CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214273Orig1s000

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA	214273
SD#	1
Sequence Number	0001
Applicant	Azurity Pharmaceuticals (formerly Eton Pharmaceuticals)
Drug	Zonisamide
Proposed Indication	Adjunctive therapy in the treatment of partial seizures in adults with epilepsy
Material Submitted	Original NDA, eCTD format
Correspondence Date	7/29/2020
Date Received	7/29/2020
Date Review Completed	5/25/21
Reviewer	Steven Dinsmore, DO

Table 1 Glossary

Abbreviation	**Definition**
SBP	Systolic blood pressure
BPM	Beats per minute
LD	Listed drug
EOS	End of Study
OORR	Out of Reference Range
TR	Treatment sequence: Period 1= Test product, Period 2= Reference product
RT	Treatment sequence: Period 1= Reference product, Period 2= Test Product
ULN	Upper limit of normal

1. Introduction

The NDA submission for proposed drug product Zonisamide Oral Suspension, 20 mg/mL, 150 mL Fill is based, in part, on the approved listed drug (LD) Zonegran (Capsule; Oral eq. 100 mg base/capsule, NDA 020789 held by Sunovion Pharmaceuticals Inc. as well as based on the literature. The proposed indication for Zonisamide oral suspension is same as the indication for the LD Zonegran which is as follows:

> Zonisamide is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

The Applicant plans to use labeling of the approved LD, Zonegran as the basis for supporting non-clinical pharmacology and toxicology as well as clinical sections of the labeling for its proposed drug product Zonisamide oral suspension.

The Agency was notified in a letter dated February 9, 2021, that ownership of NDA 214273 was transferred from Eton Pharmaceuticals to Pharmaceuticals Azurity Pharmaceuticals.

2. Clinical Study / Bridging Study

The Applicant conducted two bioequivalence (BE) studies to bridge the zonisamide oral suspension (100mg/5ml) to the listed drug (100mg capsules). Study 19-009 was performed with subjects in the fasting state while the second study, 19-010 was performed in the fed state.

The objective of both fasting and fed studies was to compare the rate and extent of absorption of Zonisamide from Zonisamide oral suspension 100mg/5ml of LM Manufacturing Limited, UK and Zonegran (Zonisamide) 100 mg Capsules, Marketing Authorization holder: (b) (4) (Reference Product) in healthy adult subjects and to monitor the safety and tolerability of a single dose of Zonisamide oral suspension 100mg/5ml in healthy adult subjects.

3. Study Design

Both studies 19-009 and 19-010 were randomized, single dose, two treatment, two sequence, two period, crossover studies. Randomization was carried out using the PROC PLAN procedure of SAS® (SAS Institute Inc., U.S.A.) version 9.4 in blocks such that the design was balanced. The order of receiving the test and reference products for each subject during the two periods of the study was determined according to the randomization schedule. Equal allocation of subjects to each sequence was ensured. In these studies, each subject received both the treatments [test drug (T) and reference drug (R)] across the two study periods. Hence, every subject acted as his own control and no separate group of subjects were required to act as the control group.

Table 2 Study Sequence (same for fasting and fed states)

	Period 1	Washout	Period 2
Sequence 1 (n=18)	Test (T)*	28d	Reference (R)†
Sequence 2 (n=18)	Reference (R)	28d	Test (T)
*100mg/5ml Suspension †100mg Tablet			

The total duration of the study was 33 days from the day of check-in of the first period till the end of the second period. Upon entering into the study, subjects were confined in the clinical facility of Synapse Labs Pvt. Ltd. (Majestic Plaza, Sr. No. 21/5, Nr. Nyati Empire, Kharadi Bypass, Kharadi, Pune, Maharashtra 411014, India) from not less than 10.50 hours pre-dose to provide pre-dose samples and to ensure an overnight fast of at least 10.00 hours before high-fat high-calorie non-vegetarian breakfast. Subjects remained in the facility up to 72.00 hours after dosing in each period.

The administration of each product was followed by a sufficiently long period of time, thus minimizing chances of measurable levels of drug being present before dosing in the following period. A washout period of 28 days (i.e., at least five elimination half-lives) was kept between each dose administration.

4. Results

Study 19-009

Table 3 Study 19-009, Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (Cmax and AUC0-72h) of Zonisamide in Fasting State (N = 34) (Including Outlier*) Source: Applicant CSR, Table 12, Page 81.

Parameters (Units)	Ln- transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)	
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
Cmax (ng/mL)	1219.0940	1211.0941	100.66	96.15	105.38
AUC0-72h (ng.hr/mL)	52826.6567	53314.1342	99.09	95.95	102.33

*Subject no (b) (6) was identified to be inconsistent in T/R (Test/Reference) ratios with the rest of the data for pharmacokinetic parameters Cmax and AUC0-72h for zonisamide. A clinical and bioanalytical investigation was done regarding outlier subject on various aspects and it was found that there was no root cause observed for inconsistent T/R ratio for this outlier subject of zonisamide. However, to avoid the biasedness in the results, the statistical analysis was performed on both the data sets i.e. including as well as excluding the outlier.

Applicant Conclusion

The 90 % confidence intervals of the differences of least squares means for the Ln-transformed pharmacokinetic parameters Cmax and AUC0-72h of zonisamide are within the bioequivalence acceptance limits of 80.00 – 125.00%. It is concluded that the test product (T) Zonisamide oral suspension 100mg/5ml of LM Manufacturing was found to be bioequivalent with reference product (R) Zonegran (Zonisamide) 100 mg Capsules, in healthy adult subjects under fasting conditions.

Study 19-010

Table 4 Study 19-010: Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (Cmax and AUC0-72h) of Zonisamide in Fed State (N = 35) (Including Outlier*) Source: Applicant CSR, Table 12, Page 83

Parameters (Units)	Ln- transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)	
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
Cmax (ng/mL)	1200.4297	1192.2964	100.68	98.00	103.44
AUC0-72h (ng.hr/mL)	54638.8153	54619.4901	100.04	98.45	101.65

*Subject no. (b) (6) was identified to be inconsistent in T/R (Test/Reference) ratios with the rest of the data for pharmacokinetic parameters Cmax for zonisamide. A clinical and bioanalytical investigation was done regarding outlier subject on various aspects and it was found that there was no root cause observed for inconsistent T/R ratio for this outlier subject of zonisamide. However, to avoid the biasedness in the results, the statistical analysis was performed on both the data sets i.e. including as well as excluding the outlier.

Applicant Conclusion

The 90 % confidence intervals of the differences of least squares means for the Ln-transformed pharmacokinetic parameters Cmax and AUC0-72h of zonisamide are within the bioequivalence acceptance limits of 80.00 – 125.00%. It is concluded that the test product (T) Zonisamide oral suspension 100 mg/5ml of LM Manufacturing was found to be bioequivalent with reference product (R) Zonegran (Zonisamide) 100 mg Capsules, in healthy adult subjects under fed conditions.

Safety

Study 19-009

Extent of Exposure

Table 5 Study 19-009 Extent of Exposure to Test Product (fasting)

Formulation	Treatment Start Date	# Subjects
CAPSULE (reference)	6/1/2019	18
CAPSULE (reference)	6/29/2019	17
SUSPENSION (Test)	6/1/2019	18
SUSPENSION (Test)	6/29/2019	17

Adverse Events

Three were 4 adverse event entries (TEAE) from three subjects in study 19-009. Clinical chemistry and hematology laboratory studies were obtained at baseline and end of study. All adverse events were identified in the post-study clinical laboratory safety evaluations. From among these adverse events the maximum severity occurred in subject (b) (6) This was an elevation to 1.8 X ULN for ALT at the EOS value, obtained 3 days after test product administration in period 2. There is no available comparator laboratory study value following reference product administered on study day 1 of period 1. There was no change from baseline in total bilirubin, direct or indirect bilirubin. The remaining TEAE clinical chemistry abnormalities were a small elevations of ALT and a small increase in serum potassium noted in the EOS values of subjects (b) (6) and (b) (6) respectively. There was no notable change in BUN or creatinine in the EOS values captured for patient (b) (6) see Table 4.

Table 6 Study 19-009 Oral Suspension BE Study (Fasting) TEAE

ID #	Laboratory Study	SAE	Severity	Study Period of Abnormality	Treatment Sequence	Baseline Value	EOS* Value	OORR± High	Multiple ULN	Test Product day	Baseline Lab Day	EOS Lab Day	Outcome	Comment
(b) (6)	ALT	N	MILD	FOLLOW-UP	RT	34.3	80.2	45	1.8	29	-16	32	Lost to Follow up†	Possibly related to test product, severity is mild based on 1.8 x ULN value of ALT with no change in total bilirubin. There is no change in Alkaline phosphatase
	AST	N	MILD	FOLLOW-UP	RT	32.1	50.3	40	1.3	29	-16	32	Lost to Follow up†	
	ALT	N	MILD	FOLLOW-UP	TR	38.3	54.3	45	1.2	1	-5	32	Lost to Follow up†	relation to test product is unlikely due to absence of temporal relationship.
	K+	N	MILD	FOLLOW-UP	RT	4	5.7	5.3	1.1	29	-4	32	Lost to Follow up†	the deviation from ULN is not reach a level of significant clinical concern.

* End of Study
† did not report to clinical facility for further follow-up
± Out of Reference Range

Reviewer Comment: There were four AEs from among 3 patients. These were laboratory value TEAE's from the SOC "investigations". The most notable laboratory abnormality was an increase in ALT value from within reference range at baseline / screening to 1.8 X ULN at EOS measurement, 3 days after test product administration. The remaining abnormal laboratory investigations included one each AST, ALT and potassium value measured at EOS. These were lessor elevations with a maximum of 1.3 X ULN. In the case of subject (b) (6) the ALT elevation is temporally proximate to the administration of the reference product treatment. Reference product treatment was administered 3 days prior to the measurement of the abnormal laboratory value and 32 days following the administration of the test product. Laboratory studies were not obtained in after each study period, only at screening (baseline), prior to period 1, and EOS, after period 2. Interpretation of the abnormal values obtained at EOS is difficult due to the absence of laboratory values from both study periods that would allow comparison of individual subject responses to both test and reference products. The limited abnormalities that are identified do not indicate a safety signal for the treatment with test product.

Dropouts

Subject nos. (b) (6) and (b) (6) did not report to the clinical facility for period 02 check in and thus were considered as 'dropout' from the study. EOS laboratory studies were not obtained from these subjects.

Clinical Laboratory Findings

Biochemistry

All EOS laboratory values are examined for deviation from reference range. There were 4 biochemistry entries at EOS that were OORR low. These were small deviations identified in BUN values in two subjects, uric acid in one subject and serum globulin in one subject. The BUN and uric acid deviations are of unlikely clinical significance and not considered further. The remaining OORR low value occurred in the serum globulin value of subject (b) (6). The measured value was 2.1 g/dl with lower limit of normal is 2.3g/dl. This deviation is not clinically significant in the context of the single dose bioequivalence study.

There were 3 biochemistry entries at EOS that were OORR high of a magnitude greater than 1.1 x ULN. These were ALT and AST identified in subject (b) (6) and AST in subject (b) (6). Both are included in adverse events discussed above, see Table 6.

Hematology

There were 6 entries from six subjects with hematology values > 1 X ULN. These occurred in the measurement of eosinophils in 5 subjects and lymphocytes in one subject. In 4 of the six entries the excess over reference range was 1.1 X ULN while in the remaining two entries, both eosinophils, the OORR high values were 1.2 and 1.3 X ULN. These deviations from reference range are not clinically significant in this context of this BE study.

There were five entries from five subjects with EOS hematology value entries that were OORR low. These all occurred in hemoglobin measurements. In one subject there was no change from baseline hemoglobin value while in a second there was an increase hemoglobin value from baseline to EOS. In the remaining 3 instances where subjects had an OORR low value, the percent changes from baseline

were -6.3%, -1.7% and -0.8%. These deviations from reference range are not clinically significant in the context of this BE study.

Vital Signs

Sampling time of observation: Test product mean Tmax in the fasting BE study 19-009 is 2.35 hours. Systolic blood pressure and pulse will be examined at baseline and +03 hours post product dosing.

Systolic Blood Pressure

Test Product

There are 21 patients with a decline in SBP with a mean decline of -7.9 mmHg while there were 9 subjects with an increase in blood pressure with a mean increase of 5.5 mmHg. The overall group mean and median percent change in systolic blood pressure from baseline (predose) to +03hrs following test product administration were -2.7 mmhg and -3.6 mmhg respectively.

Reference Product

There were 22 subjects with a decline in systolic blood pressure from baseline to +3hrs post dose with a mean decline of -7.6mmHg. There were 9 subjects with an increase in systolic blood pressure from baseline to + 3hrs post dose with a mean increase of +4.4 mmHg. The overall reference group mean and median percent change in systolic blood pressure from baseline (predose) to +03hrs following test product administration were -3.0 mmhg and -3.6 mmhg respectively.

Pulse

Test Product

There were 27 subjects with a decline in pulse (BPM) from baseline to +3hrs post dose with a mean and median decline of -7.8 BPM and -8 BPM respectively. There were 5 subjects with an increase in pulse from baseline to + 3hrs post dose with a mean and median increase of +5.6 BPM and +4 BPM respectively. The overall reference group mean and median percent change in pulse from baseline (predose) to +03hrs post test product administration were -7.0 BPM and-5.6 BPM respectively.

Reference Product

There were 24 subjects with a decline in pulse (BPM) from baseline to +3hrs post dose with a mean and median decline of -7.1 BPM and -7.0 BPM respectively. There were 7 subjects with an increase in pulse from baseline to + 3hrs post dose with a mean and median increase of 5.6 BPM and 6.0 BPM respectively. The overall reference group mean and median percent change in pulse from baseline (predose) to +03hrs (after) test product administration were -5.0 BPM and -5.7 BPM respectively.[1]

Reviewer Comment: Analysis of vital sign measurements following both test and reference product administration was performed with examination of baseline and +3hrs post dose. There was a higher

[1] Subject (b) (6) is excluded from the reference pulse assessment due to entry of a non physiologic pre-dose pulse of 15 BPM.

frequency of systolic blood pressure increase compared to decrease at the post administration measurement in both test and reference products. The distribution of these frequencies was very similar in the periods where test and reference products were administered. There was no notable difference in the group mean and median percent change in systolic blood pressure values between test and reference product. Analysis of pulse change between baseline and +3hrs after both test and reference product treatment periods was performed. The frequency of subjects with a decline in pulse was greater than those with a pulse increase with the proportions similar following test and reference period measurements. There was no notable difference in the group mean and median percent change in pulse values between test and reference product. Overall the vital sign screen did not reveal a notable difference between test and reference products.

Study 19-010

Adverse Events

There were 12 adverse events that occurred from among 8 subjects, see Table 7. Seven of these adverse events were elevation of ALT while 5 were increase in AST. Five of the 8 subjects with elevations in ALT or AST were in the TR treatment sequence with 3 subjects in the RT sequence. The distributions of ALT and AST increase in terms of multiples of upper limit of normal (ULN) are shown in Figure 1. There was a single entry for ALT that was > 2 X ULN, this occurred in subject (b) (6) in who was assigned the TR treatment sequence. The elevation of ALT thus occurred 31 days following est product administration, see Table 6. This same 31-day interval separates the test product administration day from EOS laboratory study day, resulting in an absence of temporal relationship between test product administration and the clinical laboratory abnormality for subjects (b) (6)

Subjects (b) (6) were in the RT treatment sequence where there is a temporal relationship between test product treatment and the observed OORR laboratory abnormality. Subjects (b) (6) had both elevations of ALT and AST while none exceeded 2 X ULN. Subject (b) (6) had an elevation of AST only. The total bilirubin and alkaline phosphatase values of subjects (b) (6) are examined. Values for both total bilirubin and alkaline phosphatase declined and there were no OORR high values identified in the assessment of subjects (b) (6) Subject (b) (6) whose EOS value of AST was 1.3 x ULN, had an increase in total bilirubin from 0.41mg/dl to 1.2 mg/dl with a small increase in alkaline phosphatase from 77 IU/L to 87 IU/L. Neither value was OORR high. This subject is reported as lost to follow up with no clinical laboratory measurements after the EOS value.

Figure 1 Study 19-010, ALT & AST Values as Multiple of ULN by Subject ID with Treatment Sequence Color Identifier red= RT, green= TR.

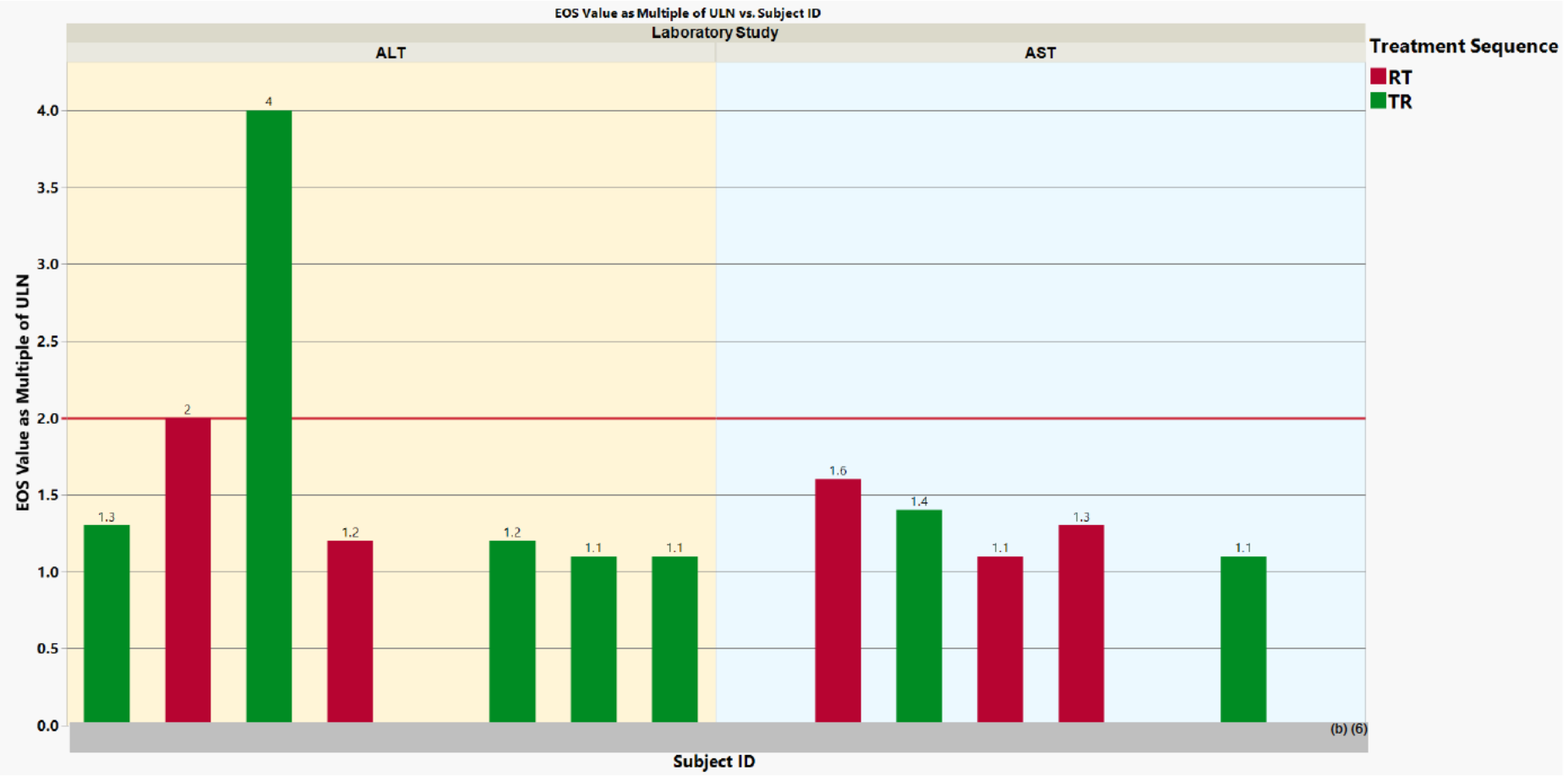

Table 7 Study 19-010 Oral Suspension BE Study (Fed) TEAE

ID #	Laboratory Study	SAE	Severity	Study Period of Abnormality	Treatment Sequence	Baseline Value	EOS* Value	OORR± High	Multiple ULN	Test Product day	Baseline Lab Day	EOS Lab Day	Outcome	Comment
(b) (6)	ALT	N	MILD	FOLLOW-UP	TR	41.5	57.2	45	1.3	1	-6	32	Lost to Follow up†	no temporal relationship to test product
	ALT	N	MILD	FOLLOW-UP	RT	19	90	45	2.0	29	-8	32	Lost to Follow up†	the baseline to post treatment elevation of ALT and AST may be related to test drug product. There is no subject comparator response to reference product. The change in values does not reach the level of significant clinical concern due to the maximum increase of 2 x ULN for ALT with a corresponding decline in total, direct and indirect bilirubin.
	AST	N	MILD	FOLLOW-UP	RT	15.6	65.5	40	1.6	29	-8	32	Lost to Follow up†	
	ALT	N	MILD	FOLLOW-UP	TR	42.1	181.6	45	4.0	1	-6	32	Lost to Follow up†	no temporal relationship to test product
	AST	N	MILD	FOLLOW-UP	TR	25.9	57	40	1.4	1	-6	32	Lost to Follow up†	
	ALT	N	MILD	FOLLOW-UP	RT	19.9	53	45	1.2	29	-7	32	Lost to Follow up†	the baseline to post treatment elevation of ALT and AST may be related to test drug product. There is no subject comparator response to reference product. The change in values does not reach the level of significant clinical concern due to the maximum increase of 1.2 x ULN for ALT with a corresponding decline in total, direct and indirect bilirubin.
	AST	N	MILD	FOLLOW-UP	RT	26.3	45.9	40	1.1	29	-7	32	Lost to Follow up†	
	AST	N	MILD	FOLLOW-UP	RT	21.7	51.6	40	1.3	29	-3	32	Lost to Follow up†	the baseline to post treatment elevation of AST may be related to test drug product. There is no subject comparator response to reference product. The change in values does not reach the level of significant clinical concern due to the maximum increase of 1.3 x ULN.
	ALT	N	MILD	FOLLOW-UP	TR	37.5	54.5	45	1.2	1	-3	32	Lost to Follow up†	
	ALT	N	MILD	FOLLOW-UP	TR	25.1	47.9	45	1.1	1	-6	32	Lost to Follow up†	no temporal relationship to test product
	AST	N	MILD	FOLLOW-UP	TR	35.8	44	40	1.1	1	-6	32	Lost to Follow up†	no temporal relationship to test product
	ALT	N	MILD	FOLLOW-UP	TR	38.6	51.6	45	1.1	1	-8	32	Lost to Follow up†	no temporal relationship to test product

* End of Study
† did not report to clinical facility for further follow-up
± Out of Reference Range

Reviewer Comment: The elevations of ALT and AST exceeded twice the upper limit of normal in only one instance, subject (b) (6) The position of test product administration 31 days before the identified abnormality does not support a causal relationship to test product. There was no elevation greater than twice the upper limit of normal in any other occurrence. In only 3 of eight subjects was the increase in ALT or AST temporally related to administration of test product. There was no associated elevation to OORR high of alkaline phosphatase or total bilirubin on examination in these subjects. Due to the observation that the maximum elevation of subject (b) (6) in the RT treatment sequence was limited to 2 X ULN with no other subject (b) (6)) had values approaching this threshold, there is no conclusion of a safety signal linked to the test product.

Clinical Laboratory Findings

Clinical Chemistry

Out of Reference Range Low

All EOS laboratory value are examined for deviation to OORR low. There was a single entry for uric acid that was OORR low at EOS. The measured value was zero at EOS compared to 5.2mg/dl at screening. The clinical significance of the absence of this breakdown product of purine found to be normal at baseline is uncertain. There is no comparative measurement available following reference product administration.

Out of Reference Range High

All EOS laboratory value are examined for deviation to OORR high. There were 16 entries from 10 subjects where a clinical chemistry value at EOS was found to be OORR high. Twelve (12) of these 16 entries were captured in the examination of adverse events above. There were 4 entries from four subjects remaining. Three of these entries are elevations of serum cholesterol. In 2 of the 3 cases the baseline cholesterol level was elevated and there was only a small additional percent increase from baseline to EOS. In the remaining case there was a 9% elevation from baseline to EOS in the TR sequence (no temporal relationship). The remaining OORR high value identified was an elevated uric acid that was elevated at baseline with an additional 13% increase at EOS. This elevation occurred in subject (b) (6) in the TR sequence.

Hematology

Out of Reference Range Low

There were 4 entries from 4 patients with EOS hematology parameters that were OORR low. These four entries were all hemoglobin values. Three of these subjects had no change or an increase in hemoglobin from baseline value. In the remaining case there was a decline from 12.8g/dl at baseline to 11.9 g/dl at EOS in the RT study sequence. The clinical significance of this change in a single dose study is uncertain. There may be a contribution from study related phlebotomy.

Out of Reference Range High

There were five entries from five patients that had OORR high values for eosinophil percent value. Two subjects had OORR high baseline values. From among the remaining 3 subjects two were in the TR

sequence with absence of temporal relationship to the test product. The remaining subject had a 29% increase in eosinophils from baseline to EOS (5.6% to 7.2%). This value is 1.2 X ULN and is not of clinical significance.

Vital Signs

Sampling time of observation: Test product mean Tmax in the fasting BE study 19-009 is 2.35 hours. Systolic blood pressure and pulse will be examined at baseline and +03 hours post dosing.

Systolic Blood Pressure

Test Product

There are 16 patients with a decline in blood pressure with a mean decline of 5.25mmHg while there were 14 subjects with an increase in blood pressure with a mean increase of 3.6mmHg. The overall group mean and median percent change in systolic blood pressure from baseline (predose) to +03hrs post test product administration were -0.8 mmhg and 0 mmhg respectively.

Reference Product

There were 25 subjects with a decline in systolic blood pressure from baseline to +3hrs post dose with a mean decline of 6.64mmHg. There were 7 subjects with an increase in systolic blood pressure from baseline to + 3hrs post dose with a mean increase of 4.9mmHg. The overall reference group mean and median percent change in systolic blood pressure from baseline (predose) to +03hrs post test product administration were -3.1 mmhg and -3.5 mmhg respectively.

Pulse

Test Product

There were 17 subjects with a decline in pulse (BPM) from baseline to +3hrs post dose with a mean and median decline of -6.4 BPM and -6 BPM respectively. There were 14 subjects with an increase in pulse from baseline to + 3hrs post dose with a mean and median increase of +4.9 BPM and +4 BPM respectively. The overall reference group mean and median percent change in pulse from baseline (predose) to +03hrs post test product administration were -1.2 BPM and 0 BPM respectively.

Reference Product

There were 22 subjects with a decline in pulse (BPM) from baseline to +3hrs post dose with a mean and median decline of -7.8 BPM and -8 BPM respectively. There were 14 subjects with an increase in pulse from baseline to + 3hrs post dose with a mean and median increase of +7.4 BPM and +6 BPM respectively. The overall reference group mean and median percent change in pulse from baseline (predose) to +03hrs (after) test product administration were -3.1 BPM and -4.2 BPM respectively.

Reviewer Comment: Examination of systolic blood pressure and pulse change from baseline to +3hrs after test product administration revealed no substantive change. The frequency of subjects with an increase in SBP and Pulse was similar to the frequency of those with a decrease in SBP and pulse on examination of the test product values. The test product group mean and median change from baseline

SBP and Pulse were small. There was a small trend toward decline from baseline to +3hrs for the metrics of SBP and Pulse following reference product administration. The reference product was noted to have a trend toward a decline in pulse not observed in the test product values.

5. Summary & Conclusion

The bridging study submitted by the applicant demonstrated bioequivalence between zonisamide oral suspension (test product) and the listed drug, Zonegran capsules (listed drug). Safety data from the fasting and fed bridging studies were reviewed including adverse events, clinical laboratory studies and vital signs.

Examination of adverse event data for the test product revealed adverse events similar to those identified in current Zonegran labeling. Change in laboratory values from screening visit to end of study were examined. The adverse event profile, laboratory data and vital sign screening revealed the test product had no safety signal that was uniquely different from the reference product.

6. Recommendation

From a clinical standpoint there is adequate support for approval of the zonisamide oral suspension.

However, the Product Quality reviewers identified issues with the proposed manufacturing sites which require a Complete Response rather than an approval in this review cycle.

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/s/

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