in the PBO treatment arm and 2 in STP treatment arm. Four of the discontinuations in the PBO 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 each for a CNS related adverse effect containing the terms “drowsiness”.

Non-Pivotal

The discontinuations from the DS patient cohort and non-DS patient cohort are examined. There were 67 discontinuations from the DS group with the following order of frequency: “lack of efficacy” (6.7%), “adverse event” (3.8%), “other” (2.8%) and “status epilepticus” (0.2%). In the non-DS pool of patients from the DIAVEY and STILON study there were 77 (41%). These discontinuations occurred with the following order of frequency “lack of efficacy” (21.9%), “adverse event” (5.9%) , “other” (5.3%) and “status epilepticus” (0%), “recovery” (4.3%), “lost to follow up” (3.2%) and “non-compliance” (0.5%).

There were no features in the profile of discontinuations in the pivotal studies that undermine study integrity. There were a higher proportion of discontinuations due to lack of efficacy in the placebo compared to the STP treatment cohort which is in alignment with a positive treatment effect.

Examination of discontinuations in the category 2 and 3, non-pivotal studies of DS and non-DS patients reveals there was a higher frequency of discontinuations overall and a higher frequency of discontinuations due to “lack of efficacy” in the non-DS cohort. This observation is in alignment with a more prominent benefit in the DS cohort.

7.11.4. **TEAE**

STICLO Studies

The only placebo controlled, parallel group safety data is provided by the STICLO studies. In the pooled STICLO France and Italy studies, from among adverse events occurring in greater than 1 patient those events with a frequency > 10% of PBO were in order of frequency “somnolence”, “decreased appetite”, “weight decreased”, “dysarthria”, and “nausea”. The frequency of these 5 events in the STP treatment arm, in the same order was 67%, 46%, 27%, 12%, and 15%. There were no instances of “neutropenia”, “thrombocytopenia” or “cachexia”. It is added here that although the frequency of somnolence was high in the STP treatment group there was 1 discontinuation each in the PBO and STP arms that included “somnolence” as an adverse event term as well as 1 SAE for “somnolence” in the PBO arm and none in the STP arm.

Category 2 and 3 Studies DS patients

The frequency of overall adverse events in these studies may be seen in Table 83, with the ten most frequent events preferred terms for each study, TAU-EAP, DIAVEY, STILON, STP-1, and STIPOP shown in Table 84.

The duration of these studies and frequency of patient contact is not homogenous across this group of studies. The ability to capture adverse events is influenced by the frequency of patient contact in each study. The duration of treatment may influence the potential to capture adverse events that are related to cumulative exposure vs events related to more acute toxicity. The STILON, TAU-EAP and DIAVEY studies were all approximately 4.3 years in duration. The estimation of patient assessments in the STILON, DIAVEY, and TAU-EAP studies was 216, 691 and 1061 respectively. A factor that is influencing the frequency – timeline distribution of adverse events is the number of study patients who are naive to STP treatment or who have been on ongoing STP therapy. Most TAU-EAP and STILON patients entered the study on ongoing STP treatment while in DIAVEY all patients have STP newly prescribed at study entry.

Pooled DS and Non-DS

Examination of the pooled DS and non-DS Category 2-3 studies reveals the highest frequency of adverse events occur in the SOC "Nervous system disorders" where 32.5% had an event in this SOC. Within this SOC the 2 most frequency contributing preferred terms are "somnolence" and "ataxia". From among these there were 62 SAEs, and 9 study discontinuations. 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 contributing preferred terms were "decreased appetite" and "cachexia". From among these there were 14 SAEs and 3 study discontinuations. Number three in frequency of adverse events in the SOC "investigations". Within this SOC the most frequency preferred terms are "GGT increased" and "AST increased". From among these were 4 SAEs and 1 study discontinuation, see Table 86.

On examination of preferred terms event frequency in the total pool of category 1-3, Dravet syndrome and non-Dravet syndrome 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 Dravet patient cohort was compared to the non-Dravet syndrome cohort the frequency was higher in the Dravet cohort in all cases except for seizures. This may reflect the younger mean age of the Dravet cohort where there may be greater susceptibility to gastrointestinal and central nervous system adverse effect. The lower rate of seizure in the Dravet syndrome cohort may reflect a better response to STP treatment, see Table 87

Overall, examination of the frequency of TEAE by SOC and preferred term reveal the most prominent signal is observed for occurrence of decreased appetite and central nervous system adverse effects of somnolence and ataxia. There is also a high frequency of events under the preferred terms Gamma-glutamyltransferase increased and Aspartate aminotransferase

increased however, from among these two preferred terms there were 4 SAEs and one discontinuation.

7.11.5. Laboratory Findings

STICLO Studies

The only clinical chemistry parameters sampled in the STICLO studies were ALT and AST. There was no signal for hepatoxicity in the analysis of those results. The features of note among the hematology laboratory studies sampled in the STICLO studies was a trend of declining neutrophil count where a single STP treatment patient had a 48% decline from baseline to end of study (EOS) resulting in an absolute count of 1.09 x 10^9/L with no associated adverse event entry. Examination of platelet count reveals a change in group mean baseline to EOS (end of study) counts, a higher frequency of absolute decline from baseline to EOS in the STP group compared to the placebo cohort, a larger magnitude of negative percent change from baseline (in those who had a baseline entry) to EOS decline in platelet count and a greater number of normal to low shifts from baseline to EOS in the STP cohort compared to the placebo cohort. At EOS there were 5 patients in the STP treatment cohort and none in the placebo cohort with a platelet count less than 150 x 10^9/L and from among the 5 STP patients with low values only one was low at baseline. However, there were no declines to critical low values at EOS in the STP group. The minimum EOS count in the STP cohort was 77 x 10^9/L at EOS after a 44% decline from baseline while the maximum percent decline from baseline in the STP group was 57%. In the placebo cohort, the minimum EOS count was 150 x 10^9/L after a 2.6% decline from baseline.

The lowest platelet and neutrophil count at EOS occurred in the same patient who had no adverse event for hematology parameters but did have 2 adverse event entries for vomiting, one for loss of appetite", one entry for "nausea", and one entry of "decreased weight", none reported as SAEs. A severe change in nutritional status may have had an effect on the patient's hematology parameters.

Non Pivotal Trials in Dravet Patients (category 2 & 3)

Clinical Chemistry

Acquisition of laboratory studies was not uniform across the non-pivotal studies, in addition critical values are not provided, reference range values are inconsistently provided and for some parameters there is a mix of qualitative (normal / abnormal) and quantitative results within the same laboratory metric in the same patient at different points along the study timeline. These studies do not have placebo comparators and baseline comparison is

inconsistent because some patients enter studies already on STP treatment. For example, patients entered the TAU-EAP study from the earlier STILON study. The panel of clinical laboratory studies was not the same in each study, see Table 88, where the STP-1 study (n= 30) was the only study with full clinical chemistry and hematology panels. With these limitations laboratory measurements were examined in each study when available, for outlier values and trends over the study timeline for abnormalities in laboratory domains that were captured.

Markers of Hepatoxicity, ALT, AST, GGT and Bilirubin

Examination of ALT, AST in the STIPOP, TAU-EAP, DIAVEY, STEV, STILON and STP-1 in addition to bilirubin (STP-1 only) did not identify an increasing trend over time or notable outliers to indicate a signal for hepatoxicity. Examination of GGT in the DIAVEY study did not reveal a time related increasing trend. There were several patients with high GGT outlier values, one as high as 36 times ULN. This very high GGT elevation was bracketed by measurements with minor elevation at the preceding and following measurements. Examination of the adverse event dataset for associated serious adverse events did not reveal events of hepatoxicity. The STP-1 study data revealed a trend of increasing GGT over time. There were two high result outliers identified, one with a ULN multiples of 9.0 the second with a ULN multiple of 6.9. In both these cases the GGT elevation peaked then declined by late in the study, days 365 and 237 to minor elevations of less than 3 times ULN, signaling some adaptation. Examination of the enzymes associated with hepatic dysfunction did not reveal a signal for STP associated hepatotoxicity.

Examination of serum creatinine in the STILON and STP-1 studies and BUN in the STP-1 study did not reveal a signal for renal toxicity although there were two patients with sporadic increases in BUN over 1 x ULN during the long-term administration period of the study and a majority portion of patients (63%) with a trend of increasing values over the long-term administration. There was only one adverse event in the “renal and urinary disorders” SOC and a survey of preferred terms did not reveal events related to renal dysfunction. Overall there was no signal for STP associated renal toxicity.

Examination of serum potassium and sodium did not reveal any abnormal trend over time or notable outlier values. Serum chloride values in the STP-1 study revealed there are larger than expected numbers of elevated serum chloride entries in this study dataset and some trend for an increase in serum chloride as STP treatment duration increases. Examination of percent change in serum chloride from baseline at selected timepoints is performed, these include week # 3 dose adjustment period, month 2 of maintenance STP treatment, month 3 of maintenance STP treatment, week 20 of post dose titration period (8 weeks post maintenance) and week 28 of post titration period (16 wk post maintenance). This analysis reveals that percent change in chloride measurements across patients at each timepoint have approximately equal magnitude of shift to greater than and less than baseline value. The finding of one patient with malnutrition who accounted for the most frequent and severe

increases suggests a possibility for observation of increase in chloride is related to nutritional status.

Examination of serum protein in the STP-1 study identified 19 patients with OORR low values at any point on the 430 day timeline. Six patients with a negative trendline in the course of the study had their adverse event dataset reviewed for potentially related adverse event terms. In five of these patients there were terms for “decreased appetite, one patient had an entry for “malnutrition” and two patients had entries for “weight decreased”. Examination of urine protein qualitative values from the STP-1 study did not reveal any trend for urine protein loss. The abnormal serum protein values may be explained by depleted nutritional status in some patients.

Hematology

General Findings

STICLO Studies

Examination of basophils, eosinophils, and monocytes revealed no consistent trend over time Placebo to STP treatment differences or notable outlier values.

Hemoglobin

An examination of the number of patients with a decline from baseline reveals 63% of patients in the STP treatment group had a decline from baseline to EOS while 44% of patients in the PBO group had a decline in Hb from baseline to EOS. In the STP group a decline from baseline to EOS was greater than 8% in only 1 patient. The shift analysis reveals more frequent shifts from normal baseline to OORR low at end of study in the STP cohort compared to the placebo cohort. Overall there is a trend to a decline in Hb in the STP cohort compared to placebo although the signal is not prominent.

Erythrocytes

The outlier analysis revealed an excess of STP treatment patients compared to placebo with a >10% decrease in erythrocyte value. The shift analysis also revealed a small excess of 2 patients in the STP treatment group with a shift from normal baseline value to OORR low at EOS. These changes are in alignment with the small decline in values for hemoglobin and hematocrit in the STP treatment group but do not reach a level of evidence for a notable safety signal.

Leukocytes

There is a mild decline trend in leukocyte values over the STP treatment interval based on examination of the mean change from baseline in the treatment compared to placebo arm as well as examination of the number of patients with a negative change in leukocyte count from baseline to EOS in the STP group compared to the placebo group.

Lymphocyte

There is no signal for decline in lymphocytes

Non-STICLO, DS and non-DS patients Category 2 & 3

Examination of leukocyte counts from studies STP1, STILON and STEV does not reveal a signal for a decline or increase in WBC count associated with STP treatment. Examination of lymphocyte counts in the STP-1 revealed a group mean decline on the order of 15% that was sustained, without continuing decline, over the 60 week STP - 1 treatment in the cohort of Dravet syndrome patients newly started on STP therapy (group 1 & 2, 24 patients). One patient with normal baseline value in this cohort had seven of 13 post baseline measurements that were OORR low with 6 in reference range. These did not occur as consistently decreasing values over the study interval.

Hematology Findings of Special Interest, Neutrophils and Platelets

Neutrophils

STICLO studies

Poole STICLO studies, examination of shift to OORR low (<1500 mm^3). This examination of the STICLO studies reveals 5 patients with ANC < 1500 at baseline, 2 in the STP group and 3 in the PBO group. At visit M3, approximately 60 days later the 3 patients in the PBO arm had an increased in neutrophil count, two into normal range (> 2000 ANC). All three STP arm patients had a further decline from baseline. At the final laboratory measurement (visit M3, visitnum 3, approximately study day 90) there were 7 patients with ANC < 1500, six were in the STP treatment arm and 1 in the PBO arm. Five of six STP treatment arm patients had ANC values > 1500 at baseline, one had a value of 1326. The PBO patient had a baseline value of 1430. The 6 patients in the STP arm had a mean and median percent decline of 29% and 30% respectively.

Pooled STICLO studies, examination of percent change from baseline group mean and median. There are 58 patients at end of study with neutrophil measurements, 27 in the PBO and 31 in STP treatment arms. Percent change from baseline to visit M3 measurement in the PBO arm reveals a group mean and median value of +18.4% and -4.2% respectively while in the STP

treatment arm the mean and median results were -4.4% and -26.8% respectively. There was no shit to critical low value in either arm and no adverse event of “neutropenia”. The adverse event dataset of the 6 STP arm patients with ANC < 1500 was examined. There were 3 events in the SOC “Infections and infestations” containing the preferred terms “bronchitis”, “rhinitis” and “varicella”, none were SAEs.

This analysis reveals an excess of decline in neutrophil count in the STP treatment arm over the PBO cohort in the pooled STICLO studies. The frequency of decline below the threshold of ANC < 1500 is more frequency in the STP arm than in the PBO arm.

Neutrophils -Non-Pivotal Studies in DS patients (category 2 & 3)

In the DIAVEY study there was one patient, an 11 month old male discontinued for “neutropenia” and “thrombocytopenia” after approximately 40 days of STP treatment. During this interval the patient had an 88% decline in neutrophil count from 7150 x 10^9/L to 850 x 10^9/L. No dechallenge information is provided. The STP-1 study reveals a declining trend in neutrophil counts in a notable proportion of patient. Thirty-eight (38%) of patients with baseline neutrophil values within reference range had a decline to ANC < 1000. Two patients with ANC < 1000 had non-serious AE entries of “neutrophil count decreased” and 7 of the (ANC < 1000) patients had SAEs related to infection and / or depleted nutritional status. All of these patients continued STP treatment. Examination of STP-1 and DIAVEY studies support a signal for neutropenia.

Neutrophils-Non-Pivotal Studies, non-DS patients (category 2 & 3)

Examination of neutrophil clinical laboratory data in the non-DS patients of the DIAVEY and STILON studies reveals two patients in the STILON study wtih a decrease neutrophil count from baseline. One patient who remained in the study for over two years had a low baseline of 1428/mm3, then reached a nadir of 1156/mm3 at minimum of 6 months later. This patient has an end of study value 2 years later of 2132/mm3. A second patient had a low baseline, reached a nadir of 536/mm3 then rebounded to a value of 1644/mm3 2 months later. There is no comment indicating discontinuation. The ISS indicates there were 2 patients who experienced low neutrophil count, one had a nadir of 1100/mm3 while the second is reported only as an AE of neutropenia that continued in the study.

Neutrophils: Exploratory Efficacy studies, non-Dravet patients

There was a single patient with and SAE of neutropenia that was reversible upon discontinuation, mild neutropenia in 5 patients and moderate in 3 patients but no follow up information or indication if and of the moderate were entered as an SAE

Neutrophil conclusions:

The information presented in the integrated summary is more expansive for the examination of neutrophils due to the significance of this safety signal. In the controlled trials, there was a higher frequency of decline in neutrophils with a larger magnitude of decline in STP vs PBO. Among the DS patients in non- STICLO studies there is 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 ANC < 1000.

Exam of the total category 2 & 3 DS and non-DS patient adverse event (AE) pool there were 30 instances of either "neutropenia" or "neutrophil count decreased" from 25 patients. From among these there was a single STP discontinuation. Almost all patient remained in study, however in the STP-1 study there were SAEs in the SOC "infections and infestations" associated with several patients who had low neutrophil counts.

Platelets

STICLO Studies

At EOS there were 5 patients in the STP treatment cohort and none in the placebo cohort with a platelet count less than 150 x 10^9/L and from among the 5 STP patients with low values only one was low at baseline. However, there were no declines to critical low values at EOS in the STP group. The minimum EOS count in the STP cohort was 77 x 10^9/L at EOS after a 44% decline from baseline while the maximum percent decline from baseline in the STP group was 57%. In the placebo cohort the minimum EOS count was 150 x 10^9/L after a 2.6% decline from baseline

Platelets: Category 2 and 3 , DS and non-DS patients

In the STP-1 study examination of the profile of all patient platelet count vs time scatter plots reveals that 66% of patients have a trend of increasing platelet count. Further review of median percent decline from baseline reveals a maximum reduction from baseline of 12% at week 4 of treatment that subsequently declines to approximately 5% from baseline.

Platelets: Pool DS and Non-DS, AE pool.

There were 21 instances of either "thrombocytopenia" or "Platelet count decreased" from 16 patients. From among these there were 2 discontinuations. The first case of discontinuation (TAU-EAP (b) (6)) reached a nadir of 43000 platelets at 43 days of treatment that resolved 6 days after discontinuation. In the second case ((b) (6)) the developed thrombocytopenia 40 days after beginning STP treatment. The platelet count is from the narrative for this DIAVEY

study patient. Platelet count is not provided in the laboratory dataset. The unit in the narrative is unclear. Dechallenge data not provided.

Two patients with an SAE of thrombocytopenia continued STP treatment, in one case (b) (6)) where platelet count declined to 41, 000 /mm^3 VPA and STP were reduced in response to the thrombocytopenia with resolution in 2 week. The patient subsequently remained in the study for an additional 37 months. In the second (STILON (b) (6)) of these two cases the patient remained on STP treatment for a total of 11 years.

Platelets: Exploratory studies in non-Dravet patients, category 4

Grade 1 thrombocytopenia is reported in one patient in the category 4 studies.

Thrombocytopenia conclusion

The magnitude and frequency of decline from baseline 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 case from an inclusion value of 183,000 /mm3. 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. This data indicates there is risk of thrombocytopenia but this may be monitored and is reversible.

7.11.6. **Vital Signs**

Weight

The placebo controlled data reveals a differential in weight loss between the placebo and STP treatment groups. The frequency of weight loss is greater in the STP group and of larger magnitude. Examination of weight trends in the STP1 study reveals a signal for “decreased appetite” and “weight decreased”. The associated serious adverse events indicate this is a signal of significant magnitude. The weight / appetite effect is best seen in the interval of 1 year in the STP1 trial that also had frequent weight documentation. This observation supports the differential in weight loss between the placebo and STP treatment groups seen in the pivotal studies.

Blood Pressure

From among the category 2 and 3 studies only STILON and STP-1 study captured systolic and diastolic blood pressure. There is no signal for consistent alteration of blood pressure during

sustained STP treatment.

Heart Rate and Temperature

Examination of heart rate in the STILON and STP1 study does not reveal a systematic increase or decrease in heart rate associated with sustained STP treatment. In the STP-1 study there was no consistent change in temperature trend identified. Short spikes of temperature elevation were associated with preferred term adverse event entries from within the “infections and infestations” SOC.

7.11.7. **ECG**

ECGs were performed in 3 phase 1 studies (STIUNI, STIVAL, and Greig); ECGs were not performed in the Pons trial. No clinically significant changes in ECG parameters were reported in these studies.

Among the clinical studies of Dravet patients the STP-1 study is the only source of ECG data. In the xpt dataset only qualitative interpretations are available. The sponsor reports that abnormalities seen at inclusion were approximately the same in frequency as those during the study. The RR and QRS interval as well as heart rate were examined using a paired t -test and Wilcoxon test and there were no baseline to treatment interval differences of significance.

The QT interval was evaluated in STP-1 (TQT study has not been waived). There was no signal for adverse impact on the QT interval.

7.11.8. **Summary:**

Examination of adverse events and clinical chemistry laboratory values reveals no evidence of a hepatotoxicity signal. The is an unexpected high frequency of serum chloride elevation in the STP-1 study with some trend for increase over time.

Examination of hematology parameters reveals a trend of hematopoiesis depression identified by a decline in hemoglobin, erythrocytes (without evidence of hemolysis or blood loss), and leukocytes in analysis of the STICLO studies. In the category 2 & 3 studies, most

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 vs PBO. Among the DS patients in non- STICLO studies there is 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 patient. Thirty-eight (38%) of patients with baseline neutrophil values within reference range had a decline to ANC < 1000.

Exam of the total category 2 & 3 DS and non-DS patient adverse event (AE) pool reveal there were 30 instances of either "neutropenia" or "neutrophil count decreased" from 25 patients. From among these there was a single STP discontinuation. There is some reassurance that adaptation develops since all but a single patient remains 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 has physiologic consequences.

The magnitude and frequency of decline from baseline 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 case from an inclusion value of 183,000 /mm3. 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. This data indicates there is risk of thrombocytopenia but this may be monitored and is reversible.

The QT interval was evaluated in STP-1 where there was no signal for adverse impact on the QT interval. The STP-1 study was evaluated by the IRT team who concluded that a TQT study is not waived on the basis of the STP-1 study. 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.

8 Advisory Committee Meeting and Other External Consultations

This application was not presented at an Advisory Committee Meeting.

9 Labeling Recommendations

9.1. Prescribing Information

Sponsor proposed indication is for patients (b) (4). This is not supported by the age range studied. Age range in the STICLO studies was age 3 years to 18 years inclusive. (b) (4) (b) (4). Labeling should be revised to "patients age 2 years and older".

Based on the evaluations of neutrophil counts and platelet counts the following additions to proposed labeling are recommended.

Section 5:

5.3 Neutropenia & Thrombocytopenia

(b) (4)

Hematologic testing should be obtained prior to starting treatment with DIACOMIT and then every 6 months.

9.2. Patient Labeling

A medication guide to cover AED suicidality class effect should be applied. The CNS adverse effects, appetite and weight loss should be included.

9.3. Nonprescription Labeling

N/A

10 Risk Evaluation and Mitigation Strategies (REMS)

10.1. Safety Issue(s) that Warrant Consideration of a REMS

None proposed

10.2. Conditions of Use to Address Safety Issue(s)

None proposed

10.3. Recommendations on REMS

None proposed

11 Postmarketing Requirements and Commitments

TQT study must be performed

12 Appendices

12.1. References

Mechanism of Action

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12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): STICLO FRANCE AND STICLO ITALY

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 32		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in S Sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes NA ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

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/

STEVEN T DINSMORE
08/15/2018

PHILIP H SHERIDAN
08/17/2018