Review and Evaluation of Clinical Data

NDA	**214679**
SD#	**1**
SEQ	**0001**
Sponsor	**Azurity Pharmaceuticals**
Drug	**Topiramate oral solution**
Proposed Indication	• **Epilepsy: Initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older; adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older.** • **Preventive treatment of migraine in patients 12 years of age and older.**
Material Submitted	**New/NDA**
Correspondence Date	**10/6/2020**
Date Received / Agency	**10/6/2020**
Date Review Completed	**10/6/21**
Reviewer	**Steven T. Dinsmore, DO**

1. Introduction

The NDA 505 (b)(2) submission for proposed drug product Topiramate Oral Solution is based on the approved listed drug Topamax.

The proposed indications for Topiramate Oral Solution are same as the indication for the LD Topamax which are as follows:

- Monotherapy Epilepsy: Topiramate is indicated as initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older.

- Adjunctive Therapy Epilepsy: Topiramate is indicated as adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older.

- Migraine: Topiramate is indicated for the preventive treatment of migraine in patients 12years of age and older. Azurity plans to use labeling of the approved RLD, ZONEGRAN as the basis of supporting non-clinical pharmacology and toxicology as well as clinical sections of the labeling for its proposed drug product Zonisamide oral suspension.

2. Regulatory Pathway

The NDA submission for proposed drug product Topiramate Oral Solution, 25 mg/mL, 473 mL Fill is based on the approved listed drug (LD) NDA020844 TOPAMAX (topiramate) sprinkle capsules for oral use, 25 mg, held by Janssen Pharmaceuticals, Inc.

In accordance with FDA product specific draft guidance published on June 2013 for Topiramate Sprinkle Capsule; Oral, Azurity performed the following comparative bioequivalence studies (BE):

An Open-Label, Randomized, Single-Dose, Three-Period, Three-Sequence, Three-Way Crossover, Fasting Relative Bioavailability Study of Topiramate Oral Solution 25 mg/mL Versus TOPAMAX® (Topiramate capsule) Sprinkle Capsule 25 mg and Food- Effect Study on Topiramate Oral Solution 25 mg/mL in Normal, Healthy, Adult, Non-Smoking Male Subjects. This BE study is submitted with the NDA and is the focus of clinical safety review in this application.

3. Pediatric Development

The Pediatric Research Equity Act (PREA) Post Marketing requirements (PMRs) for this oral solution formulation of topiramate were discussed at the Pediatric Research Committee (PeRC) meeting of 10/5/2021. The PeRC concurred that this pediatric extrapolation is appropriate.

4. Sources of Clinical Data

Study 0786-19: An Open-Label, Randomized, Single-Dose, Three-Period, Three-Sequence, Three-Way Crossover, Fasting Relative Bioavailability Study of Topiramate Oral Solution 25 mg/mL Versus TOPAMAX® (Topiramate capsule) Sprinkle Capsule 25 mg and Food-Effect Study on Topiramate Oral Solution 25 mg/mL in Normal, Healthy, Adult, Non-Smoking Male Subjects

Clinical Study Dates

Study initiation date	:	09 January 2020
Study completion date	:	21 February 2020

Table 1 Number of subjects (planned and analyzed):

Planned for inclusion		24
Enrolled and Checked In		30 (Subject Nos. (b) (6) and 6 overnight standby subjects)
Pre-dose dismissed/withdrew		3
Dosed	Period-I	24

Planned for inclusion		24
Enrolled and Checked In		30 (Subject Nos. (b) (6) and 6 overnight standby subjects)
	Period-II	22
	Period-III	22
Post-dose dismissed		2
Analyzed		22
Considered for statistical analysis		22

Table 2 Test – Reference by Sequence and Period

Sequence	***Period 1***	***Period 2***	***Period 3***
1	***Test Product fasting***	***Test Product fed***	***Reference product fasting***
2	***Reference Product fasting***	***Test Product fasting***	***Test Product Fed***
3	***Test Product Fed***	***Reference Product Fasting***	***Test Product Fasting***

Table 3 Schedule of Study Assessments

		Period 1, 2 and 3				
Procedure	**Screening**	**Check-in**	**Day 1**	**Day 2**	**Day 3 to Day 5**	**EOS[1]**
Informed Consent	X	X[2]				
Demographic information, including height and weight	X					
Medical History	X					
Medication History	X	X				
Physical Examination	X					
Vital Signs Measurement	X	X[3]	X[4]	X[5]		X
Health Status Evaluation			X[4]	X[5]		X
ECG	X					
Biochemistry	X					X
Serology	X					
Hematology	X					X

		Period 1, 2 and 3				
Procedure	**Screening**	**Check-in**	**Day 1**	**Day 2**	**Day 3 to Day 5**	**EOS[1]**
Urinalysis	X					X
Drug and Nicotine (Cotinine) Screens	X	X				
Alcohol Screen	X	X				
PHQ-9	X					
Blood Collection for PK Analysis[6]			X	X	X	X

[1]EOS procedures were conducted during the last return blood draw prior to discharge from the clinic in Period-III. For discontinued subjects: at the time of discontinuation if possible, or as soon as possible after discontinuation.

[2]Period-I only.

[3]BP, PR, Temperature and RR

[4]Vital examination (BP and PR) at 1.00, 2.00, 4.00, 8.00 and 10.00 hours post-dose, Health status evaluation at pre-dose (0.00), 1.00, 2.00, 4.00, 8.00 and 10.00 hours post-dose.

[5]At the end of confinement only.

[6]Test product (T1) and Reference product (R): Pre-dose (0.000) and at 0.167, 0.333, 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.333, 2.667, 3.000, 3.500, 4.000, 5.000, 6.000, 8.000, 10.000, 12.000, 16.000, 24.000, 36.000, 48.000, 60.000, 72.000 and 96.000 hours post-dose.

Test product (T2): Pre-dose (0.000) and at 0.500, 1.000, 2.000, 3.000, 4.000, 5.000, 5.500, 6.000, 6.500, 7.000, 7.500, 8.000, 9.000, 10.000, 12.000, 14.000, 16.000, 20.000, 24.000, 36.000, 48.000, 60.000, 72.000 and 96.000 hours post-dose.

As noted in Table 3, clinical chemistry, hematology and urinalysis samples are collected at baseline and End of Study (EOS) only.

5. Bioequivalence findings of Study 0786-19

The OCP review finds:
"the PK bridging acceptable and recommends the approval of topiramate oral solution, 25 mg/mL for the treatment of monotherapy epilepsy and adjunctive therapy for pediatric patients 2 years of age and older, as well as migraine in pediatric patients 12 years age and older."

6. Review of Clinical Safety

6.1.1. Adverse Events from AdAM dataset ADAE

There were 14 adverse event entries from 6 subjects with no SAE's or study withdrawal due to an adverse event. Three subjects were discontinued before dosing in period 1. These were subjects (b) (6) and (b) (6), the reasons for

study discontinuation were a withdrawal due to personal reasons, a positive urine screen for THC and an out of range vital sign, respectively.

One subject ((b) (6)) had two adverse event entries temporally associated with reference product treatment. The five remaining subjects had 12 adverse event entries in temporal relationship to the test product treatment periods.

The most common AE preferred term was “blood pressure increased”. This occurred in subject (b) (6) in treatment period 1 and 2 resulting in an overall total of 5 adverse event entries. During treatment period 1 this subject also experienced AE preferred term entries of headache and nausea. It is possible that in treatment period 1 the discomfort of headache and nausea were drivers of a blood pressure increase. In treatment period 2 this subject had an entry for “blood pressure increase” and “blood glucose increased”. This subject had a screening blood glucose value of 114mg/dl with an increase to 187mg/dl at EOS (4 days after administration of test product in fed state). A follow up glucose value was obtained 5 days later and found to be 115mg/dl.

Subject (b) (6) had an entry for elevated ALT. The reference range is seen to be 37U/L where the baseline value was 41 and the EOS value was 43U/L. This does not represent a meaningful clinical change and does not represent a safety signal.

All 9 remaining adverse event entries had a single occurrence each and may be seen in Table 4. All were designated as mild by the investigator and have entries in the listed drug label, seen in treatment of POS or Migraine, in pediatric or adult patients.

Table 4 Adverse Events, Map of Adverse Event Date to Treatment Period & Product Assignment†

Subject ID	Treatment Pd 1 (Test-reference)	Treatment Pd 2 (Test-reference)	Treatment Pd 3 (Test-reference)	Treatment Period 1 End Date	Treatment Period 2 End Date	Treatment Period 3 End Date	Adverse Event Start Date	Preferred Term	Severity	Sponsor Causality Assignment
(b) (6)	Test1	Test2	Reference				(b) (6)	Fatigue	MILD	PROBABLY
	Test1	Test2	Reference					Diarrhoea	MILD	PROBABLY
	Reference	Test1	Test2					Aspartate aminotransferase increased	MILD	PROBABLY
	Reference	Test1	Test2					Blood pressure increased	MILD	UNLIKELY
	Reference	Test1	Test2					Headache	MILD	PROBABLY
	Reference	Test1	Test2					Nausea	MILD	PROBABLY
	Reference	Test1	Test2					Blood pressure increased	MILD	UNLIKELY
	Reference	Test1	Test2					Blood glucose increased	MILD	PROBABLY
	Test1	Test2	Reference					Heart rate decreased	MILD	PROBABLY
	Test2							Flushing	MILD	PROBABLY
	Test2							Dizziness	MILD	PROBABLY
	Test2							Headache	MILD	PROBABLY

† Shaded cells of treatment period (Pd) map to corresponding shaded cells of treatment period end date & adverse event start date

Reviewer Comment: Adverse event entries had a frequency of 10.9% and 4.5% related to test product and reference product exposures respectively. The etiology does not appear strongly related to fed or fasting state. Three of the five subjects had AE entries associated with administration of test product in the fasting state and two subject had AEs associated with administration of test product administration in the fed state. All events were judged as mild. These events do not represent a new safety signal.

6.1.2. Clinical Laboratory Studies

All clinical laboratory entries with a high, low or abnormal reference range indicator are captured from the ADLB dataset. From among these entries only those associated with period 3 test product fasting or fed sequence are retained. Those associated with reference product are not examined for abnormal values due to the 19-day washout interval from any earlier test dose sequence and is thus too long for expectations of an interpretable temporal relationship to the observed laboratory abnormality as well as the confounding by administration of reference product in more proximal relation to the observed abnormality.

Based on the aforementioned filters there are 14 entries of high, low or abnormal reference range indicators from 8 subjects. Eight of these entries are urinalysis examinations. The abnormalities identified are high urine specific gravity in two subjects. These values are 1.032 and 1.034 where the high normal reference range is 1.030. This represents only a mild elevation. The remaining values are measures of ketones (1), calcium oxalate crystals (1), macroscopic blood -small (1), leukocytes- trace (1), macroscopic blood- moderate (1), and erythrocytes HPF- 5 (1).

There are 6 clinical chemistry values from 5 subjects that remain after the application of filters are applied. These results are shown in Table 5. Subject (b) (6) had an ALT out of reference range (OORR) high value observed to be 1.3 X ULN. Subject (b) (6) had an elevated serum glucose value with a normal baseline value. This abnormality was entered as an AE and is discussed above in the section on adverse events. The remaining four abnormal laboratory values are seen to have a minimum elevation over both the reference high value and the subject's baseline value.

Table 5 Clinical Chemistry and Hematology entries with a high, low or abnormal reference range indicator are captured from ADLB

SUBJID	Treatment Assignment Sequence	Laboratory Parameter	Value	Abnormal Flag	Reference Low	Reference High	Baseline value
(b) (6)	Reference - Test1 - Test2	Creatinine (umol/L)	111	HIGH	60	110	100
	Reference - Test1 - Test2	Alanine (U/L)	61	HIGH	0	45.99	46
	Reference - Test1 - Test2	Aspartate Aminotransferase (U/L)	43	HIGH	0	36.99	41
	Test2 - Reference - Test1	Creatinine (umol/L)	114	HIGH	60	110	113
	Reference - Test1 - Test2	Glucose (mmol/L)	10.4	HIGH	3.6	7.7	6.3
		Glucose (mg/dl)	187		65	138	114
	Test2 - Reference - Test1	Leukocytes (10^9/L)	9.7	HIGH	3.2	9.4	9

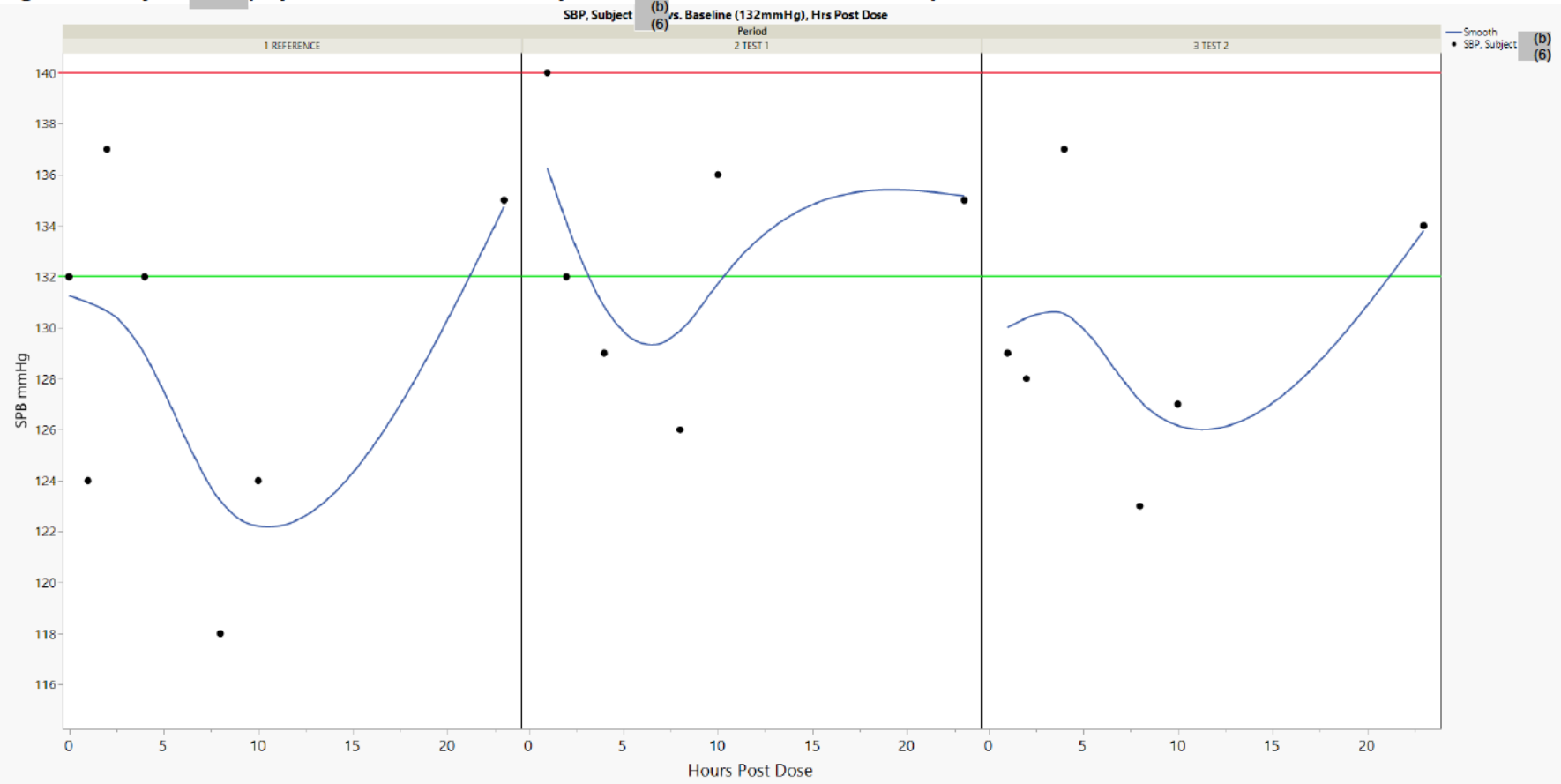
Reviewer Comment: On examination of clinical chemistry, hematology and urine assessments there is a single abnormal result that is notable. Subject (b) (6) had an increase in serum glucose from 114mg/dl at baseline to 187mg/dl at EOS. A follow up value 5 days after the EOS measurement. The follow up glucose value was 115mg/dl that was equal to 2mg/dl over baseline. This event is unlikely to be causally related to test product. Overall, there is no new safety signal for test product identified in the laboratory studies of the 24 healthy volunteer cohort.

6.1.3. Vital Signs

Systolic Blood Pressure

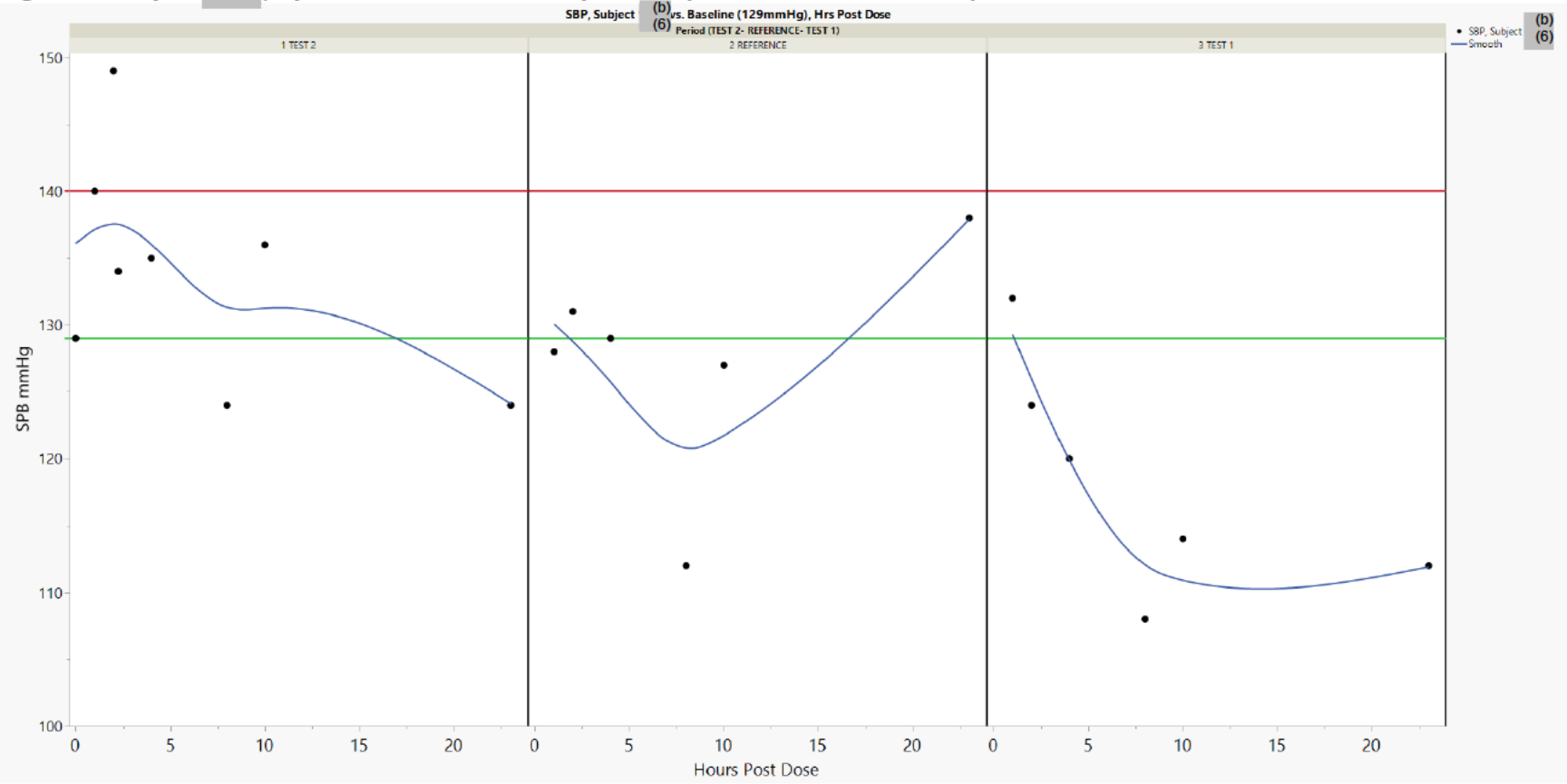
The distribution of all systolic blood pressure measurements obtained in the 1 hr to 10-hour post dosing interval as well as day 1 post dose check-out measurements were examined for outlier entries less than or equal to 95mmHg and greater than or equal to 140mmHg. Outlier values occurring in relation to reference product treatment are excluded from the analysis. There were 5 instances of outlier systolic blood pressure measurements from 3 subjects. One of these measurements occurred in check out period following reference drug administration and is not considered further. The full profile of all systolic blood pressure measurements obtained in the three study periods from the outlier subjects is captured and examined for evidence of a sustained shift in systolic blood pressure values. The systolic blood pressure profiles for each of these four subjects is shown graphically in Figure 1, Figure 2, and Figure 3 below. The graphical presentation allows examination of the outlier value compared to broader array of measurements that were obtained and also allows a visual comparison of the test to reference product values. In the graphical presentation the outlier threshold is displayed as a red line at the y axis value of systolic blood pressure while a green horizontal line intersects the y axis at the baseline, pre-dose value, of period 1.

Figure 1 Subject [redacted], Systolic Blood Pressure by Period (Reference-Test1-Test2) & Hours Post Dose



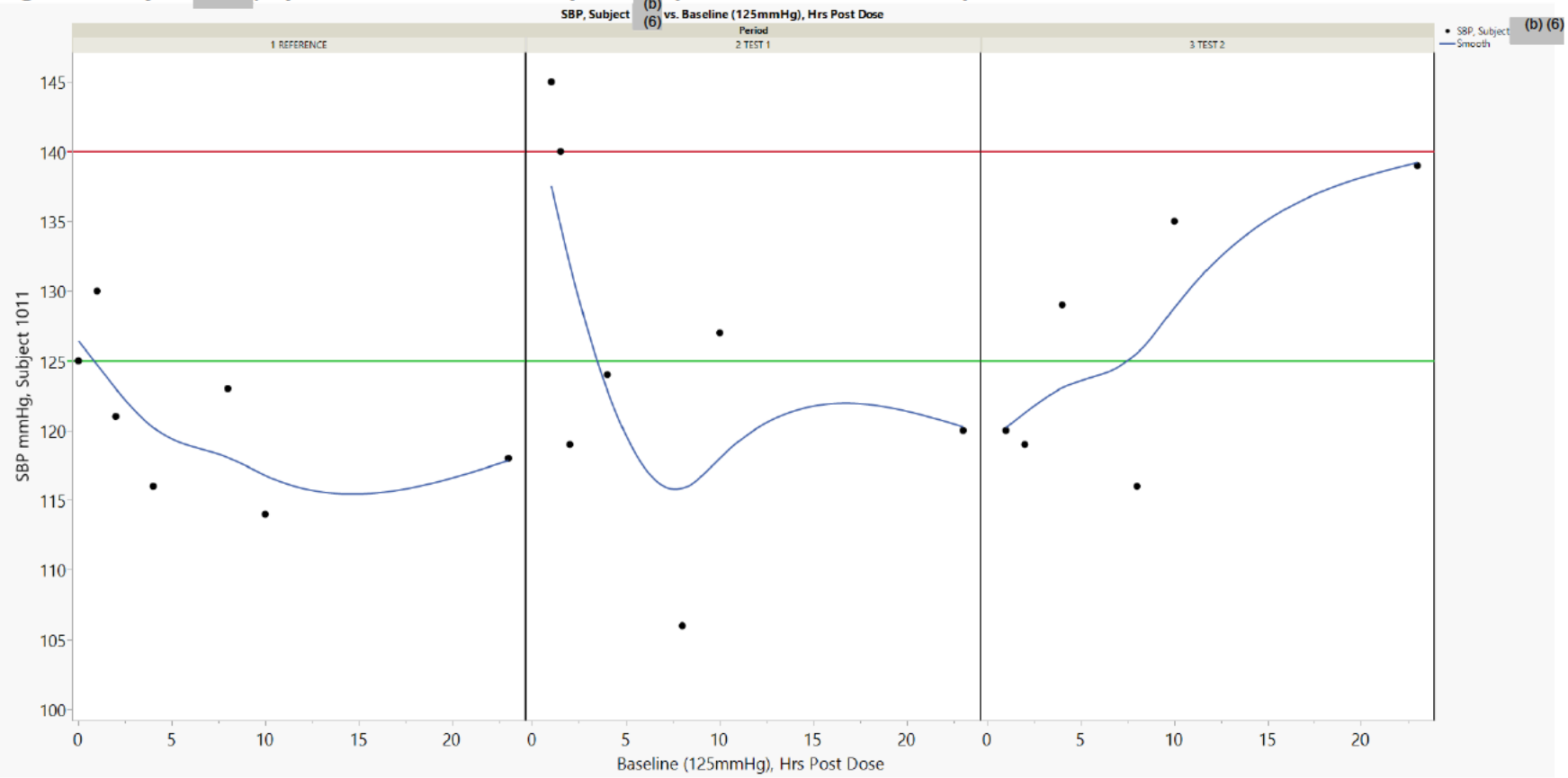
Subject [redacted] had a single elevated SBP value of 140mmHg at the 1-hour post dose measurement in period 2 after administration of test product in the fasting state. There are no recurrences of this elevation and the distribution of values around baseline is similar to those following the administration of test product in the fed state. There is less variability in post dose values following test product administration compared to reference product.

Figure 2 Subject (b) (6), Systolic Blood Pressure by Period (Test2- Reference-Test1) & Hours Post Dose



Subject (b) (6) had two outlier elevations of SBP at hour 1 and hour 2 post administration of test product in the fed state. There were no further occurrences of SBP outliers related to test product administration. SBP appears to trend lower than baseline following test product administration in period 3.

Figure 3 Subject (b) (6), Systolic Blood Pressure by Period (Reference-Test 1-Test 2) & Hours Post Dose



Subject (b) (6) had two outlier elevations of 145mmHg and 140mmHg SBP at hour 1 and 1.5 hours respectively. These outlier values occurred post administration of test product in the fasting state in period 2.

Distribution of Change from Baseline Systolic Blood Pressure

All systolic blood pressure measurement changes from baseline obtained at hours 1 to 10 following administration of test and reference product in the fasting state are examined. There is a small trend toward lower blood pressure following administration of test product based on a mean and median decline of 4mmHg from baseline compared to a mean and median decline of 3.5mmHg and 2mmHg observed following administration of reference product. The greatest decline from baseline (35mmHg) and largest range are observed following reference product administration, see Table 6.

Table 6 Systolic Blood Pressure, Test and Reference, fasting, group measures of central tendency with maximum decline and elevation.

	# measurements	Mean	SD	Median	Min(CHG)	Max(CHG)	Range(CHG)
TEST 1	113	-4.0	9.5	-4	-25	20	45
REFERENCE	113	-3.5	9.8	-2	-35	17	52

Reviewer Comment: There was no sustained trend of SBP elevation or decline observed in those patients with outlier SBP. There was no notable difference in group mean, median, maximum decline or increase from baseline SBP between the test and reference products administered in fasting state.

Diastolic Blood Pressure

Examination of diastolic blood pressure include a comparison of test and reference post dosing measures of central tendency as well as group minimum and maximum diastolic blood pressure values. An outlier analysis and subject level examination of diastolic blood pressure changes during test and reference product are not performed

Distribution of Change from Baseline Diastolic Blood Pressure

All diastolic blood pressure measurement changes from baseline obtained at hours 1 to 10 following administration of test and reference product in the fasting state are examined. There is little overall change in central tendency and maximum decline from baseline, see Table 7.

Table 7 Diastolic Blood Pressure, Test and Reference, fasting, group measures of central tendency with maximum decline and elevation.

DIASTOLIC	# Measurements	Mean	SD	Median	Min(CHG)	Max(CHG)	Range(CHG)
TEST	113	-3.1	8.3	-3	-29	16	45
REFERENCE	110	-4.6	8.0	-4	-24	12	36

Reviewer Comment: There was no notable difference in group mean, median, maximum decline or increase from baseline DBP between the test and reference products administered in fasting state.

Heart Rate

All heart rate measurement changes from baseline obtained at hours 1 to 10 following administration of test and reference product in the fasting state are examined. There is little overall change in central tendency and maximum decline from baseline, see Table 8

Table 8 Pulse, Test and Reference, fasting, group measures of central tendency with maximum decline and elevation.

PULSE	# measurements	Mean	SD	Median	Min(CHG)	Max(CHG)	Range(CHG)
TEST	113	-2.9	9.3	-3	-27	19	46
REFERENCE	113	-1.0	8.9	-1	-26	18	44

The applicant identified an outlier value for heart rate, subject (b) (6), in period 1 (test 1- fasting state). The subject has a baseline heart rate of 56 with a decline to 45 seen at 2 hours post dose. The subjects is observed to have a similar decline at 2 hours post reference product dose in period 3 where heart rate declined to 46 BPM.

Reviewer comment: There is no evidence of a systematic change in heart rate following administration of test and reference product in the fasting state.

FINANCIAL DISCLOSURE- See Appendix 1 for Sponsor and Investigator Documentation

Covered Clinical Study: 0786-19

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none		
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)): **N/A** Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____		

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
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) **N/A**		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Reviewer Comment: The Applicant did not submit disclosure on a form 3454. The Lambda Therapeutic Research signature pages provided for the Principal Investigator and Sub-Investigator are adequate in Lieu of form 3454 based on the response to Question H5 (page 28) of the "Guidance for Clinical Investigators, Industry and FDA Staff: Financial Disclosure by Clinical Investigators"[1]. This documentation is provided in **Appendix 1** below. The Applicant provided investigator signature pages that did not reveal disclosable financial interests, therefore a form 3455 was not necessary. In conclusion, there are no disclosable financial interests identified.

7. Summary and Conclusion

PK bridging to the listed drug was acceptable to support approval of this topiramate oral 25mg/ml for the treatment of monotherapy epilepsy and adjunctive therapy for pediatric patients 2 years of age and older, as well as migraine in pediatric patients 12 years age and older. The safety assessment of study 0786-19 revealed no characteristics out of alignment with current topiramate labeling and no new safety signal was detected.

8. Appendix 1 – Financial Disclosure Documentation

3 Pages have been Withheld in Full as b6 (PPI) immediately following this page

[1] https://www.fda.gov/media/85293/download

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/

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11/03/2021 09:07:28 AM

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