

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 211280 / Serial Number 0001 -

Drug Name: Lasmiditan (LY573144)
50 mg, 100 mg (b) (4) tablets to be taken orally

Indication(s): Acute Migraine with or without Aura in Adults

Applicant: Eli Lilly and Company

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Biometrics Division: Division of Biometrics 1

Statistical Reviewer: Jinnan Liu, Ph.D., Statistical Reviewer

Concurring Reviewers: Kun Jin, Ph.D., Statistical Team Leader
Hsien Ming Hung, Ph.D., Division Director

Medical Division: Division of Neurology Products

Clinical Team: Viveca Livezey, M.D., Clinical Reviewer
Heather Fitter, M.D., Clinical Team Leader
Nicholas Kozauer, M.D., Associate Director
Eric Bastings, M.D., Deputy Director
Billy Dunn, M.D., Division Director

Project Manager: (Andrew) Emiliou Papanastasiou, Pharm D

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1 EXECUTIVE SUMMARY

This NDA submission is to obtain marketing authorization for Lasmiditan in the treatment of acute migraine in adults. The study doses are 50 mg, 100 mg and 200 mg tablet.

The pivotal efficacy evidence is from two Phase III studies 301 (LAHJ) and 302 (LAHK).

1.1 Conclusions and Recommendations

The two pivotal studies in patients with acute migraine presented a statistical evidence that Lasmiditan, at 50 mg, 100 mg, or 200 mg tablets to be taken orally is efficacious for the treatment of acute migraine based on increased rate of pain free and MBS (Most Bothersome Symptom) free at two hours post dose. The Lasmiditan treated groups show an efficacy result better than that of the placebo control group.

1.2 Brief Overview of Clinical Study 301 (LAHJ) and 302 (LAHK)

The Phase 3 study 301 is a study for acute migraine with two dose levels 100 mg and 200 mg, The Phase 3 study 302 is a study for acute migraine with three dose levels 50 mg, 100 mg and 200 mg,

Both studies are multi-center, randomized, double-blinded, parallel group and placebo controlled. Both studies are complete and the results are included in the current submission.

1.3 Statistical Issues and Findings

No major statistical issues were found.

2 INTRODUCTION

Two studies: 301 (LAHJ) and 302(LAHK) are included in this statistical review for the efficacy evaluation.

2.1 Overview

Lasmiditan is being developed as a novel acute therapy for acute migraine with a distinct mechanism of action from triptans. It selectively targets 5-hydroxytryptamine (5HT)-1F receptors on neurons in the central and peripheral trigeminal system to alleviate migraine and lacks the vasoconstrictor activity inherent with triptans.

Table 1 List of All Studies included in Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
301/LAHJ	MC, R, DB, PG, PC trial (up to 8 wks or within 7 days of treating single migraine attack)	LTN 100 mg/ N = 503	Primary: Pain Free at 2 hours	28.2% in LTN 100 mg
		LTN 200 mg/ N = 518		32.2 % in LTN 200 mg
		Placebo/ N _p = 524	Key Secondary: MBS Free at 2 hours	15.3% in Placebo With p value versus Placebo both <.001
302/LAHK	MC, R, DB, PG, PC trial (up to 8 wks or within 7 days of treating single migraine attack)	LTN 50 mg/ N = 556	Primary: Pain Free at 2 hours	40.9% in LTN 100mg
		LTN 100mg/ N = 532		40.7% in LTN 200 mg
		LTN 200 mg/ N = 528	Key Secondary: MBS Free at 2 hours	29.5% in Placebo With p value versus Placebo both <.001
		Placebo/ N _p = 540		28.6% in LTN 50 mg 31.4% in LTN 100 mg 38.8 % in LTN 200 mg 21.3% in Placebo With p value versus Placebo as 0.003, <.001, and < .001

MC: multi-center, R: randomized, DB: double-blinded, PG: parallel group, PC: placebo controlled.
(Source: Sponsor' result)

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form.

At the time of review the following is the link to the EDR Location:

<\\CDSESUB1\evsprod\NDA211280\0001>

Additional SAS codes and datasets have been provided in this link:

<\\CDSESUB1\evsprod\NDA211280\0022>

The additional SAS codes and datasets were provided in the Module 5, among other things under Sequence number 0022 on 4/2/2019, by the sponsor in their regulatory response to our mid-cycle communication.

- (1) SAS Programs used to create each of the ADaM datasets from SDTM datasets with TOC (Table of Content): [SAS Programs TOC_ADaM_301](#) and [SAS Programs TOC_ADaM_302](#).
- (2) A supplemental dataset (SUPPEX.xpt) for each of the Phase 3 Studies 301/LAHJ and 302/LAHK, along with a corresponding define document, which contains the timestamp data for when patients entered their dosing information.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are some minor issues with the data quality and analysis in both studies 301 and 302.

- (1) There were a very small number of patients who did not treat a qualified migraine being that the pain severity was 0 or 1 on a scale of 4 (0 =no pain, 1 = mild, 2= moderate, 3= severe). The protocol specified that the patient should wait till the pain reaches 2 or 3. We do not know whether this is a data entry error or data processing error. We have conducted worst case scenario sensitivity analysis. It did not alter the efficacy conclusion.
- (2) There were about half of patients who did not enter the MBS (Most Bothersome Symptom) choice in the e-diary at the time of the headache attack prior to taking the drug, but after taking the drug. The sponsor has sent in information amendment. Most of the patients did enter this information within 5 minutes of dosing, which we consider reasonable.

In summary, the above data quality issues appear to be minor, and do not seem to affect the results of primary analyses.

3.2 Evaluation of Efficacy Study – 301(LAHJ)

3.2.1 Description of the Study

This study had its first subject enrolled on 27 April 2015, and the last subject completed on 12 August 2016. The study report was created on the date of 20 February 2017.

The study was conducted at 99 centers in the United States of America.

The purpose of this study was to evaluate the effect of Lasmiditan 100 mg and 200 mg compared to placebo on the rates of pain free at 2 hours and MBS free at 2 hours in subjects with acute migraine.

Eligible subjects were adults 18 years of age or above with history of disabling migraine for at least 1 year with 3 to 8 migraine attacks per month, with < 15 headache days per month, with migraine onset before the age of 50 years.

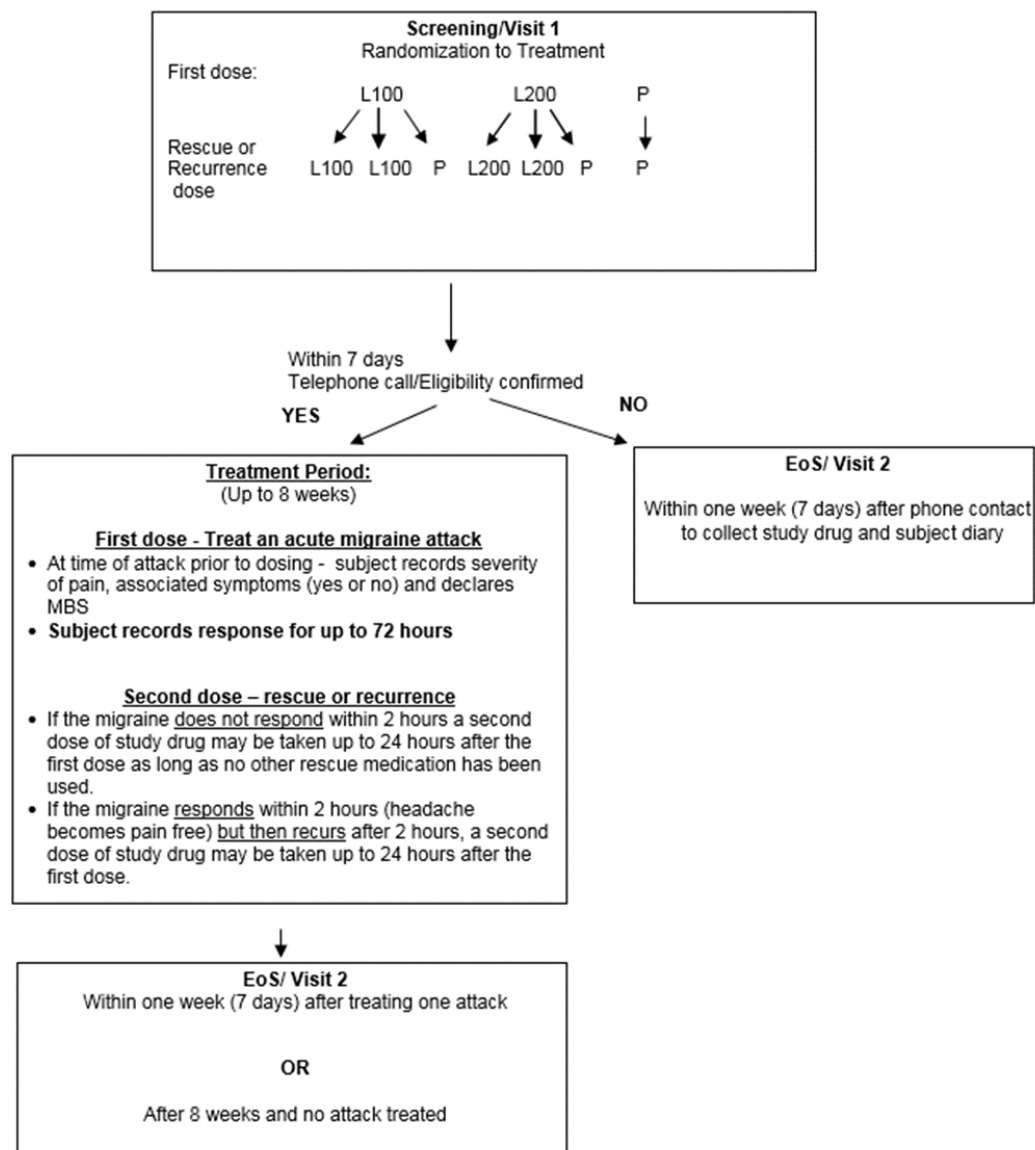
The total time on study was approximately 11 weeks. At the screening visit (Visit 1), potential eligible subjects were identified, randomized, dispensed study drug, and instructed not to treat an attack until their eligibility had been confirmed by phone within 7 days once all screening evaluations were complete. Once their eligibility was confirmed by the phone, subjects were asked to treat a qualifying migraine attack with study drug on an outpatient basis for a treatment period of up to 8 weeks. Within 1 week (7 days) of treating a migraine attack, subjects were asked to return for an end of study (EoS) visit (Visit 2).

Headache pain-free was defined as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0) at the 2 hours post dose timepoint. The protocol specifies that the patient should wait till the pain reaches “Moderate” to “Severe” to take the study drug.

About the randomization, subjects were centrally randomized to receive 100 mg or 200 mg or placebo for the first dose in a 1:1:1 ratio and the second dose for rescue or recurrence of migraine (if needed). Subjects were stratified (yes or no) for use of concomitant medications that reduced the frequency of migraine episodes. The efficacy analysis was planned to be based on the first dose data only.

Planned sample size was to recruit about 742 per group (total 2225) to undergo screening to ensure that at least 570 per group complete the treatment period. A sample size of 570 per group were needed to detect with power > 90% a difference in pain free response rates of 7.4%, 13.6% and 18.8% between placebo, 100 mg and 200 mg respectively. These rates were taken from the Phase 2 study COL-MIG-202.

Figure 1 Schematic of Study Design – Study 301(LAHJ)



EoS = End of Study; L100 = lasmiditan 100 mg, L200 = lasmiditan 200 mg; MBS = Most Bothersome Symptom; P = placebo.

(Source: study protocol.)

3.2.2 Efficacy Variables

3.2.2.1 Primary Endpoints

The two co-primary endpoints for this study were rates of pain free at 2 hours and MBS free at 2 hours post the first dose treating a qualifying acute migraine attack during the double-blind treatment phase.

3.2.2.2 Secondary Endpoints

Secondary efficacy endpoints included:

- 1) Pain relief at 2 hours.
- 2) 24-hour sustained pain free at 24 hours.

Subjects used an electronic diary (e-Diary) to record their response to the first dose over the next 48 hours and may continue to record their responses up to 72 hours depending on whether a second dose was used.

The sponsor has listed many secondary endpoints as exploratory with no pre-specified plan to control the Type 1 error. We decided not to include those results in our review except the above two that were considered relevant and potentially supportive efficacy evidence by the clinical review team.

3.2.3 Statistical Analysis Methods

Efficacy analyses were based on the corrected mITT population, which included subjects who had a qualified migraine attack and took the investigational product within 4 hours of onset and completed at least 1 post dose e-Diary measurement. Subjects were grouped based on the assigned treatment. Efficacy analyses were based on the first dose.

The primary and secondary endpoints were analyzed using a logistic regression model with treatment group and background use of medication to reduce the frequency of migraine episodes as covariates. The missing data were imputed as nonresponses.

For treatment comparisons, an estimate of the rate of achieving a response, as well as the corresponding p-value using Wald's test, will be computed.

3.2.3.1 Multiplicity Adjustment

The multiplicity adjustment method was pre-specified and deemed to be adequate.

A gatekeeping procedure was pre-specified to maintain the 2-sided study-wise Type I error at 0.05 between the two drug doses and the two co-primary endpoints.

The following hypotheses will be tested sequentially, in the following order:

- (1) Treatment comparison, between 200 mg and placebo, as measured by subjects who are pain-free at 2 hours post-dose.
- (2) Treatment comparison, between 200 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.
- (3) Treatment comparison, between 100 mg and placebo, as measured by subjects who are pain-free at 2 hours post-dose.
- (4) Treatment comparison, between 100 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.

If one of the analyses is not statistically significant, then all subsequent analyses will be exploratory rather than confirmatory.

3.2.4 Patient Results

3.2.4.1 Patient Disposition

Due to the pre-specified rule that the primary analyses should be based on the first dose, only first dose data will be used in the efficacy analyses.

A total of 2231 subjects were randomized: 496 subjects to receive 100 mg and 100 mg; 248 subjects to receive 100 mg and Placebo; 496 subjects to receive 200 mg and 200 mg; 249 subjects to receive 200 mg and Placebo; 742 subjects to receive Placebo and Placebo.

Overall, 1922 (86.1%) subjects completed the study and 309 (13.9%) subjects discontinued the study for the following reasons: randomization failure, lost to follow-up, subject request, and non-compliance with protocol, adverse event, death, pregnancy, investigator request, and sponsor request.

Table 2 Patient Disposition (1st Dose and 2nd Dose) – Study 301 (LAHJ)

Subject Disposition	L100 mg/ L100 mg N=496	L100 mg/ Placebo N=248	L200 mg/ L200 mg N=496	L200 mg/ Placebo N=249	Placebo/ Placebo N=742	All Subjects N=2231
Randomized, n (%)	496 (100.0%)	248 (100.0%)	496 (100.0%)	249 (100.0%)	742 (100.0%)	2231 (100.0%)
Treated With 1 st Dose	433 (87.3%)	197 (79.4%)	406 (81.9%)	203 (81.5%)	617 (83.2%)	1856 (83.2%)
Treated With 2 nd Dose	203 (40.9%)	86 (34.7%)	159 (32.1%)	79 (31.7%)	401 (54.0%)	928 (41.6%)
Completed Study, n (%)	439 (88.5%)	209 (84.3%)	419 (84.5%)	212 (85.1%)	643 (86.7%)	1922 (86.1%)
Treated	421 (95.9%)	192 (91.9%)	397 (94.7%)	196 (92.5%)	599 (93.2%)	1805 (93.9%)
Not Treated	18 (4.1%)	17 (8.1%)	22 (5.3%)	16 (7.5%)	44 (6.8%)	117 (6.1%)
Discontinued, n (%)	57 (11.5%)	39 (15.7%)	77 (15.5%)	37 (14.9%)	99 (13.3%)	309 (13.9%)
Treated	12 (21.1%)	5 (12.8%)	9 (11.7%)	7 (18.9%)	18 (18.2%)	51 (16.5%)
Not Treated	45 (78.9%)	34 (87.2%)	68 (88.3%)	30 (81.1%)	81 (81.8%)	258 (83.5%)

Treated but Did Not Return for End of Study Visit, n (%)	9 (1.8%)	3 (1.2%)	5 (1.0%)	5 (2.0%)	9 (1.2%)	31 (1.4%)
Reason for Discontinuation N= 309						
Discontinued, n (%)	57(100%)	39(100%)	77(100%)	37(100%)	99(100%)	309 (100%)
Adverse event	0	0	1 (1.3%)	1 (2.7%)	0	2 (0.6%)
Death	0	0	1 (1.3%)	0	0	1 (0.3%)
Lost to follow-up	16 (28.1%)	21 (53.8%)	23 (29.9%)	11 (29.7%)	42 (42.4%)	113 (36.6%)
Non-compliance with	8 (14.0%)	2 (5.1%)	8 (10.4%)	3 (8.1%)	7 (7.1%)	28 (9.1%)
Pregnancy	0	0	1 (1.3%)	0	1 (1.0%)	2 (0.6%)
Subject request	10 (17.5%)	2 (5.1%)	9 (11.7%)	7 (18.9%)	14 (14.1%)	42 (13.6%)
Investigator request	1 (1.8%)	1 (2.6%)	0	1 (2.7%)	0	3 (1.0%)
Sponsor request	0	0	2 (2.6%)	0	1 (1.0%)	3 (1.0%)
Randomization failure	22 (38.6%)	13 (33.3%)	32 (41.6%)	14 (37.8%)	34 (34.3%)	115 (37.2%)

(Source: modified from the Table 10.1 in the sponsor's study report, verified by the statistical reviewer.)

A total 1856 subjects used at least 1 dose of the study drug either the first dose or the second dose and were analyzed for safety.

A total of 1671 subjects used the first dose and provided at least 1 post dose measurement and were included in the ITT population. A total of 1545 subjects treated a qualifying migraine attack within 4 hours onset with the first dose and provided at least 1 post dose assessment and were included in the mITT population.

In our own analysis, we found 29 patients out of the 1545 mITT population whose pain severity were 0 or 1 at the time of dosing (the pre-specified protocol requires the pain severity to reach 2 or 3). The efficacy result presented by the sponsor still holds in the sense that p-values did not change (all remain <.001) by removing these 29 patients, but the estimates of the rates were slightly different.

After discussion with the clinical review team, we decided to remove these 29 patients. A total of 1516 subjects were analyzed for efficacy as the "corrected mITT population".

Table 3 Patient Disposition (1st Dose) - Study 301 (LAHJ)

Analysis Populations, n (%)	L100 mg N=744	L200 mg N=745	Placebo N=742	All Subjects N=2231
Safety Population	630 (84.7%)	609 (81.7%)	617 (83.2%)	1856 (83.2%)
ITT Population	562 (75.5%)	555 (74.5%)	554 (74.7%)	1671 (74.9%)
mITT Population	503 (67.6%)	518 (69.5%)	524 (70.6%)	1545 (69.3%)
<i>Mild Headache Recorded at Time of Dosing</i>	5	15	9	29
Corrected mITT Population	498 (66.9%)	503 (67.5%)	515 (69.4%)	1516 (67.95%)
PP Population	435 (58.5%)	464 (62.3%)	465 (62.7%)	1364 (61.1%)

(Source: modified from the Table 11.1 in the sponsor's study report, verified by the statistical reviewer.)

3.2.4.2 Patient Demographics

Of the 1516 subjects in the corrected mITT population, majority were women (83.6%), white (77.8%), and the mean age was 41.8 (18 to 78) years. The treatment groups were balanced for these baseline demographic characteristics.

Table 4 Patient Baseline Demographics – corrected mITT – Study 301 (LAHJ)

	L100 mg N=498	L200 mg N=503	Placebo N=515	All Subjects N=1516
Age (years), n	498	503	515	1516
Mean (SD)	42.06 (11.59)	41.28 (12.08)	42.01 (12.44)	41.79 (12.04)
Median	42.0	41.0	42.0	41.00
Minimum	18	18	18	18
Maximum	74	72	78	78
Gender, n (%)	498	503	515	1516
Female	402 (80.72%)	424 (84.29%)	441 (85.63%)	1267 (83.6%)
Male	96 (19.28%)	79 (15.71%)	74 (14.37%)	249 (16.4%)
Race, n (%)	498	503	515	1516
American Indian or Alaska Native	4 (0.80%)	5 (0.99%)	1 (0.19%)	10 (0.66%)
Asian	2 (0.40%)	2 (0.40%)	2 (0.39%)	6 (0.40%)
Black or African American	87 (17.47%)	98 (19.48%)	86 (16.70%)	271 (17.88%)
Native Hawaiian or other Pacific Islander	1 (0.20%)	2 (0.40%)	1 (0.19%)	4 (0.26%)
White	384 (77.11%)	382 (75.94%)	414 (80.39%)	1180 (77.84%)
Other	10 (2.01%)	9 (1.79%)	6 (1.17%)	25 (1.65%)
Multiple	10 (2.01%)	5 (0.99%)	5 (0.97%)	20 (1.32%)
BMI (kg/m²), n	497	502	513	1512
Mean (SD)	30.28(8.039)	31.44(8.44)	29.996 (7.36)	30.57 (7.97)
Median	28.80	29.85	28.80	29.20
Minimum	16.90	16.10	16.10	16.10
Maximum	68.90	67.20	61.10	68.90

BMI = body mass index

(Source: Reviewer's own analysis.)

3.2.4.3 Patient Baseline Disease Characteristics

Baseline disease characteristics were consistent with a migraine population and well balanced across the treatment groups.

The mean (SD) duration of years with migraine at baseline was 19.32 (12.998), 18.93(12.84) and 19.26(12.47) years in the 100 mg, 200 mg, and the placebo groups, respectively.

The mean (SD) migraine per month in the past 3 months at baseline was 5.03 (1.74), 5.13(1.73), and 5.22(1.77), respectively.

Table 5 Patient Baseline Disease Characteristics -corrected mITT - Study 301 (LAHJ)

	L100 mg N=498	L200 mg N=503	Placebo N=515	All Subjects N=1516
Smoking History, n (%)	475	478	490	1443
Never	330 (69.47%)	330 (69.04%)	347 (70.82%)	1007 (69.79%)
Former	79 (16.63%)	83 (17.36%)	80 (16.33%)	242 (16.77%)
Currently	66 (13.89%)	65 (13.60%)	63 (12.86%)	194 (13.44%)
Family History of CAD, n (%)	498	503	515	1516
Yes	184 (36.95%)	170 (33.80%)	173 (33.59%)	527 (34.76%)
No	314 (63.05%)	333 (66.20%)	342 (66.41%)	989 (65.24%)
CV Risk Factors, n (%)	498	503	515	1516
Female	402	424	441	1267
Yes	321 (64.46%)	349 (69.38%)	355 (68.93%)	1025 (67.61%)
No	81 (16.27%)	75 (14.91%)	86 (16.70%)	242 (15.96%)
Male	96	79	74	249
Yes	86 (17.27%)	69 (13.72%)	67 (13.01%)	222 (14.64%)
No	10 (2.01%)	10 (1.99%)	7 (1.36%)	27 (1.78%)
Duration of Migraine History (years), n	498	503	515	1516
Mean (SD)	19.32 (12.998)	18.93 (12.84)	19.26 (12.47)	19.17(12.76)
Median	17.71	17.84	17.42	17.56
Minimum	0	0	0	0
Maximum	63.54	59.42	72.76	72.76
Avg Migraines/Month in Past 3 Months, n	498	503	515	1516
Mean (SD)	5.03 (1.74)	5.13 (1.73)	5.22 (1.77)	5.13 (1.75)
Median	5.0	5.0	5.0	5.0
Minimum	1	3	3	1
Maximum	12	10	16	16
Experienced Migraine W/O Aura, n (%)	498	503	515	1516
With Aura	155 (31.12%)	159 (31.61%)	157 (30.49%)	471 (31.07%)
Without Aura	343 (68.88%)	344 (68.39%)	358 (69.51%)	1045 (68.93%)
Use of Medication Reducing Migraines, n (%)	498	503	515	1516
Yes	126 (25.30%)	128 (25.45%)	129 (25.05%)	383 (25.26%)
No	372 (74.70%)	375 (74.55%)	386 (74.95%)	1133 (74.74%)

CAD = coronary artery disease; CV = cardiovascular;
(Source: Reviewer's own analysis.)

3.2.5 Results and Conclusions

3.2.5.1 Efficacy Results of the Primary Endpoints

The results reported by the sponsor were mostly confirmed except the 29 patients whose treated migraine attacks did not reach the required severity at the time of dosing which we decided to exclude from the analyses after discussion with the clinical review team.

The efficacy result presented by the sponsor still holds in the sense that p-values did not change by removing these 29 patients, but the estimates of the rates were slightly different, as can be seen in the following table which shows side by side our result versus the sponsor's result.

Table 6 Primary Endpoint Analyses- Study 301 (LAHJ)

	Corrected mITT			mITT		
	Lasmiditan			Lasmiditan		
	100 mg	200 mg	Placebo	100 mg	200 mg	Placebo
Pain Moderate to Severe at time of dosing	498	503	515	503	518	524
Pain Free at 2 hours	141	160	79	142	167	80
%	28.31%	31.81%	15.34%	28.2%	32.2%	15.3%
p-value	<.001	<.001		<.001	<.001	
MBS recorded at time of dosing	464	467	480	469	481	488
MBS Free at 2 hours	191	190	142	192	196	144
%	41.16%	40.69%	29.58%	40.9%	40.7%	29.5%
p-value	<.001	<.001		<.001	<.001	

P-values were from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates. (Source: reviewer's own analysis and sponsor's analysis verified by the reviewer.)

The primary analysis for Pain free status at 2 hours included 1516 patients. There was a statistically significant increase in the rate of pain free at 2 hours without rescue medication from 15.34% in the placebo group to 28.31% in the 100 mg group and 31.81% in the 200 mg group. The p-values versus placebo were both < .001.

The primary analysis for MBS free status at 2 hours included 1411 patients. There was a statistically significant increase in the rate of MBS free at 2 hours without rescue medication from 29.58% in the placebo group to 41.16% in the 100 mg group and 40.69% in the 200 mg group. The p-values versus placebo were both < .001.

Patients with missing data at 2-hour time point were counted as treatment failures. As a clinical rule, patients with rescue medication use prior to the 2-hour time point were considered as treatment failures.

3.2.5.2 Missing Data and Sensitivity Analyses

The overall missing rate was relatively low for this study and were similar among the groups as can be seen from the following table which shows the missing data patient counts for each group.

If the subject did not record a pain severity at the time of dosing, then this subject was not included in the analysis. If the subject did not record a pain severity rating at 2 hours post dosing, then this subject's pain free status at 2 hours was set as missing.

Table 7 Patient Counts at Time of Dosing and Two Hours (rescue*= failure)– Study 301(LAHJ)

	Pain at Time 0	Pain at 2 Hours	Missing n	Missing %	MBS at Time 0	MBS at 2 Hours	Missing n	Missing %
100 mg	498	431	67	13.45%	464	405	61	13.15%
200mg	503	426	77	15.31%	467	405	73	15.63%
placebo	515	442	73	14.17%	480	421	68	14.17%

(Source: Reviewer's own analysis.)

Similarly, if the subject did not provide a symptom of migraine (either nausea, phonophobia, or photophobia) at the time of dosing, this subject was not be included in the MBS analysis. If the subject failed to record a symptom rating at 2 hours post dosing, then this subject's MBS status at 2 hours post dosing was set as missing. If the subject provided at least a symptom at the time of dosing, but did not designate one as the most bothersome, this subject was considered MBS-free only if all symptoms present at time of dosing were no longer present at the 2 hours timepoint.

As a clinical rule, if the subject took any rescue medication prior to the 2 hours timepoint, then this patient was considered as treatment failure.

In the primary efficacy analysis, subjects with missing data at 2 hours timepoint were counted as treatment failures.

Table 8, 9 and 10 show the breakdown of patient counts with or without actual efficacy measurements at 2 hours (Yes/No/Missing); the rescue medication use; and the patient efficacy results after applying the clinical rule of rescue medication use before 2 hours = failure.

Table 8 Descriptive Patient Counts for Data Status at 2 Hours – corrected mITT- Study 301 (LAHJ)

	Pain			MBS		
100 mg	498	163	Yes	464	214	Yes
		264	No		186	No
		71	2-Hour missing		64	2-Hour Missing
200 mg	503	173	Yes	467	206	Yes
		248	No		184	No
		82	2-Hour missing		77	2-Hour Missing
Placebo	515	88	Yes	480	155	Yes
		350	No		254	No
		77	2-Hour missing		71	2-Hour Missing

(Source: Reviewer's own analysis.)

Table 9 Descriptive Patient Counts for Rescue Meds before 2-hours – corrected mITT- Study 301 (LAHJ)

	Pain			MBS		
100 mg	45	22	Yes	41	23	Yes
		19	No		15	No
		4	2-Hour missing		3	2-Hour missing
200 mg	34	13	Yes	29	16	Yes
		16	No		9	No
		5	2-Hour missing		4	2-Hour missing
Placebo	31	9	Yes	27	13	Yes
		18	No		11	No
		4	2-Hour missing		3	2-Hour missing

(Source: Reviewer's own analysis.)

Table 10 Counts for Patients' Data Status at 2H (rescue* = failure) – corrected mITT- Study 301 (LAHJ)

	Pain			MBS		
100 mg	498	141	Yes	464	191	Yes
		290	No		212	No
		67	2-Hour Missing		61	2-Hour Missing
200 mg	503	160	Yes	467	190	Yes
		266	No		204	No
		77	2-Hour Missing		73	2-Hour missing
Placebo	515	79	Yes	480	142	Yes
		363	No		270	No
		73	2-Hour Missing		68	2-Hour Missing

(Source: Reviewer's own analysis.)

In the sensitivity analysis performed by the sponsor the following MI (multiple imputation) was used:

- (1) Subjects with missing data from the placebo group were assumed to respond similarly with similar placebo subjects with available data.
- (2) Missing data for subjects from the drug groups were imputed using a model drift towards the mean response of the placebo group.

Results for the sensitivity analyses using MI were consistent with those observed for the primary analysis. Results from the per-protocol analysis were also consistent with the efficacy analysis.

Table 11 Sensitivity Analyses – Study 301 (LAHJ)

	Corrected mITT using Multiple Imputation			mITT using Multiple Imputation			Per-Protocol		
	Lasmiditan			Lasmiditan			Lasmiditan		
	100 mg	200 mg	Placebo	100 mg	200mg	Placebo	100 mg	200 mg	Placebo
Pain Moderate to Severe at time of dosing	498	503	515	503	518	524	435	464	465
Pain Free at 2 hours	151	172	90	162	195	94	136	163	77
%	30.3%	34.2%	17.5%	32.3%	37.7%	18.0%	31.3%	35.1%	16.6%
p-value	<.001	<.001		<.001	<.001		<.001	<.001	
MBS recorded at time of dosing	464	467	480	469	481	488	405	433	436
MBS Free at 2 hours	209	212	162	221	233	171	183	188	138
%	45.0%	45.4%	33.8%	47.2%	48.4%	36.1%	45.2%	43.4%	31.7%
p-value	<.001	<.001		<.001	<.001		<.001	<.001	

(Source: reviewer's analysis and Table 14.2.1.4, 14.2.1.3 and Table 14.2.2.4 from the study report, verified by the reviewer.)

3.2.5.3 Efficacy Results of the Secondary Endpoints

Pain relief at 2 hours

Pain relief was defined as a reduction in pain severity from moderate (2) or severe (3) at the time of dosing to mild (1) or none (0), or a reduction from mild (1) to none (0), at the indicated assessment time, with no rescue medication before the 2 hours timepoint. Since the definition for pain relief included pain rating of 1 at time of dosing, the mITT population was used for the analysis. The proportions of subjects with pain relief at 2 hours were 53.68%, 55.02%, and 39.50% for the 100 mg, 200 mg and placebo groups, respectively ($p < .001$ for both versus placebo). The sponsor's result on Pain Relief at 2 Hours in Table 11-16 in the study report was not accurate for two reasons: it was based on the ITT population which included patient who treated the migraine attack 4 hours after the onset and it did not set patients with rescue medication use before 2 hours as failure.

Table 12 Responder Rate: Pain Relief at 2 Hours – mITT Population - Study 301 (LAHJ)

	L100 mg	L200 mg	Placebo
Mild, Moderate, or Severe Headache Recorded at Time of Dosing	503	518	524
Headache Relief, n (%)			
2 hours post-dose	270 (53.68%)	285 (55.02%)	207 (39.50%)
p-value* vs Placebo	<.001	<.001	

P-value* = nominal significant only. (Source: reviewer's own analysis).

24-hour sustained pain free at 24 hours

Sustained pain-free at 24 hours was defined as pain-free at 2 hours after first dose and at the 24 hours, having not used any medications after the first dose. The proportions of subjects with sustained pain free at 24 hours were 15.1%, 18.9%, and 7.8% for the 100 mg, 200 mg and placebo groups, respectively ($p < .001$ for both versus placebo).

Table 13 Responder Rate: Sustained Pain Free at 24 Hours – mITT - Study 301 (LAHJ)

	Lasmiditan		Placebo
	100 mg	200 mg	
Pain Mild, Moderate to Severe at time of dosing	503	518	524
Pain Free at 2 hours	142	167	80
%	28.2%	32.2%	15.3%
p-value	<.001	<.001	
Pain Free at 24 Hours	157	201	122
%	31.2%	38.8%	23.3%
p-value* vs placebo	<.001	<.001	
Sustained Pain Free at 24 hours	76	98	40
%	15.1%	18.9%	7.6%
p-value* vs placebo	<.001	<.001	

P-value* = nominal significant only. (Source: sponsor's analysis, verified by the reviewer).

These results should be used as supportive evidence only since there was no pre-specified plan to control for Type 1 error for exploratory secondary endpoints.

3.3 Evaluation of Efficacy Study – 302(LAHK)

3.3.1 Description of the Study

This study had its first subject enrolled on 19 May 2016, and the last subject completed on 29 June 2017. The study report was created on the date of 18 December 2017. The study was conducted at 125 sites in the United States, the United Kingdom, and Germany.

The purpose of this study was to evaluate the effect of Lasmiditan 50 mg, 100 mg and 200 mg compared to placebo on the rates of pain free at 2 hours and MBS free at 2 hours in subjects with acute migraine.

Eligible subjects were adults 18 years of age or above with history of disabling migraine for at least 1 year with 3 to 8 migraine attacks per month, with < 15 headache days per month, with migraine onset before the age of 50 years.

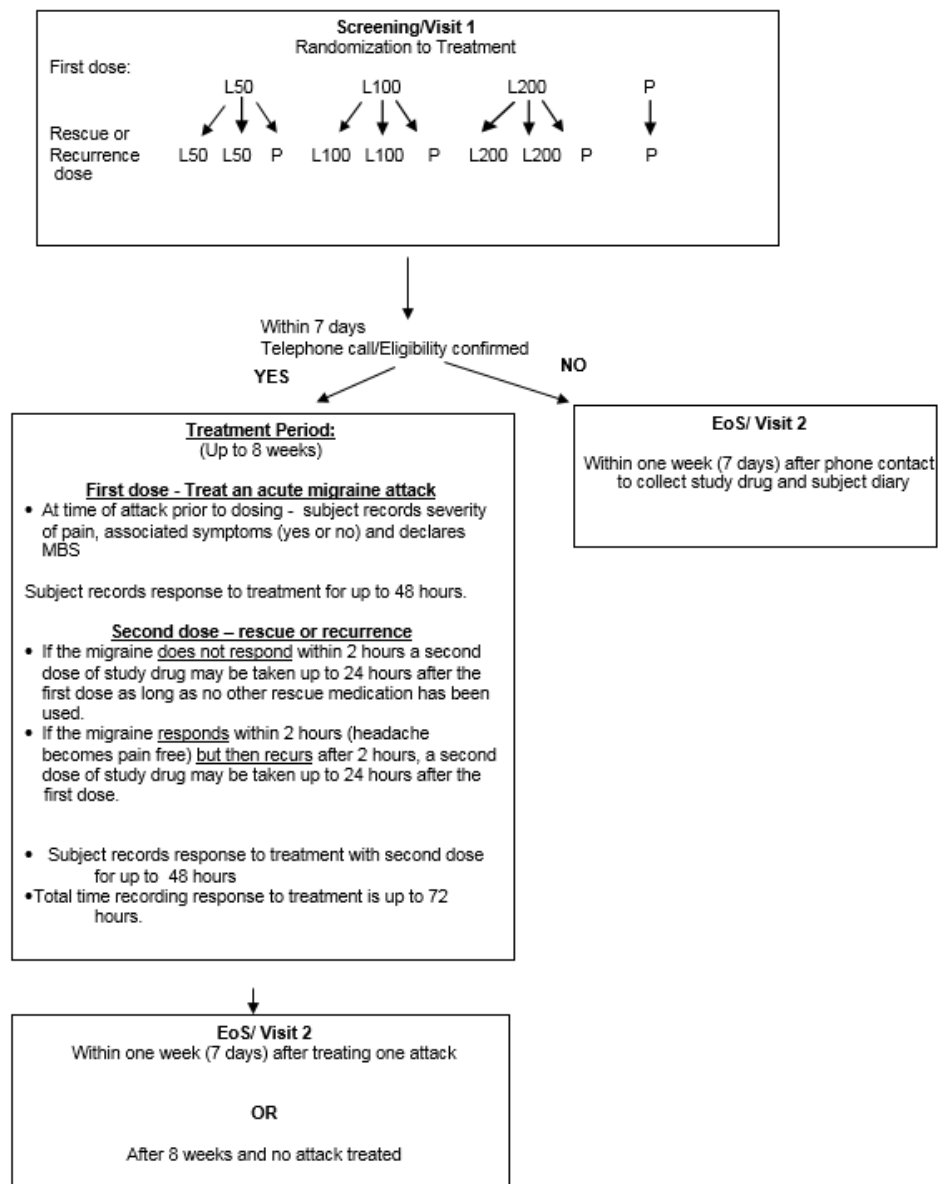
The total time on study was approximately 11 weeks. At the screening visit (Visit 1), potential eligible subjects were identified, randomized, dispensed study drug, and instructed not to treat an attack until their eligibility had been confirmed by phone within 7 days once all screening evaluations were complete. Once their eligibility was confirmed by the phone, subjects were asked to treat a qualifying migraine attack with study drug on an outpatient basis for a treatment period of up to 8 weeks. Within 1 week (7 days) of treating a migraine attack, subjects were asked to return for an end of study (EoS) visit (Visit 2).

Headache pain-free was defined as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0) at the 2 hours post dose timepoint. The protocol specifies that the patient should wait till the pain reaches “Moderate” to “Severe” to take the study drug.

About the randomization, subjects were centrally randomized to receive 50mg, 100 mg or 200 mg or placebo for the first dose in a 1:1:1:1 ratio and the second dose for rescue or recurrence of migraine (if needed). Subjects were stratified (yes or no) for use of concomitant medications that reduced the frequency of migraine episodes. The efficacy analysis was planned to be based on the first dose data only.

Planned sample size was to ensure that at least 570 per group complete the treatment period. A sample size of 570 per group were needed to detect with power > 90% a difference in pain free response rates of 7.4%, 13.9%, 13.6% and 18.8% between placebo, 50 mg, 100 mg and 200 mg respectively. These rates were taken from the Phase 2 study COL-MIG-202.

Figure 2 Schematic of Study Design – Study 302(LAHK)



Abbreviations: EoS = End of study; L50 mg = lasmiditan 50 mg; L100 mg = lasmiditan 100 mg; L200 mg = lasmiditan 200 mg; MBS = Most Bothersome Symptom; P = Placebo
(Source: study protocol.)

3.3.2 Efficacy Variables

3.3.2.1 Primary Endpoint

The two co-primary endpoints for this study were rates of pain free at 2 hours and MBS free at 2 hours post the first dose treating a qualifying acute migraine attack during the double-blind treatment phase.

3.3.2.2 Secondary Endpoints

Secondary efficacy endpoints included:

- 3) Pain relief at 2 hours.
- 4) 24-hour sustained pain free at 24 hours.

Subjects used an electronic diary (e-Diary) to record their response to the first dose over the next 48 hours and may continue to record their responses up to 72 hours depending on whether a second dose was used.

The sponsor has listed many more secondary endpoints as exploratory with no pre-specified plan to control the Type 1 error. We decided not to include those results in our review except the above two that were considered relevant and potentially supportive efficacy evidence by the clinical review team.

3.3.3 Statistical Analysis Methods

Efficacy analyses were based on the corrected mITT population, which included subjects who had a qualified migraine attack and took the investigational product and completed at least 1 post dose e-Diary measurement. Subjects were grouped based on the assigned treatment. Efficacy analyses were based on the first dose.

The primary and secondary endpoints were analyzed using a logistic regression model with treatment group and background use of medication to reduce the frequency of migraine episodes as covariates. The missing data were imputed as nonresponses.

For treatment comparisons, an estimate of the rate of achieving a response, as well as the corresponding p-value using Wald's test, will be computed.

3.3.3.1 Multiplicity Adjustment

The multiplicity adjustment method was pre-specified and deemed to be adequate.

A gatekeeping procedure was pre-specified to maintain the 2-sided study-wise Type I error at 0.05 between the two drug doses and the two co-primary endpoints.

The following hypotheses will be tested sequentially, in the following order:

- (1) Treatment comparison, between 200 mg and placebo, as measured by subjects who are pain-free at 2 hours post-dose.
- (2) Treatment comparison, between 200 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.
- (3) Treatment comparison, between 100 mg and placebo, as measured by subjects who are pain-free at 2 hours post-dose.
- (4) Treatment comparison, between 100 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.
- (5) Treatment comparison, between 50 mg and placebo, as measured by subjects who are pain-free at 2 hours post-dose.
- (6) Treatment comparison, between 50 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.

If one of the analyses is not statistically significant, then all subsequent analyses will be exploratory rather than confirmatory.

3.3.4 Patient Results

3.3.4.1 Patient Disposition

Due to the pre-specified rule that the primary analysis should be based on the first dose, only first dose data will be used in the efficacy analysis.

A total of 3005 subjects were randomized. A total of 2583 (86.0%) subjects used at least 1 dose of study drug and were analyzed for safety. Overall, 2617 (87.1%) subjects completed the study and 373 (12.4%) subjects discontinued the study.

Table 14 Subject Disposition by First Dose (All Subjects) - Study 302 (LAHK)

Subject Disposition	L50 mg N = 750	L100 mg N = 754	L200 mg N = 750	Placebo N = 751	All Subjects N = 3005
Randomized, n (%)	750 (100.0%)	754 (100.0%)	750 (100.0%)	751 (100.0%)	3005 (100.0%)
Confirmed Eligibility, n (%)	716 (95.5%)	721 (95.6%)	721 (96.1%)	711 (94.7%)	2869 (95.5%)
Treated, n (%)	654 (87.2%)	635 (84.2%)	649 (86.5%)	645 (85.9%)	2583 (86.0%)
Completed Study, n (%)	657 (87.6%)	640 (84.9%)	661 (88.1%)	659 (87.7%)	2617 (87.1%)
Treated	633 (96.3%)	606 (94.7%)	626 (94.7%)	628 (95.3%)	2493 (95.3%)
Not Treated	24 (3.7%)	34 (5.3%)	35 (5.3%)	31 (4.7%)	124 (4.7%)
No Migraine	9 (37.5%)	12 (35.3%)	21 (60.0%)	14 (45.2%)	56 (45.2%)
No Eligible Migraine	12 (50.0%)	17 (50.0%)	12 (34.3%)	11 (35.5%)	52 (41.9%)
No Study Medication	2 (8.3%)	2 (5.9%)	2 (5.7%)	6 (19.4%)	12 (9.7%)
Missing	1 (4.2%)	3 (8.8%)	0	0	4 (3.2%)
Discontinued, n (%)	87 (11.6%)	112 (14.9%)	85 (11.3%)	89 (11.9%)	373 (12.4%)
Treated	18 (20.7%)	27 (24.1%)	20 (23.5%)	16 (18.0%)	81 (21.7%)
Not Treated	69 (79.3%)	85 (75.9%)	65 (76.5%)	73 (82.0%)	292 (78.3%)
Reason for Discontinuation, n (%)	87	112	85	89	373

Adverse event	0	1 (0.9%)	4 (4.7%)	0	5 (1.3%) ^b
Lost to follow-up	27 (31.0%)	37 (33.0%)	30 (35.3%)	29 (32.6%)	123 (33.0%)
Treated	4 (4.6%)	13 (11.6%)	7 (8.2%)	9 (10.1%)	33 (8.8%)
Not Treated	23 (26.4%)	24 (21.4%)	23 (27.1%)	20 (22.5%)	90 (24.1%)
Non-compliance with protocol	14 (16.1%)	20 (17.9%)	14 (16.5%)	12 (13.5%)	60 (16.1%)
Pregnancy	1 (1.1%)	2 (1.8%)	0	0	3 (0.8%)
Subject request	15 (17.2%)	25 (22.3%)	10 (11.8%)	15 (16.9%)	65 (17.4%)
Investigator request	2 (2.3%)	0	0	3 (3.4%)	5 (1.3%)
Randomization failure	28 (32.2%)	27 (24.1%)	27 (31.8%)	30 (33.7%)	112 (30.0%)

(Source: modified from the Table 10.1 in the sponsor's study report, verified by the statistical reviewer.)

In this study, discontinuation was defined as the failure to return for the follow-up study visit. There were 373 subjects (12.4%) who discontinued the study. The percentage of subjects who discontinued the study was similar across the treatment groups (L50 mg, 11.6%; L100 mg, 14.9%; L200 mg, 11.3%; placebo, 11.9%). The most common reasons for discontinuation from the study were lost to follow-up (123/373 subjects, 33.0%), randomization failure (112/373 subjects, 30.0%), subject request (65/373 subjects, 17.4%) and non-compliance (60/373 subjects, 16.1%).

Table 15 Analysis Populations (All Subjects Randomized) - Study 302 (LAHK)

Analysis Populations n (%)	L50 mg N = 750	L100 mg N = 754	L200 mg N = 750	Placebo N = 751	All Subjects N = 3005
Safety Population	654 (87.2%)	635 (84.2%)	649 (86.5%)	645 (85.9%)	2583 (86.0%)
ITT Population	598 (79.7%)	571 (75.7%)	565 (75.3%)	576 (76.7%)	2310 (76.9%)
mITT Population	556 (74.1%)	532 (70.6%)	528 (70.4%)	540 (71.9%)	2156 (71.7%)
<i>Mild Headache Recorded at Time of Dosing</i>	12	9	7	6	34
Corrected mITT Population	544 (72.53%)	523 (69.36%)	521 (69.47%)	534 (71.11%)	2122 (70.62%)
PP Population	524 (69.9%)	488 (64.7%)	492 (65.6%)	506 (67.4%)	2010 (66.9%)

(Source: modified from the Table 11.1 in the sponsor's study report, verified by the statistical reviewer.)

There were 2310 subjects (76.9%) who used at least 1 dose of study drug, had post-dose headache assessments and were included in the ITT population. There were 2156 subjects (71.7%) who treated a qualifying migraine within 4 hours of onset and were included in the mITT population. A total of 2010 subjects (66.9%) were included in the PP population. The percentage of subjects in each treatment group was similar in the Safety, ITT, mITT and PP populations.

The condition of “within 4 hours of onset” imposed in this study is an adaptation to the observation in the Phase 2 study that some patients may not always carry the investigated drug and the e-Dairy device with them at the time of the onset of the migraine in real life settings during the up to 8 weeks study period to treat a qualifying migraine after the randomization.

We consider this condition acceptable. Please refer to the clinical reviewer’s review for more details on this point.

Headache pain-free was defined as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0) at the 2 hours post dose timepoint. The protocol specifies that the patient should wait till the pain reaches “Moderate” to “Severe” to take the study drug.

In our own analysis, we found 34 patients recorded the headache pain severity as “None” or “Mild” at the time of dosing. We decided to exclude these 34 patients from the efficacy analysis. Please refer to the clinical reviewer’s review for more details.

A total of 2122 (70.62%) subjects who treated a qualifying migraine within 4 hours of onset were included in the “corrected mITT population” for the primary efficacy evaluation.

3.3.4.2 Patient Demographics

Of the 2122 subjects in the corrected mITT population, majority were women (84.6%), white (82.3%), and the mean age was 42.7 years. The treatment groups were balanced for these baseline demographic characteristics.

Table 16 Demographics – corrected mITT – Study 302 (LAHK)

	L50 mg	L100 mg	L200 mg	Placebo	All Subjects
Age (years), n	544	523	521	534	2122
Mean (SD)	42.82(13.28)	42.54 (12.33)	41.75 (12.22)	42.80 (12.74)	42.72 (12.66)
Median	42	44.0	42.0	42.5	43.00
Minimum	18	18	18	18	18
Maximum	77	77	79	77	79
Gender, n (%)	544	523	521	534	2122
Female	462 (84.93%)	448 (85.66%)	431 (82.73%)	454(85.02%)	1795 (84.59%)
Male	82(15.07%)	75 (14.34%)	90 (17.27%)	80(14.98%)	327(15.41%)
Race, n (%)	544	523	520	534	2121
American Indian or Alaska Native	3(0.55%)	2(0.38%)	0	5 (0.94%)	10 (0.47%)
Asian	5(0.92%)	5 (0.96%)	7 (1.35%)	3 (0.56%)	20 (0.94%)
Black or African American	80 (14.71%)	77 (14.72%)	71 (13.65%)	74 (13.86%)	302 (14.24%)
Native Hawaiian or other Pacific Islander	2(0.37%)	0	2 (0.38%)	2 (0.37%)	6 (0.28%)
White	443 (81.43%)	428 (81.84%)	432 (83.08%)	442 (82.77%)	1745 (82.27%)
Other	4(0.74%)	6 (1.15%)	4 (0.77%)	3 (0.56%)	17 (0.80%)
Multiple	7(1.29%)	5 (0.96%)	4 (0.77%)	5 (0.94%)	21 (0.99%)
BMI (kg/m2), n	543	522	520	533	2118
Mean (SD)	29.58(7.41)	30.10(8.41)	30.299(8.399)	30.12(11.52)	30.02 (9.06)
Median	28.3	28.40	28.9	29	28.60

Minimum	16	16	17.5	16.3	16
Maximum	71.1	63.50	90.5	239	239

BMI = body mass index;

(Source: Reviewer's analysis using the Sponsor's ADAM datasets.)

3.3.4.3 Patient Baseline Disease Characteristics

The baseline disease characteristics were consistent with a migraine population and well balanced across the treatment groups.

Subjects in the study had experienced migraines for a mean ($\pm$ SD) duration of 18.4 (12.896) years and had a mean ($\pm$ SD) of 5.2 (2.02) migraines per month in the past 3 months.

Table 17 Summary of Data Related to Migraine -corrected mITT - Study 302 (LAHK)

	L50 mg	L100 mg	L200 mg	Placebo	All Subjects
Smoking History, n (%)	496	484	474	494	1948
Never	355 (71.57%)	312 (64.46%)	298 (62.87%)	349 (70.65%)	1314 (67.45%)
Former	77 (15.52%)	93 (19.21%)	102 (21.52%)	74 (14.98%)	346 (17.76%)
Currently	64 (12.90%)	79 (16.32%)	74 (15.61%)	71 (14.37%)	288 (14.78%)
Family History of CAD, n (%)	544	523	521	534	2122
Yes	146 (26.84%)	140 (26.77%)	126 (24.18%)	146 (27.34%)	558 (26.30%)
No	398 (73.16%)	383 (73.23%)	395 (75.82%)	388 (72.66%)	1564 (73.70%)
CV Risk Factors, n (%)	544	523	521	534	2122
Female	462	448	431	454	1795
Yes	342 (62.86%)	351 (67.11%)	346 (66.41%)	358 (67.04%)	1397 (65.83%)
No	120 (22.06%)	97 (18.55%)	85 (16.32%)	96 (17.98%)	398 (18.76%)
Male	82	75	90	82	327
Yes	69 (12.68%)	68 (13.00%)	79 (15.16%)	69 (12.92%)	285 (13.43%)
No	13 (2.39%)	7 (1.34%)	11 (2.11%)	13 (2.43%)	42 (1.98%)
Duration of Migraine History (years), n	544	523	520	534	2121
Mean (SD)	18.68 (12.91)	19.37 (13.39)	17.66 (12.38)	17.87 (12.85)	18.397(12.896)
Median	16.47	17.08	15.16	15.49	16.11
Minimum	0	0.27	0	0	0
Maximum	64.18	61.62	59.60	55.18	64.18
Avg Migraines/Month in Past 3 Months, n	544	523	520	534	2121
Mean (SD)	5.24 (1.957)	5.24 (1.82)	5.23 (1.88)	5.41 (2.38)	5.28 (2.02)
Median	5	5	5	5	5
Minimum	3	3	3	3	3
Maximum	18	13	18	36	36
Experienced Migraine With and Without Aura, n (%)	541	523	518	532	2114
With Aura	189 (34.94%)	205 (39.20%)	183 (35.33%)	201 (37.78%)	778 (36.80%)
Without Aura	352 (65.06%)	318 (60.80%)	335 (64.67%)	331 (62.22%)	1336 (63.20%)

Use of Medication Reducing Migraines, n (%)	544	523	520	533	2120
Yes	103 (18.93%)	101 (19.31%)	93 (17.88%)	106 (19.89%)	403 (19.01%)
No	441 (81.07%)	422 (80.69%)	427 (82.12%)	427 (80.11%)	1717 (80.99%)

CAD = coronary artery disease; CV = cardiovascular

(Source: Reviewer's analysis using the Sponsor's ADAM datasets.)

3.3.5 Results and Conclusions

3.3.5.1 Efficacy Results of the Primary Endpoints

The results reported by the sponsor were mostly confirmed except the 34 patients whose treated migraine attacks did not reach the required severity at the time of dosing. The efficacy result presented by the sponsor still holds in the sense that p-values did not change by removing these 34 patients, but the estimates of the rates were slightly different, as can be seen in the following table.

Table 18 Primary Endpoint Analyses – Study 302 (LAHK)

	Corrected mITT				mITT			
	Lasmiditan				Lasmiditan			
	50 mg	100 mg	200 mg	Placebo	50 mg	100 mg	200 mg	Placebo
Pain Moderate to Severe at time of dosing	544	523	521	534	556	532	528	539
Pain Free at 2 hours	154	164	202	112	159	167	205	115
%	28.31%	31.36%	38.77%	20.97%	28.6%	31.4%	38.8%	21.3%
p-value	.006	<.001	<.001		.003	<.001	<.001	
MBS recorded at time of dosing	502	491	478	509	512	500	483	514
MBS Free at 2 hours	205	216	233	169	209	221	235	172
%	40.84%	43.99%	48.74%	33.20%	40.8%	44.2%	48.7%	33.5%
p-value	.014	<.001	<.001		.009	<.001	<.001	

P-values were from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates. (Source: reviewer's own analysis and Table 11-6, 11-7 sponsor's analysis verified by the reviewer.)

The primary analysis for Pain free status at 2 hours included 2122 patients. There was a statistically significant increase in the rate of pain free at 2 hours timepoint post first dose without rescue medication from 20.97% in the placebo group to 28.31% in the 50 mg group, 31.36% in the 100 mg group and 38.77% in the 200 mg group. The p-values versus placebo were .006, < 0.001, <.001 respectively.

The primary analysis for MBS free status at 2 hours included 1980 patients. There was a statistically significant increase in the rate of MBS free at 2 hours timepoint post first dose without rescue medication from 33.20% in the placebo group to 40.84% in the 50 mg group,

43.99% in the 100 mg group and 48.74% in the 200 mg group. The p-values versus placebo were .014, < 0.001 and <.001 respectively.

Patients with missing data at 2-hour time point were counted as treatment failures. As a clinical rule, patients with rescue medication use prior to the 2-hour time point were considered as treatment failures.

3.3.5.2 Missing Data and Sensitivity Analyses

The overall missing rate was relatively low for this study and were similar among the groups as can be seen from the following table which shows the missing data patient counts for each group.

If the subject did not record a pain severity at time of dosing, then this subject was not included in the analysis. If the subject did not record a pain severity rating at 2 hours post dosing, then this subject's pain free status at 2 hours was set as missing.

Table 19 Patient Counts at Time of Dosing and Two Hours (rescue*= failure)- Study 302(LAHK)

	Pain at Time 0	Pain at 2 Hours	Missing n	Missing %	MBS at Time 0	MBS at 2 Hours	Missing n	Missing %
50 mg	544	493	51	9.38%	502	455	47	9.36%
100 mg	523	475	48	9.18%	491	446	45	9.16%
200mg	521	469	52	9.98%	478	430	48	10.04%
Placebo	534	482	52	9.74%	509	461	48	9.43%

(Source: Reviewer's own analysis.)

Similarly, if the subject did not provide a symptom of migraine (either nausea, phonophobia, or photophobia) at the time of dosing, this subject was not be included in the MBS analysis. If the subject failed to record a symptom rating at 2 hours post dosing, then this subject's MBS status at 2 hours post dosing was set as missing. If the subject provided at least a symptom at the time of dosing, but did not designate one as the most bothersome, this subject was considered MBS-free only if all symptoms present at time of dosing were no longer present at the 2 hours timepoint.

As a clinical rule, if the subject took any recue medication prior to the 2 hours timepoint, then this patient was considered as treatment failure. In the primary efficacy analysis, subjects with missing data at 2 hours timepoint were counted as treatment failures.

Table 20, 21 and 22 show the breakdown of patient counts with actual efficacy measurements at 2 hours (Yes/No/Missing); the rescue medication use; and the patient efficacy results after applying the clinical rule of rescue medication use before 2 hours = failure.

Table 20 Descriptive Patient Counts for Data Status at 2 Hours – corrected mITT- Study 302 (LAHK)

	Pain			MBS		
50 mg	544	163	Yes	502	215	Yes
		327	No		237	No
		54	2-Hour missing		50	2-Hour Missing
100 mg	523	180	Yes	491	235	Yes
		291	No		207	No
		52	2-Hour missing		49	2-Hour Missing
200 mg	521	216	Yes	478	246	Yes
		250	No		181	No
		55	2-Hour missing		51	2-Hour Missing
Placebo	534	120	Yes	509	177	Yes

	359	No	281	No
	55	2-Hour missing	51	2-Hour Missing

(Source: Reviewer's own analysis.)

Table 21 Descriptive Patient Counts for Rescue Meds before 2-hours – corrected mITT- Study 302 (LAHK)

		Pain			MBS	
50 mg	30	9	Yes	27	10	Yes
		18	No		14	No
		3	2-Hour missing		3	2-Hour missing
100 mg	41	16	Yes	40	19	Yes
		21	No		17	No
		4	2-Hour missing		4	2-Hour Missing
200 mg	33	14	Yes	29	13	Yes
		16	No		13	No
		3	2-Hour missing		3	2-Hour missing
Placebo	26	8	Yes	24	8	Yes
		15	No		13	No
		3	2-Hour missing		3	2-Hour missing

(Source: Reviewer's own analysis.)

Table 22 Counts for Patients' Data Status at 2H (rescue* = failure) – corrected mITT- Study 302 (LAHK)

		Pain			MBS	
50 mg	544	154	Yes	502	205	Yes
		339	No		250	No
		51	2-Hour Missing		47	2-Hour Missing
100 mg	523	164	Yes	491	216	Yes
		331	No		230	No
		48	2-Hour Missing		45	2-Hour Missing
200 mg	521	202	Yes	478	233	Yes
		267	No		197	No
		52	2-Hour Missing		48	2-Hour missing
Placebo	534	112	Yes	509	169	Yes
		370	No		292	No
		52	2-Hour Missing		48	2-Hour Missing

(Source: Reviewer's own analysis.)

In the sensitivity analysis performed by the sponsor the following MI (multiple imputation) was used:

- (1) Subjects with missing data from the placebo group were assumed to respond similarly with similar placebo subjects with available data.
- (2) Missing data for subjects from the drug groups were imputed using a model drift towards the mean response of the placebo group.

Results for the sensitivity analyses using MI were consistent with those observed for the primary analysis. Results from the per-protocol analysis were also consistent with the efficacy analysis.

Table 23 Sensitivity Analyses – Study 302 (LAHK)

	Corrected mITT using MI				mITT using MI				Per Protocol			
	Lasmiditan				Lasmiditan				Lasmiditan			
	50 mg	100 mg	200 mg	Placebo	50 mg	100 mg	200 mg	Placebo	50 mg	100 mg	200 mg	Placebo
Pain recorded at time 0	544	523	521	534	556	532	528	540	524	488	492	506
Pain Free at 2 hours	165	174	213	123	172	185	224	128	158	166	204	115
%	30.3%	33.3%	40.9%	23.0%	30.9%	34.8%	42.4%	23.7%	30.2%	34.0%	41.5%	22.7%
p-value	.007	<.001	<.001		.008	<.001	<.001		.004	<.001	<.001	
MBS recorded at time 0	502	491	478	509	512	500	483	514	483	457	451	482
MBS Free at 2 hours	221	231	249	185	230	244	258	192	207	217	234	171
%	44.0%	47.0%	52.1%	36.3%	44.9%	48.8%	53.4%	37.4%	42.9%	47.5%	51.9%	35.5%
p-value	.0147	<.001	<.001		.0159	<.001	<.001		.010	<.001	<.001	

(Source: reviewer's analysis and table 14.2.1.3, table 14.2.1.4, table 14.2.2.3 and table 14.2.2.4 from the study report, verified by the reviewer.)

3.3.5.3 Efficacy Results of the Secondary Endpoints

Pain relief at 2 hours

Pain relief was defined as a reduction in pain severity from moderate (2) or severe (3) at the time of dosing to mild (1) or none (0), or a reduction from mild (1) to none (0), at the indicated assessment time, with no rescue medication before the 2 hours timepoint. Since the definition for pain relief included pain rating of 1 at time of dosing, the mITT population was used for the analysis.

The proportions of subjects with pain relief at 2 hours were 55.58%, 60.90%, 60.80%, and 45.19% for the 50 mg, 100 mg, 200 mg and placebo groups, respectively.

The sponsor's result on Pain Relief at 2 Hours in Table 11-17 in the study report was not accurate for two reasons: it was based on the ITT population which included patient who treated the migraine attack 4 hours after the onset and it did not set patients with rescue medication use before 2 hours as failure.

Table 24 Responder Rate: Pain Relief at 2 Hours – mITT Population - Study 302 (LAHK)

	L50	L100	L200	Placebo
Mild, Moderate, or Severe Headache Recorded at Time of Dosing	556	532	528	539
Headache Relief, n (%)				
2 hours post-dose	309 ((55.58%))	324(60.90%)	321 (60.80%)	244 (45.27%)
p-value* vs Placebo	<.001	<.001	<.001	

P-value* = nominal significant only. (Source: reviewer's own analysis).

24-hour sustained pain free at 24 hours

Sustained pain-free at 24 hours was defined as pain-free at 2 hours after first dose and at the 24 hours, having not used any medications after the first dose. The proportions of subjects with sustained pain free at 24 hours were 17.4%, 18.6%, 23.5%, and 13.0% for the 50 mg, 100 mg, 200 mg and placebo groups, respectively.

Table 25 Responder Rate: Sustained Pain Free at 24 Hours – mITT - Study 302 (LAHK)

	Lasmiditan			
	50 mg	100 mg	200 mg	Placebo
Pain Mild, Moderate to Severe at time of dosing	556	532	528	539
Pain Free at 2 hours	159	167	205	115
%	28.6%	31.4%	38.8%	21.3%
p-value	.003	<.001	<.001	
Pain Free at 24 Hours	194	189	217	151
%	34.9%	35.5%	41.1%	28.0%
p-value* vs placebo	.0160	.0087	<.001	
Sustained Pain Free at 24 hours	97	99	124	70
%	17.4%	18.6%	23.5%	13.0%
p-value* vs placebo	.0437	.0120	<.001	

P-value* = nominal significant only. (Source: sponsor's analysis, verified by the reviewer).

These results should be used as supportive evidence only since there was no pre-specified plan to control for Type 1 error for exploratory secondary endpoints.

3.4 Evaluation of Safety

Please refer to the clinical review for details on safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region – Study 301 (LAHJ)

In the study 301 (LAHJ), the median age of the subjects was about 41 to 42 years, with the percentage of female as 84% in the 200 mg drug group, 81% in the 100 mg group and 86% in the placebo group, and the majority being either black or white, with the percentage of being white 77%, 76% and 80%, being black as 17%, 19% and 17%.

There is no need to subgroup by region, since the entire study was conducted in the US.

Table 26 Age, Gender, and Race Summaries by Treatment Group - Study 301 (LAHJ)

	Age (Median)	Gender (%F)	Race (%White)	Race (%Black)
100 mg	42	80.72	77.11	17.47
200 mg	41	84.29	75.94	19.48
Placebo	42	85.63	80.39	16.70
Overall	41	83.58	77.84	17.88

(Reviewer's result.)

For study 301 (LAHJ), analyses for the treatment effect across clinically meaningful subgroups such as age, gender, and race were performed.

The trend in treatment success appears to be similar across subgroups.

Table 27 Findings in Subgroup Populations – Age, Gender and Race – Study 301(LAHJ)

Pain Free 2 hours	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate
	Age < Median			Age >= Median					
100 mg	241	76	31.54%	257	65	25.29%			
200 mg	251	92	36.65%	252	68	26.98%			
Placebo	249	42	16.87%	272	37	13.91%			
	Gender = Female			Gender = Male					
100 mg	402	111	27.61%	96	30	31.25%			
200 mg	424	142	33.49%	79	18	22.78%			
Placebo	441	68	15.42%	74	11	14.86%			
	Race = White			Race = Black			Race = All Other		
100 mg	384	102	26.56%	87	31	35.63%	27	8	29.63%
200 mg	382	122	31.94%	98	32	32.65%	23	6	26.09%
Placebo	414	58	14.01%	86	20	23.26%	15	1	6.67%
MBS Free 2 hours	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate
	Age < Median			Age >= Median					
100 mg	229	96	41.92%	235	95	40.43%			
200 mg	234	103	44.02%	233	87	37.34%			
Placebo	231	72	31.17%	249	70	28.11%			
	Gender = Female			Gender = Male					
100 mg	374	148	39.57%	90	43	47.78%			
200 mg	396	159	40.15%	71	31	43.66%			
Placebo	413	123	29.78%	67	19	28.36%			

	Race = White			Race = Black			Race = All Other		
100 mg	362	148	40.88%	77	31	40.26%	25	12	48.00%
200 mg	358	151	42.18%	88	31	35.23%	21	8	38.10%
Placebo	389	106	27.25%	79	33	41.77%	12	3	25.00%

(Reviewer's result)

4.2 Gender, Race, Age and Geographic Region – Study 302 (LAHK)

In the study 302 (LAHK), the median age of the subjects was about 42 to 44 years, with the percentage of female as 83% in the 200 mg drug group, 86% in the 100 mg group, 85% in the 50 mg group and 85% in the placebo group, and the majority being either black or white, with the percentage of being white 81%, 82%, 83% and 83%, being black as 15%, 14%, 15% and 14%.

The study was conducted in the United States, the United Kingdom, and Germany. 83.79% were from the USA, 6.46% were from Germany, and 9.75% were from the United Kingdom among the 2122 corrected mITT population.

Table 28 Age, Gender, Race and Country Summaries by Treatment Group - Study 302 (LAHK)

	Age (Median)	Gender (%F)	Race (%White)	Race (%Black)	Country (%USA)	Country (%GBR)	Country (%DEU)
50 mg	42	84.93	81.43	14.72	83.46	6.80	9.74
100 mg	44	85.66	81.84	13.63	85.28	5.54	9.18
200 mg	42	82.73	82.92	14.71	83.30	6.53	10.17
Placebo	42.5	85.02	82.77	13.86	83.15	6.93	9.93
Overall	43	84.59	82.23	14.23	83.79	6.46	9.75

(Reviewer's result.)

For study 302 (LAHK), analyses for the treatment effect across clinically meaningful subgroups such as age, gender, race and country were performed.

The trend in treatment success appears to be similar across subgroups.

Table 29 Findings in Subgroup Populations – Age, Gender, Race and Country – Study 302(LAHK)

Pain Free 2 hours	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate
	Age < Median			Age >= Median					
50 mg	256	74	28.91%	288	80	27.78%			
100 mg	250	79	31.60%	273	85	31.14%			
200 mg	255	85	33.33%	266	117	43.98%			
Placebo	267	48	17.98%	267	64	23.97%			
	Gender = Female			Gender = Male					
50 mg	473	143	30.23%	83	16	19.28%			
100 mg	455	139	30.55%	77	28	36.36%			
200 mg	436	173	39.68%	92	32	34.78%			
Placebo	459	95	20.70%	81	20	24.69%			
	Race = White			Race = Black			Race = All Other		
50 mg	443	117	26.41%	80	30	37.50%	21	7	33.33%
100 mg	428	137	32.01%	77	21	27.27%	18	6	33.33%
200 mg	432	166	38.43%	71	29	40.85%	18	7	38.89%
Placebo	442	85	19.23%	74	23	31.08%	18	4	22.22%
	Country = USA			Country = GBR			Country = DEU		
50 mg	454	136	29.96%	37	7	18.92%	53	11	20.75%
100 mg	446	142	31.84%	23	6	20.69%	48	16	33.33%
200 mg	434	179	41.24%	28	6	17.65%	53	17	32.08%
Placebo	444	107	24.10%	37	4	10.81%	53	1	1.89%

MBS Free 2 hours	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate
	Age < Median			Age >= Median					
50 mg	240	91	37.92%	262	114	43.51%			
100 mg	242	107	44.21%	249	109	43.78%			
200 mg	241	115	47.72%	237	118	49.79%			
Placebo	259	78	30.12%	250	91	36.40%			
	Gender = Female			Gender = Male					
50 mg	429	182	42.42%	73	23	31.51%			
100 mg	424	181	42.69%	67	35	52.24%			
200 mg	400	197	49.25%	78	36	46.15%			
Placebo	434	142	32.72%	75	27	36.00%			
	Race = White			Race = Black			Race = All Other		
50 mg	410	167	40.73%	71	31	43.66%	21	7	33.33%
100 mg	403	180	44.67%	71	31	43.66%	17	5	29.41%
200 mg	400	196	49.00%	60	30	50%	18	7	38.89%
Placebo	420	133	31.67%	71	30	42.25%	18	6	33.33%
	Country = USA			Country = GBR			Country = DEU		
50 mg	420	174	41.43%	35	14	40.00%	47	17	36.17%
100 mg	422	190	45.02%	25	8	32.00%	44	18	40.91%
200 mg	401	199	49.63%	31	8	25.81%	46	26	56.52%
Placebo	425	149	35.06%	34	8	23.53%	50	12	24.00%

(Reviewer's result)

4.3 Other Special/Subgroup Populations

None.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The two pivotal studies collectively provided sufficient statistical evidence that Lasmiditan at doses 50 mg, 100 mg or 200 mg is effective in treating patients with acute migraine. No major statistical issues were identified.

5.2 Conclusions and Recommendations

The efficacy results obtained from the statistical analyses of the two pivotal studies support the conclusion that Lasmiditan is effective in treating patients with acute migraine.

5.3 Labeling Recommendations

(b) (4)



(Source: reviewer's own analysis using Sponsor's ADAM datasets.)

6 REFERENCES

[1] FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. <http://www.fda.gov/cder/guidance/1397fnl.pdf>

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JINNAN LIU
09/10/2019 01:55:22 PM

KUN JIN
09/10/2019 03:42:40 PM
I concur with the review.

HSIEN MING J HUNG
09/11/2019 02:15:57 PM



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 211280
Drug Name: lasmiditan
Indication: Acute treatment of migraine
Study number: H8H-MC-LAHB
Applicant: Eli Lilly and Company
Date(s): Date of Document: Oct 11, 2018
Completion date: July 17, 2019
Review Priority: Standard
Biometrics Division: DBVI
Statistical Reviewer: Anna Sun, Ph.D., Mathematical Statistician, OB/DBVI
Concurring Reviewers: Qianyu Dang, Ph.D., Lead Mathematical Statistician, OB/DBVI
Yi Tsong, Ph.D., Division Director, OB/DBVI
Medical Division: Control Substance Staff
The CSS Team: Shalini Bansil, Medical officer, OMPT/CDER/OCD/CSS
Project Manager: Sandra Saltz, Project Manager, CSS

Keywords: *Crossover design, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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1. Executive Summary

This was a Phase 1, randomized, subject- and investigator-blind, placebo- and active-controlled, crossover study to assess the abuse liability of Lasmiditan in recreational poly-drug users.

The primary objective of this trial was to assess the abuse potential of Lasmiditan compared to the positive control alprazolam and placebo using the maximal effect score (Emax) of the at-the-moment 100-mm bipolar Drug Liking VAS.

The study consisted of a Screening phase, Qualifying phase, Treatment phase and a Follow-up phase. The Treatment Phase was a subject- and investigator-blind, placebo- and active-controlled, 5-period crossover design. Subjects were randomized to 1 of 10 dosing sequences. Each dosing sequence consisted of 5 dosing periods that evaluated the abuse liability of 1 of the 5 study treatments: placebo, 2 mg alprazolam, 100 mg Lasmiditan, 200 mg Lasmiditan, and 400 mg Lasmiditan.

The reviewer analyzed the primary PD endpoint of Emax Drug Liking and the secondary PD endpoints: High VAS, Overall Drug Liking VAS and Take Drug Again. The results from the statistical reviewer's analyses indicate that:

- For the validation test: The validity of the study was determined from the comparison of Emax VAS score between positive control and placebo. Emax of Alprazolam was significantly higher than placebo (p value < 0.01), for Drug Liking (by the margin of 15), High VAS, Overall Drug Liking VAS and Take Drug Again, thereby confirming the study validity.
- For the relative abuse potential test: Lasmiditan was evaluated by the comparison of Emax scores of positive control versus each dose of Lasmiditan. For Drug Liking, Drug High, Overall Drug Liking and Take Drug Again, all doses of Lasmiditan (100 mg, 200 mg and 400 mg) had mean Emax score significantly lower than 2 mg Alprazolam (all p values < 0.01).

Note: For Drug Liking, the reviewer used 0 as the test margin for the relative abuse potential test, while the sponsor used 5 as the test margin in their protocol, if margin=5 is used, then there is no significant difference between Alprazolam and Lasmiditan 400 mg (P value=0.065).

- For the absolute abuse potential test: Lasmiditan was evaluated by the comparison of Emax score between Lasmiditan and placebo with the margin of 11. All doses of Lasmiditan (100 mg, 200 mg and 400 mg) were significantly higher than placebo (P values are close to 1).

In Summary, Lasmiditan has a strong abuse potential signal.

2. Review Report on Study H8H-MC-LAHB

2.1 Introduction

Lasmiditan is a small molecule 5-hydroxytryptamine (5-HT)_{1F} receptor agonist being developed for the acute treatment of migraine. Triptans, which are 5-HT_{1B/1D} receptor agonists, are well established as an acute therapy for migraine, though they are not effective in all patients or attacks. Triptans were developed as cerebral vasoconstrictors, mediated via their affinity for 5-HT_{1B} receptors located on vascular smooth muscle. Inherent in this mechanism of action is a liability for coronary vasoconstriction, and therefore, triptans are contraindicated in patients with cardiovascular disease. Unlike triptans, lasmiditan is a highly selective and potent agonist at the 5-HT_{1F} receptor with >470-fold higher affinity for the 5-HT_{1F} receptor than for 5-HT_{1B/1D} receptors. Lasmiditan is under development as a neurally acting treatment for migraine without the vasoconstrictor liability of triptans. This molecule has been developed by Lilly as LY573144 and by CoLucid Pharmaceuticals, Inc. (CoLucid) as COL-144.

Because lasmiditan penetrates the central nervous system (CNS) and adverse events (AEs) which may represent a sign of abuse liability have been reported in completed clinical studies, the risk of abuse was evaluated in accordance with the United States Food and Drug Administration (FDA) Guidance for Industry: Assessment of Abuse Potential of Drugs (FDA 2017).

2.1.1 Objectives of the study

The primary objective of this trial was to assess the abuse potential of lasmiditan compared to the positive control alprazolam and placebo.

The secondary objectives of the trial were:

- Further characterize the abuse potential of lasmiditan with additional Drug Effects and Drug Similarity Visual Analog Scale (VAS) measures
- Safety evaluations
- Pharmacokinetics (PK) of lasmiditan

2.1.2 Overall Study Design and Plan: Description

This was a Phase 1, randomized, subject- and investigator-blind, placebo- and active-controlled, crossover study to assess the abuse liability of lasmiditan in recreational poly-drug users. The study included 4 phases:

Screening Phase: Subjects signed an informed consent form before entry to the study and completion of screening procedures. Screening visits occurred within 28 days of dosing in the Qualification Phase.

Qualification Phase: To identify subjects who were able to discriminate an alprazolam test dose from placebo. The Qualification Phase was a subject- and investigator-blind, placebo-controlled, 2-period crossover study in which subjects were randomized to a test dose of 1 mg alprazolam and placebo in a crossover manner. “Drug Liking” response was assessed before and after alprazolam and placebo administration using a 100-mm bipolar Drug Liking VAS. Only subjects

who demonstrated the ability to discriminate an alprazolam test dose from placebo were eligible to enter the Treatment Phase.

Treatment Phase: To evaluate the abuse liability of 100, 200, and 400 mg lasmiditan compared with placebo and positive control, 2 mg alprazolam. The Treatment Phase was a subject- and investigator-blind, placebo- and active-controlled, 5-period crossover design. Subjects were randomized to 1 of 10 dosing sequences. Each dosing sequence consisted of 5 dosing periods that evaluated the abuse liability of 1 of the 5 study treatments: placebo, 2 mg alprazolam, 100 mg lasmiditan, 200 mg lasmiditan, and 400 mg lasmiditan.

Follow-up Phase: Subjects had a follow-up visit approximately 1 week after their last dose of study drug, and presented to the CRU for discharge from the study as deemed appropriate by the investigator.

Pharmacodynamic Endpoints:

Drug Liking, on a bipolar 0 to 100 mm VAS was the primary pharmacodynamic endpoint.

The Drug Effects VAS Battery, a tool to evaluate the different subjective effects of the abuse liability of the study drug, was used to assess the primary objective. The Drug Effects VAS Battery includes the following scales: Drug Liking and Overall Drug Liking (where 0 = strong disliking and 100 = strong liking); Take Drug Again, Good Effects, and Bad Effects (where 0 = definitely not and 100 = definitely so); Alertness/Drowsiness (where 0 = very drowsy and 100 = very alert); Agitation/Relaxation (where 0 = very relaxed and 100 = very agitated); High (where 0 = not at all high and 100 = extremely high); and Hallucination (where 0 = not at all and 100 = extremely). Lasmiditan was compared to the positive control, alprazolam, and to placebo using the maximal effect score (Emax) (or minimal effect score [Emin], where appropriate) of the at-the-moment 100-mm bipolar Drug Liking VAS. The remaining questions in the Drug Effects VAS Battery and the Drug Similarity VAS Battery were assessed as secondary endpoints. The Drug Similarity VAS Battery included 30 questions in which subjects were asked “how familiar” they were with 15 classes of drugs of abuse (where 0 = definitely not familiar and 100 = definitely familiar) and “how similar” the study treatment was to each of those classes (where 0 = definitely not similar and 100 = definitely similar). The “how familiar” questions were asked in the Qualification Phase only (baseline), whereas the “how similar” questions were asked in both the Qualification Phase and Treatment Phase. Drug classes covered by the Drug Similarity VAS Battery were: cocaine (including crack), caffeine, ecstasy (3,4-methylenedioxymethamphetamine [MDMA]), D-amphetamine or methamphetamine, phencyclidine (PCP), codeine or morphine, heroin, lysergic acid diethylamide (LSD), nicotine, pseudoephedrine, cannabis, benzodiazepines, ketamine, mushrooms, and barbiturates.

Subjects marked a point on a 100-mm horizontal line that best represented their response to the given question. The endpoints of each electronic scale were marked with descriptive anchors on a scale from 0 to 100.

2.1.3 Number of subjects

Planned: An appropriate number of subjects were to be screened to allow for approximately 130 subjects to enter into the Qualification Phase so that approximately 60 subjects were randomized in the Treatment Phase and approximately 50 subjects completed the study.

Randomized and treated (at least 1 dose): 96 subjects enrolled in the Qualification Phase, 58 of whom went on to enroll in the Treatment Phase.

Completed: 53 subjects completed the study (Qualification Phase and Treatment Phase).

2.1.4 Pharmacodynamic Statistical Methodology used in Sponsor's analyses

Descriptive statistics for the Drug Liking VAS were reported for each treatment and for each paired difference among treatments.

The Emax was derived as the maximum at-the-moment Drug Liking VAS score among all the individual values that were collected at the scheduled postdose assessment time points. The time to Emax was the corresponding time point at which the maximum score occurred. These were derived for both the Qualification Phase and Treatment Phase separately for each treatment.

A linear mixed-effects model, including period, sequence, and treatment as fixed effects, and subject as a random effect, was used to evaluate the hypothesis tests of primary interest (at-the moment Drug Liking) at the Emax at a significance level of 0.05 (1-sided). The following pairwise comparisons were made:

- Alprazolam minus placebo, with null hypothesis that the difference is ≤ 15 mm. The null hypothesis was rejected if the lower limit of the 90% confidence interval (CI) was greater than 15 mm, showing assay sensitivity.
- Alprazolam minus each dose of lasmiditan, with the null hypothesis that the difference is ≤ 5 mm. The null hypothesis was rejected if the lower limit of the 90% CI was greater than 5 mm, showing that alprazolam had a higher Emax of Drug Liking score than lasmiditan.
- Each dose of lasmiditan minus placebo, with the null hypothesis that the difference is ≥ 14 mm. The null hypothesis was rejected if the upper limit of the 90% CI was lower than 14 mm, showing that lasmiditan did not have a clinically relevant higher Drug Liking score than placebo.

Least squares (LS) mean estimates and 90% CIs were reported for each treatment and for each paired difference among treatments.

As secondary analyses, a paired sample t-test and a nonparametric test were also performed. For the nonparametric analysis, pairwise treatment comparisons were assessed using the Wilcoxon signed-rank test on the within-subject differences, and median and interquartile range were reported.

To determine which analysis was the most suitable, the following were assessed:

1. The suitability of the mixed-effects model was assessed first by examination of plots of the residuals. The residuals were investigated for normality using the Q-Q plot.
2. If the mixed-model was not deemed appropriate, the paired t-test was deemed suitable if histograms of the individual differences appeared to be normally distributed.

3. If the normality assumption of the paired t-test was also violated, the Wilcoxon signed-rank test was selected.

Descriptive statistics for each other element of the Drug Effects VAS Battery, aside from the Drug Liking VAS, and for time to peak effect were reported for each study phase and treatment. Mean ($\pm$ standard error) plots of Drug Effects VAS scale data were presented by treatment over time for the Treatment Phase only. Similar statistical analyses to those employed for the Emax of Drug Liking VAS were employed for each other element of the Drug Effects VAS Battery.

After reviewing the data for the Alertness/Drowsiness and Agitation/Relaxation VAS scales, the minimal effect score (Emin) was also derived for these 2 scales as the minimum VAS score among all the individual values that were collected at the scheduled postdose assessment time points. Similar statistical analyses to those described above for Emax were performed for the Emin values.

Descriptive statistics for each element of the Drug Similarity VAS Battery were reported for each study phase and treatment.

The pattern of missing data was assessed in the population of subjects who entered into the Treatment Phase and took at least 1 dose of study drug in the Treatment Phase by looking at the trend of dropout rates among the first 4 periods, as well as comparing the dropout rates among the 5 treatments.

For each statistical analysis performed (primary analysis [linear mixed-effects model], paired sample t-test, and nonparametric test), a sensitivity analysis was performed on all subjects who entered into the Treatment Phase and received at least 1 dose of study drug in the Treatment Phase, regardless of completion of all the 5 periods. The same model and model diagnosis procedure as the original analysis was implemented. In addition, a second sensitivity analysis was performed in response to the observation that variability in Emax was different between treatments (being much lower for placebo than for any other treatment). This analysis used the same mixed-effects model as the primary analysis but allowed for different variance components for treatment.

2.1.5 Sponsor's Pharmacodynamic Conclusions

- Similarity of lasmiditan to placebo in terms of the primary Drug Effects VAS parameter, Emax of at-the-moment Drug Liking, was not demonstrated at any dose tested; ie, the possibility that lasmiditan had a higher abuse liability than placebo could not be ruled out. In addition, dissimilarity of lasmiditan to the positive control, 2 mg alprazolam, in terms of Emax of Drug Liking score was not demonstrated at the supratherapeutic dose of lasmiditan, although it was demonstrated at the 2 clinical doses.
- Mean Drug Liking scores were consistently greater for alprazolam than for all doses of lasmiditan. Alprazolam reached a greater Emax and the score remained elevated for longer, returning to baseline by 24 hours postdose compared to 8 hours postdose for lasmiditan.
- The results of the statistical analyses of Emax or Emin of the secondary parameters of the Drug Effects VAS generally indicated that all doses of lasmiditan tested had a higher abuse liability than placebo but a lower abuse liability than 2 mg alprazolam. Notable exceptions were the mean Emin of Agitation/Relaxation was similar between alprazolam and the

supratherapeutic dose of lasmiditan, and the median E_{max} of Hallucinations differed from that of placebo at only the supratherapeutic dose of lasmiditan.

- The results of the Drug Similarity VAS assessments indicated that poly-drug users considered the effects of lasmiditan to be more similar to those of benzodiazepines than those of any other drug class, with mean similarity VAS scores for lasmiditan to benzodiazepines of 57.2 to 74.6 compared to 88.1 for alprazolam to benzodiazepines.
- There was a dose-related trend in the incidence of AEs which may represent a sign of abuse liability for lasmiditan, especially somnolence, euphoria, and feeling of relaxation.
- No safety concerns were noted in the clinical laboratory, vital signs, or ECG data during the study.
- There was a dose-dependent increase in systemic exposure (C_{max} and AUC[0-∞]) to lasmiditan with increasing dose from 100 to 400 mg lasmiditan.

2.2 Data Location

The analysis datasets are located at

<\\CDSESUB1\evsprod\NDA211280\0017\m5\datasets\h8h-mc-lahb\analysis\programs>

2.3 Reviewer's Assessment

All analyses were conducted from the stand point of the pharmacodynamics analysis.

2.3.1 Descriptive Statistics

The descriptive statistics of E_{max} and TE_{max} for the primary PD endpoint Drug Liking, and secondary PD endpoints, High, Overall Drug Liking and Take Drug Again are provided in Table 1 and Table 2. Table 1 summarizes the mean, standard deviation, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum of E_{max} for the five treatments in the study. Table 2 summaries the information of TE_{max}.

Table 1. E_{max} Descriptive Statistics for Drug Liking, High, Overall Drug Liking and Take Drug Again, PD Population (N=53)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking	A-Alprazolam	85.13	11.41	53.00	79.00	87.00	94.00	100.00
	B-LY 100	68.53	16.20	50.00	50.00	65.00	81.00	100.00
	C-LY 200	73.23	16.95	50.00	56.00	76.00	86.00	100.00
	D-LY 400	76.43	15.24	50.00	63.00	77.00	88.00	100.00
	E-Placebo	52.72	7.65	50.00	50.00	50.00	50.00	89.00
High	A-Alprazolam	76.68	16.71	15.00	69.00	81.00	86.00	100.00
	B-LY 100	43.53	34.16	0.00	1.00	51.00	72.00	99.00
	C-LY 200	55.91	35.48	0.00	17.00	72.00	83.00	98.00
	D-LY 400	66.60	28.68	0.00	54.00	74.00	87.00	100.00
	E-Placebo	8.04	19.46	0.00	0.00	0.00	1.00	89.00

Overall Drug Liking	A-Alprazolam	85.85	14.41	50.00	76.00	91.00	96.00	100.00
	B-LY 100	71.60	19.96	16.00	50.00	74.00	88.00	100.00
	C-LY 200	72.25	20.70	0.00	57.00	74.00	88.00	100.00
	D-LY 400	77.15	19.40	17.00	66.00	83.00	91.00	100.00
	E-Placebo	52.89	8.26	45.00	50.00	50.00	50.00	83.00
Take Drug Again	A-Alprazolam	85.74	14.77	50.00	76.00	88.00	100.00	100.00
	B-LY 100	71.15	23.37	0.00	50.00	74.00	93.00	100.00
	C-LY 200	72.85	22.31	0.00	50.00	74.00	94.00	100.00
	D-LY 400	77.13	22.06	0.00	65.00	83.00	93.00	100.00
	E-Placebo	51.94	10.26	5.00	50.00	50.00	50.00	85.00

In Table 1, for Drug Liking VAS, mean Emax value for Alprazolam (85.13) is the highest, Placebo score is around neutral with mean of 52.72. Lasmiditan scores are higher than placebo but lower than Alprazolam, with mean Emax responses of 68.53, 73.23, and 76.43 for doses of 100 mg, 200 mg, and 400 mg, respectively.

For unipolar High VAS score, Alprazolam Emax has mean of 76.68 in the PD Population. Placebo has lower mean response of 8.04. Lasmiditan Drug High Emax values are higher than placebo but lower than Alprazolam, with mean responses of 43.53, 55.91 and 66.60 for 100 mg, 200 mg, and 400 mg Lasmiditan, respectively.

For Overall Drug Liking VAS, mean Emax value for Alprazolam (85.85) is the highest, Placebo score is around neutral with mean of 52.89. Lasmiditan scores are higher than placebo but lower than Alprazolam, with mean Emax responses of 71.60, 72.25, and 77.15 for doses of 100 mg, 200 mg, and 400 mg, respectively.

For Take Drug Again VAS, mean Emax value for Alprazolam (85.74) is the highest, Placebo score is around neutral with mean of 51.94. Lasmiditan scores are higher than placebo but lower than Alprazolam, with mean Emax responses of 71.15, 72.85, and 77.13 for doses of 100 mg, 200 mg, and 400 mg, respectively.

Table 2. TEmax (hours) Descriptive Statistics for Drug Liking and High, PD Population (N=53)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking	A-Alprazolam	3.94	3.55	0.50	2.00	3.00	4.50	24.00
	B-LY 100	2.21	3.74	0.00	0.00	1.50	2.00	24.00
	C-LY 200	1.42	1.38	0.00	0.50	1.50	1.50	6.00
	D-LY 400	2.15	2.42	0.00	1.00	1.50	2.50	12.00
	E-Placebo	0.59	1.82	0.00	0.00	0.00	0.00	12.00
High	A-Alprazolam	2.87	1.89	0.50	2.00	2.00	3.50	12.00
	B-LY 100	1.26	1.06	0.00	0.00	1.00	2.00	4.00
	C-LY 200	1.18	0.94	0.00	0.50	1.00	1.50	4.00
	D-LY 400	1.44	0.96	0.00	1.00	1.00	1.50	4.50
	E-Placebo	0.84	2.03	0.00	0.00	0.00	1.00	12.00

In Table 2, for Drug Liking VAS, the mean TEmax is more than one hour delayed for Alprazolam (3.94) comparing with Lasmiditan, the values are 2.21, 1.42 and 2.15 for doses of 100 mg, 200 mg, and 400 mg, respectively. For High VAS, the mean TEmax is also more than

one hour delayed for Alprazolam (2.87) comparing with Lasmiditan, the values are 1.26, 1.18 and 1.44 for doses of 100 mg, 200 mg, and 400 mg, respectively.

Figure 1 shows that following oral administration of a single dose of lasmiditan, there was a dose-dependent increase in Drug Liking score during the first 2 hours post-dose, which gradually returned to pre-dose levels by approximately 8 hours post-dose. For placebo, the mean Drug Liking score remained at approximately 50 (neither like nor dislike) at all time points. Following the positive control, 2 mg alprazolam, Drug Liking score increased at a similar rate to that following lasmiditan dosing but reached a greater score than any dose of lasmiditan (with Emax reached at approximately 2 hours post-dose) and the score remained elevated for longer before returning to 50's by 24 hours postdose.

Figure 1. Mean Drug Liking VAS Scores over time (PD Population, N=53)

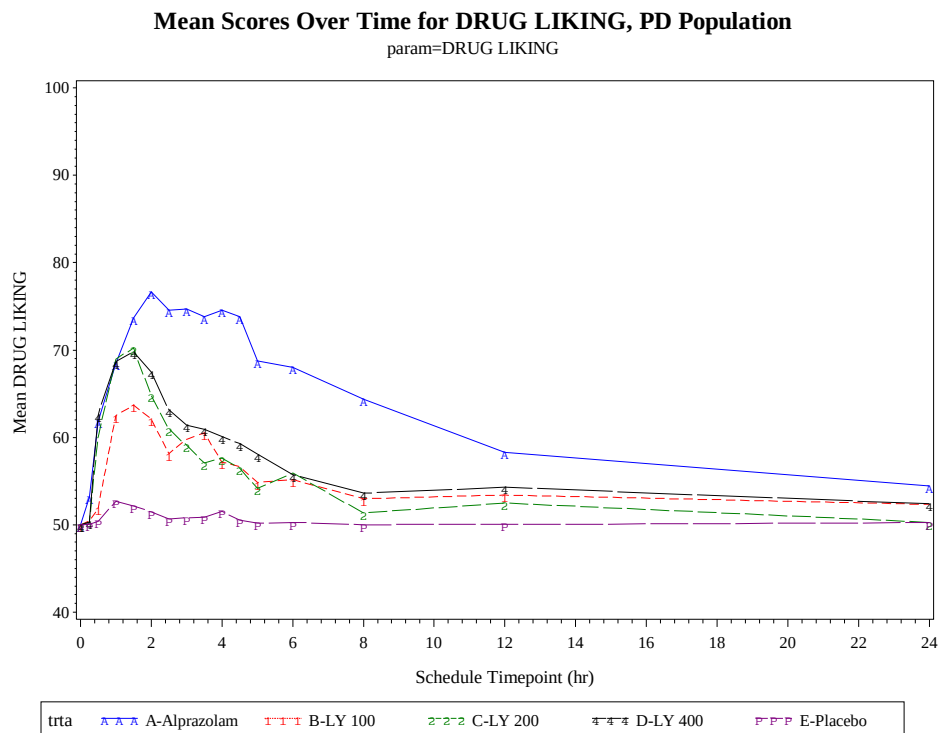


Figure 2. Mean High VAS Scores over time (PD Population, N=53)
Mean Scores Over Time for HIGH, PD Population

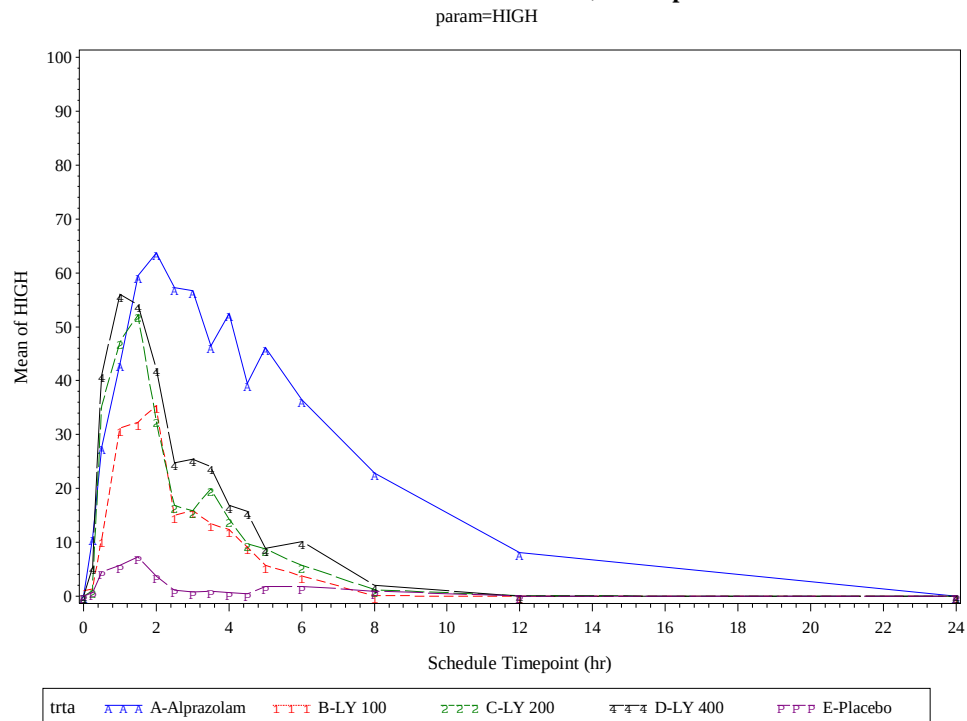


Figure 2 presents the Mean High VAS scores over time. Following oral administration of a single dose of lasmiditan, there was a dose-dependent increase in Drug Liking score during the first 1 hour post-dose, which gradually returned to pre-dose levels by approximately 8 hours post-dose. For placebo, the mean Drug Liking score remained <10 at all time points. Drug Liking score of alprazolam increased at a similar rate to that of lasmiditan, but reached a greater E_{max} after 1 hour post-dose, and the score remained elevated for longer before returning to baseline by 24 hours post-dose.

Individual E_{max} scores are displayed by subject for all treatments from Figure 3 to Figure 6. Each row represents one patient with 5 treatments. The darker color means more liking. The heatmaps show general more liking for Alprazolam comparing with lasmiditan 100 mg, but no significant difference between Alprazolam and lasmiditan 200 mg and 400mg.

Figure 3. Heatmap for Emax of Drug Liking VAS by treatment

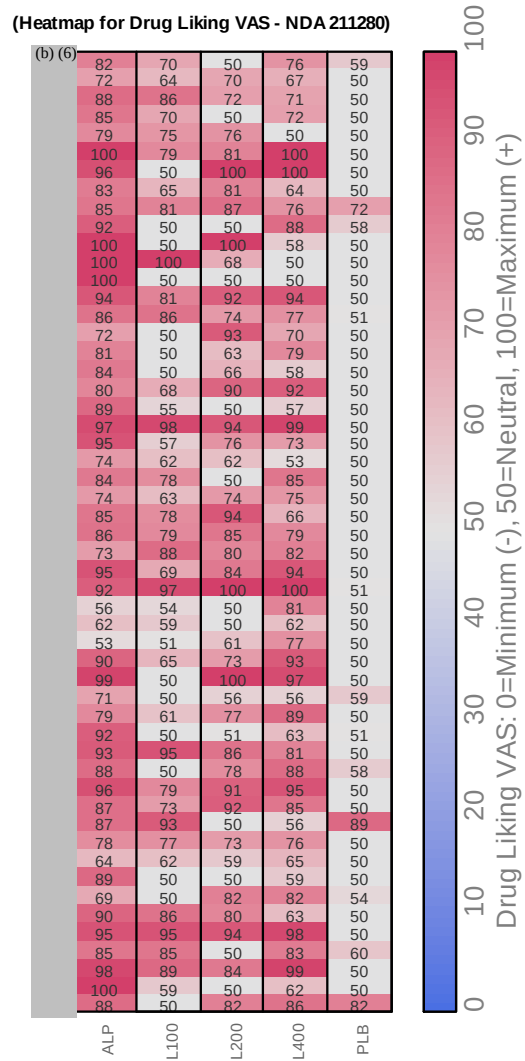


Figure 4. Heatmap for Emax of High VAS by treatment

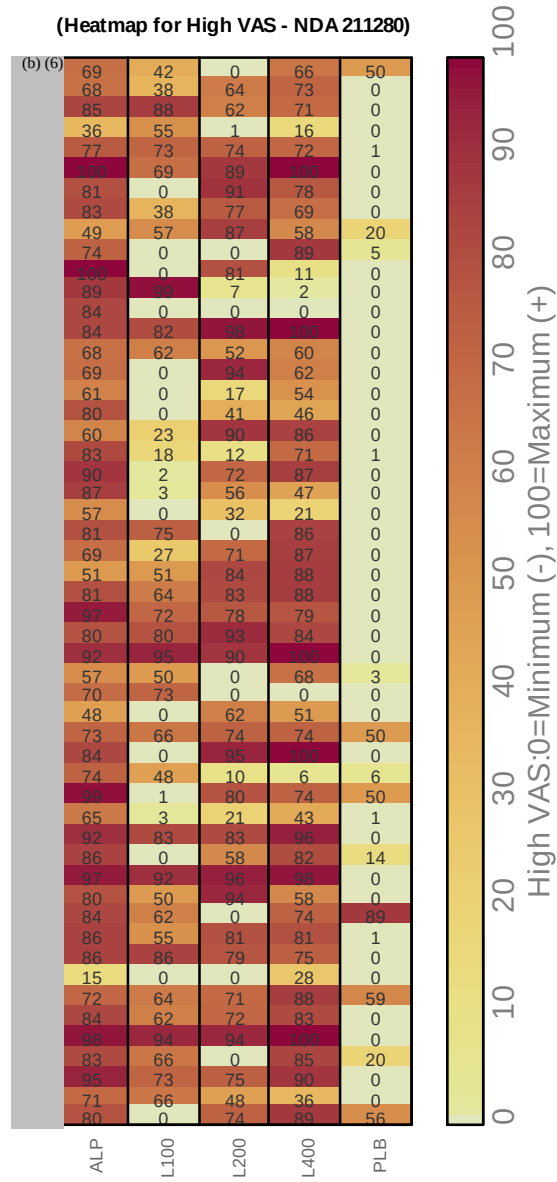


Figure 5. Heatmap for Emax of Overall Drug Liking VAS by treatment

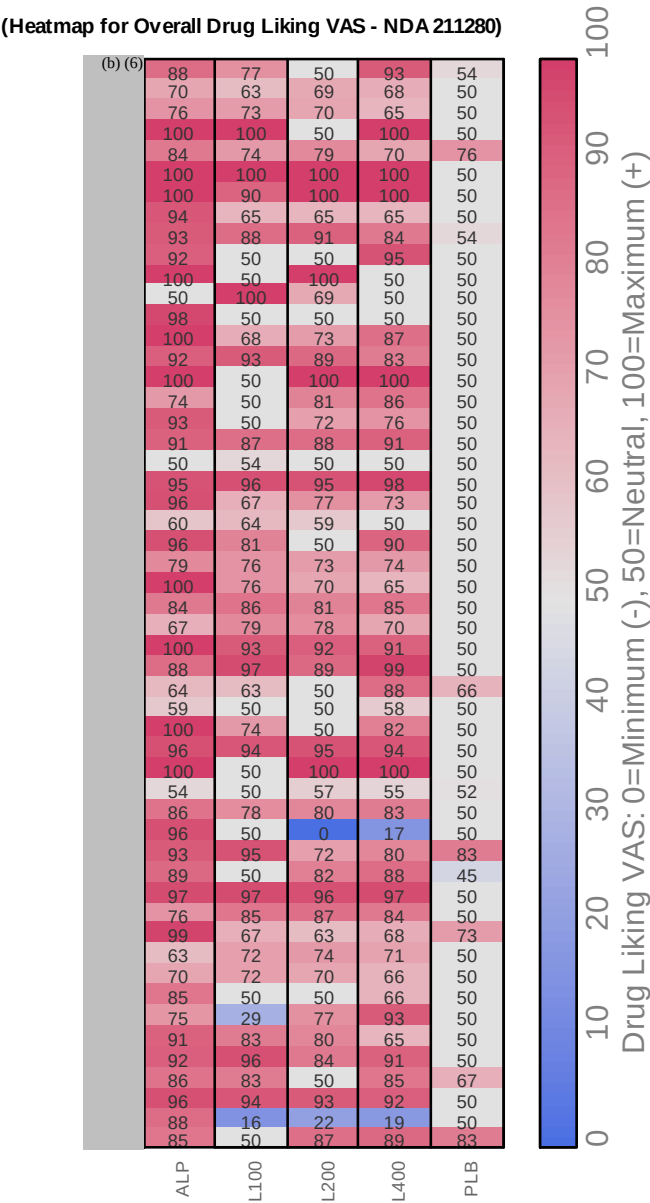
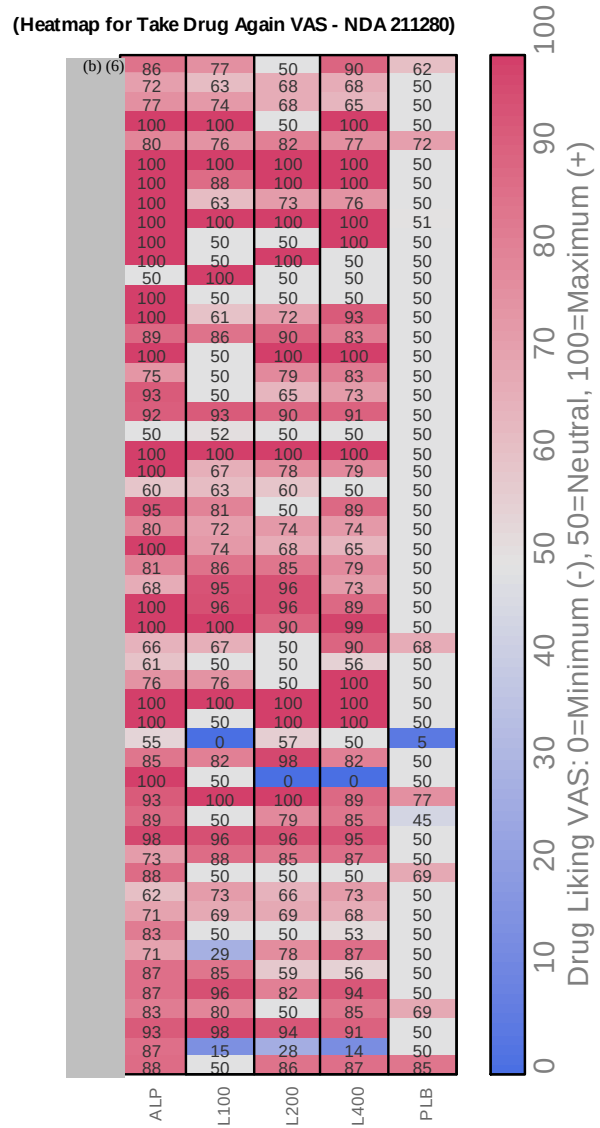


Figure 6. Heatmap for Emax of Take Drug Again VAS by treatment



2.3.2 Statistical Analysis

The statistical analysis of a HAP study should address whether:

- The known drug of abuse (positive control) produces reliable abuse-related responses compared to placebo.
- The test drug produces abuse-related responses that are smaller than the positive control.
- The test drug produces abuse-related responses that are similar to placebo.

To address these issues, the following hypotheses should be tested:

1. Validation of the Appropriateness of the Positive Control

(1) Primary endpoint: Drug Liking Emax

For study validity purpose, the primary endpoint, Emax for Drug Liking VAS, will be compared between each of the positive controls and placebo. Each comparison will assess the null hypothesis that the mean difference in Drug Liking Emax between the positive control and placebo is less than or equal to 15 against the alternative hypothesis that the mean difference in Drug Liking Emax between the positive control and placebo is greater than 15. The hypothesis can be expressed as:

$$H_0: \mu_C - \mu_P \leq 15 \text{ versus } H_a: \mu_C - \mu_P > 15$$

where μ_C is the mean for the positive controls, and μ_P is the mean for placebo. If the treatment difference is statistically significant and the lower confidence limit for the difference exceeds 15, then validity is established for the study.

2. Comparison between the positive controls and the test drug

Comparison between the positive controls (Alprazolam), and Lasmiditan can be expressed as (where μ_T is the mean for the Lasmiditan dose):

$$H_0: \mu_C - \mu_T \leq 0 \text{ versus } H_a: \mu_C - \mu_T > 0$$

3. Comparisons between each dose of the test drug and placebo

The hypothesis for comparison between each dose of Lasmiditan, and placebo will be:

$$H_0: \mu_T - \mu_P \geq 11 \text{ versus } H_a: \mu_T - \mu_P < 11$$

The primary endpoint and key secondary endpoints will be analyzed using a mixed-effect model if the distribution of the residuals is normal. The model will include treatment, period, sequence, as fixed effects, and subject as a random effect. If this criterion is not met, each paired difference will be investigated for normality using the Shapiro-Wilk W-test. If the p-value for the distribution of the paired difference is ≥ 0.05 or the distribution is quite symmetric (skewness between -0.5 and 0.5), a paired t-test will be used. Means, SE, and one-sided 95% CIs for treatment differences will be presented. P-values will be provided for the contrasts from the paired t-tests. If the paired differences are not normally distributed and not symmetric, pairwise treatment comparisons will be assessed using the sign test. The median, first and third quartiles,

1-sided 95% CI, and the p-value for the paired difference will be presented. In this study, the normality assumption tests were met.

Note, in this NDA study, sponsor used 14 as the test margin, the conclusions are the same by using margin 11.

Table 3 summaries the results of Comparison of Drug Liking VAS Emax for the three tests.

Table 3. Comparison of Drug Liking VAS Emax – Primary endpoint, PD Population

Treatments	LS Mean	StdE	Lower	Upper	
A-Alprazolam	85.38	1.61	82.15	88.61	
B-LY 100	68.59	2.22	64.14	73.04	
C-LY 200	73.33	2.30	68.71	77.95	
D-LY 400	76.60	2.05	72.50	80.70	
E-Placebo	53.00	1.13	50.70	55.30	
Contrasts	LS Mean	StdE	P-value	Lower	Upper
Positive Controls vs. Placebo (Trial Validity, $H_0: \mu_C - \mu_P \leq 15$)					
A-Alprazolam vs. E-Placebo	32.38	1.79	<.0001	29.39	Infy
Positive Controls vs. Lasmiditan (Relative Abuse Potential, $H_0: \mu_C - \mu_T \leq 0$)					
A-Alprazolam vs B-LY 100	16.79	2.62	<.0001	12.43	Infy
A-Alprazolam vs C-LY 200	12.05	2.69	0.0053	7.57	Infy
A-Alprazolam vs D-LY 400	8.78	2.47	0.0003	4.67	Infy
Lasmiditan vs. Placebo (Absolute Abuse Potential, $H_0: \mu_T - \mu_P \geq 11$)					
B-LY 100 vs. E-Placebo	15.59	2.35	0.9722	-Infy	19.52
C-LY 200 vs. E-Placebo	20.33	2.44	0.9999	-Infy	24.39
D-LY 400 vs. E-Placebo	23.60	2.19	1	-Infy	27.25

Table 3 presents, for Emax Drug Liking:

- For the validation test: The validity of the study was determined from the comparison of Drug Liking Emax between positive control and placebo. Emax of Alprazolam was significantly higher than placebo by the margin of 15 (p value< 0.01), thereby confirming study validity.
- For the relative abuse potential test: Lasmiditan was evaluated by the comparison of Drug Liking Emax scores of positive control versus each dose of Lasmiditan. All doses of Lasmiditan were significantly lower than Alprazolam on mean Emax (p value< 0.01).

Note: The reviewer used 0 as the test margin for the relative abuse potential test, while the sponsor used 5 as the test margin in their protocol, if margin=5 is used, then there is no significant difference between Alprazolam and Lasmiditan 400 mg (P value=0.065).

- For the absolute abuse potential test, Lasmiditan was evaluated by the comparison of Drug Liking Emax between each dose of Lasmiditan and placebo. The null hypothesis was defined as a mean difference in Drug Liking Emax of ≥ 11 points. If the null hypothesis was not rejected, then the results supported that the test drug was not similar to placebo. All doses of Lasmiditan (100 mg, 200 mg and 400 mg) were significantly higher than placebo (P value close to 1). Indicating that Lasmiditan has a strong abuse potential signal.

Note: For the absolute abuse potential test, sponsor used 14 as the test margin, the p values for the comparisons will be equal to 0.7493, 0.9942, 1.0 respectively, conclusions are the same.

Table 4. Comparison of High VAS Emax – PD Population

Treatments	LS Mean	StdE	Lower	Upper	
A-Alprazolam	77.15	2.31	72.50	81.81	
B-LY 100	43.65	4.71	34.21	53.08	
C-LY 200	56.10	4.66	46.75	65.44	
D-LY 400	66.90	3.64	59.61	74.20	
E-Placebo	8.56	3.04	2.41	14.72	
Contrasts	LS Mean	StdE	P-value	Lower	Upper
Positive Controls vs. Placebo (Trial Validity, H ₀ : μ _C - μ _P ≤ 15)					
A-Alprazolam vs. E-Placebo	68.59	3.24	<.0001	63.20	Infty
Positive Controls vs. Lasmiditan (Relative Abuse Potential, H ₀ : μ _C - μ _T ≤ 0)					
A-Alprazolam vs B-LY 100	33.51	4.84	<.0001	25.42	Infty
A-Alprazolam vs C-LY 200	21.06	4.80	<.0001	13.04	Infty
A-Alprazolam vs D-LY 400	10.25	3.81	0.0046	3.89	Infty
Lasmiditan vs. Placebo (Absolute Abuse Potential, H ₀ : μ _T - μ _P ≥ 11)					
B-LY 100 vs. E-Placebo	35.08	5.22	1	-Infty	43.78
C-LY 200 vs. E-Placebo	47.53	5.18	1	-Infty	56.16
D-LY 400 vs. E-Placebo	58.34	4.29	1	-Infty	65.48

Table 4 shows that for High VAS:

- For the validation test: Emax of Alprazolam was significantly higher than placebo (p value < 0.01), thereby confirming study validity.
- For the relative abuse potential test: All Lasmiditan doses (100 mg, 200 mg, and 400 mg) were significantly lower than Alprazolam on mean Emax (P value < 0.01).
- For the absolute abuse potential: Lasmiditan was evaluated by the comparison of High Emax between Lasmiditan and placebo. All doses of Lasmiditan (100 mg, 200 mg and 400 mg)

were significantly higher than placebo (P values are all equal 1), indicating that Lasmiditan has a strong abuse potential signal.

Table 5. Comparison of Overall Drug Liking VAS Emax – PD Population

Treatments	LS Mean	StdE	Lower	Upper	
A-Alprazolam	86.20	1.92	82.35	90.06	
B-LY 100	71.61	2.67	66.25	76.97	
C-LY 200	72.15	2.70	66.74	77.57	
D-LY 400	77.37	2.46	72.43	82.30	
E-Placebo	53.04	1.33	50.29	55.80	
Contrasts	LS Mean	StdE	P-value	Lower	Upper
Positive Controls vs. Placebo (Trial Validity, $H_0: \mu_C - \mu_P \leq 15$)					
A-Alprazolam vs. E-Placebo	33.16	2.08	<.0001	29.7	Infy
Positive Controls vs. Lasmiditan (Relative Abuse Potential, $H_0: \mu_C - \mu_T \leq 0$)					
A-Alprazolam vs B-LY 100	14.60	3.12	<.0001	9.4	Infy
A-Alprazolam vs C-LY 200	14.05	3.14	<.0001	8.8	Infy
A-Alprazolam vs D-LY 400	8.84	2.94	0.0018	3.9	Infy
Lasmiditan vs. Placebo (Absolute Abuse Potential, $H_0: \mu_T - \mu_P \geq 11$)					
B-LY 100 vs. E-Placebo	18.57	2.80	0.9956	-Infy	23.2
C-LY 200 vs. E-Placebo	19.11	2.82	0.9972	-Infy	23.8
D-LY 400 vs. E-Placebo	24.32	2.59	1	-Infy	28.7

Table 5 shows that for Overall Drug Liking VAS:

- For the validation test: Emax of Alprazolam was significantly higher than placebo (p value< 0.01), thereby confirming study validity.
- For the relative abuse potential test: All Lasmiditan doses (100 mg, 200 mg, and 400 mg) were significantly lower than Alprazolam on mean Emax (all P values <0.01).
- For the absolute abuse potential: Lasmiditan was evaluated by the comparison of Overall Drug Liking Emax between Lasmiditan and placebo. All doses of Lasmiditan (100 mg, 200 mg and 400 mg) were significantly higher than placebo (P values are close to 1), indicating that Lasmiditan has a strong abuse potential signal.

Table 6 Comparison of Take Drug Again VAS Emax – PD Population

Treatments	LS Mean	StdE	Lower	Upper	
A-Alprazolam	86.06	2.22	81.64	90.48	
B-LY 100	71.03	3.20	64.66	77.40	
C-LY 200	72.63	3.08	66.50	78.77	
D-LY 400	77.28	2.95	71.40	83.16	
E-Placebo	52.06	1.96	48.11	56.00	
Contrasts	LS Mean	StdE	P-value	Lower	Upper
Positive Controls vs. Placebo (Trial Validity, $H_0: \mu_C - \mu_P \leq 15$)					
A-Alprazolam vs. E-Placebo	34.00	2.07	<.0001	30.56	Infy
Positive Controls vs. Lasmiditan (Relative Abuse Potential, $H_0: \mu_C - \mu_T \leq 0$)					
A-Alprazolam vs B-LY 100	15.03	3.26	<.0001	9.59	Infy
A-Alprazolam vs C-LY 200	13.43	3.15	<.0001	8.17	Infy
A-Alprazolam vs D-LY 400	8.78	3.02	0.0025	3.74	Infy
Lasmiditan vs. Placebo (Absolute Abuse Potential, $H_0: \mu_T - \mu_P \geq 11$)					
B-LY 100 vs. E-Placebo	18.97	3.09	0.9939	-Infy	24.13
C-LY 200 vs. E-Placebo	20.58	2.97	0.999	-Infy	25.54
D-LY 400 vs. E-Placebo	25.23	2.84	1	-Infy	29.96

Table 6 shows that for Take Drug Again:

- For the validation test: Emax of Alprazolam was significantly higher than placebo (p value< 0.01), thereby confirming study validity.
- For the relative abuse potential test: All Lasmiditan doses (100 mg, 200 mg, and 400 mg) were significantly lower than Alprazolam on mean Emax (all P values <0.01).
- For the absolute abuse potential: Lasmiditan was evaluated by the comparison of Take Drug Again Emax between Lasmiditan and placebo. All doses of Lasmiditan (100 mg, 200 mg and 400 mg) were significantly higher than placebo (P values are close to 1), indicating that Lasmiditan has a strong abuse potential signal.

3. Conclusions

The primary objective of this trial was to assess the abuse potential of Lasmiditan compared to the positive control alprazolam and placebo.

The reviewer analyzed the primary PD endpoint of Drug Liking and the secondary PD endpoints: High VAS, Overall Drug Liking VAS and Take Drug Again. The results from the statistical reviewer's analyses indicate that:

- For the validation test: The validity of the study was determined from the comparison of Emax VAS score between positive control and placebo. Emax of Alprazolam was significantly higher than placebo (p value < 0.01), for Drug Liking (by the margin of 15), High VAS, Overall Drug Liking VAS and Take Drug Again, thereby confirming the study validity.
- For the relative abuse potential test: Lasmiditan was evaluated by the comparison of Emax scores of positive control versus each dose of Lasmiditan. For Drug Liking, Drug High, Overall Drug Liking and Take Drug Again, all doses of Lasmiditan (100 mg, 200 mg and 400 mg) had mean Emax score significantly lower than 2 mg Alprazolam (all p values < 0.01).

Note: For Drug Liking, the reviewer used 0 as the test margin for the relative abuse potential test, while the sponsor used 5 as the test margin in their protocol, if margin=5 is used, then there is no significant difference between Alprazolam and Lasmiditan 400 mg (P value=0.065).

- For the absolute abuse potential test: Lasmiditan was evaluated by the comparison of Emax score between Lasmiditan and placebo with the margin of 11. All doses of Lasmiditan (100 mg, 200 mg and 400 mg) were significantly higher than placebo (P values are close to 1).

In Summary, Lasmiditan has a strong abuse potential signal.

4. References

- 1) Guidance for Industry: Assessment of Abuse Potential for Drugs (January 2017)
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>

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YI TSONG
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation
CARCINOGENICITY STUDY

IND/NDA Number: NDA 211280

Drug Name: Lasmiditan

Indication: Acute treatment of migraine with or without aura in adults.

Applicant: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Test Facility for Rats and mice Studies: (b) (4)



Documents Reviewed: Study reports (Study 8302172 and 8302174) submitted on October 11, 2018 via NDA211280/0001; Electronic data submitted on April 1, 2019 via NDA211280/0020;

Biometrics Division: Division of Biometrics -6

Statistical Reviewer: Zhuang Miao, Ph.D.
Concurring Reviewer: Feng Zhou, MS
Karl Lin, Ph.D.

Medical Division: Division of Neurology Products

Reviewing Pharmacologist: Edmund Nesti, Ph.D.
Project Manager: Papanastasiou, Emilios

Keywords: Carcinogenicity, Dose response

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1. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in CrI:CD(SD) rats and one in CByB6F1-Tg(HRAS)2Jic hemizygous transgenic mice. These studies were intended to assess the carcinogenic potential of lasmiditan when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study: Two hundred and forty CrI:CD(SD) rats of each sex were randomly assigned to the treated and vehicle control group in equal size of 60 rats per group. The dose levels for treated groups were 10, 25, and 75 mg/kg/day. The rats in the vehicle control group received the vehicle (0.25% (w/v) methylcellulose (400 cps) in reverse osmosis water, pH 4.0 $\pm$ 0.05).

Survival analysis: For male rats, the survival analyses showed a statistically significant dose response relationship in mortality across the vehicle control group and treated groups. The pairwise comparisons showed a statistically significant differences in mortality between the vehicle control group and the high dose group.

Tumor analysis: For male rats, the trend test showed a statistically significant positive dose response in incidence in M-Carcinoma in Zymbal Gland (P-value=0.007 < 0.025). For male rats, the pairwise comparisons between the vehicle control and the individual treated groups showed a statistically significant increase in incidence in M-Fibrosarcoma in Skin/Subcutis (P-value=0.0459 < 0.05) in the 10 mg/kg/day group and in combined tumor of Fibrosarcoma and Sarcoma in Skin/Subcutis (P-value=0.0459 < 0.05) in the 10 mg/kg/day group when compared with the vehicle control group.

Mouse Study: One hundred CByB6F1-Tg(HRAS)2Jic mice of each sex were randomly assigned to the treated and vehicle control group in equal size of 25 mice per group. There are 10 mice of each sex in the positive control group. The dose levels for treated groups were 20, 50, and 150 mg/kg/day for male mice and 25, 80, and 250 mg/kg/day for female mice.

Survival analysis: The pairwise comparisons showed a statistically significant increase in mortality in the positive control group when compared to the vehicle control for the male and female mice.

Tumor analysis:

1. For female mice, the trend test showed statistically significant positive trends in incidence in M-Carcinoma, Bronchiolo-Alv in Lung (P-value=0.0186 < 0.05) and in combined tumor of Carcinoma and Adenoma, Bronchiolo-Alv in Lung (P-value=0.0138 < 0.05).
2. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of M-Malignant Lymphoma in Hemolympho-Reticu (P-value=0.0035), in B-Papilloma, Squamous Cell in Skin/Subcutis (P-value<0.001), in B-Papilloma, Squamous Cell in Stomach, Nonglandu (P-value<0.001), B-Carcinoma, Squamous Cell in Stomach, Nonglandu (P-value=0.0125), in Adenoma, Bronchiolar Alveolar in Lung (P-value=0.0108), Lymphoma in Multicentric Neopl (P-value=0.0136), in combined tumor of Adenoma, Bronchiolar Alveolar and Carcinoma in Lung (P-value=0.0423), and in Papilloma, Squamous Cell in Skin (P-value=0.0431) in male mice.
3. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of M-Malignant Lymphoma in Hemolympho-Reticu (P-value<0.001), of B-Papilloma, Squamous Cell in Skin/Subcutis (P-value<0.001), of M-Carcinoma, Squamous Cell in Skin/Subcutis (P-value=0.0323), and of B-Papilloma, Squamous Cell in Stomach, Nonglandu (P-value<0.001) in female mice.

2. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Crl:CD(SD) rats and one in CByB6F1-Tg(HRAS)2Jic hemizygous transgenic mice. These studies were intended to assess the carcinogenic potential of lasmiditan when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Edmund Nesti. This review analyzed the SAS data sets of these studies received from the sponsor on April 1, 2019 via NDA211280/0020.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as the dose increases.

3. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and forty Crl:CD(SD) rats of each sex were randomly assigned to the treated and vehicle control group in equal size of 60 rats per group. The dose levels for treated groups were 10, 25, and 75 mg/kg/day. The rats in the vehicle control group received the vehicle (0.25% (w/v) methylcellulose (400 cps) in reverse osmosis water, pH 4.0 $\pm$ 0.05). The study for the rats was designed to continue for up to 104 weeks. In accordance with study termination criteria, all surviving male rats were sacrificed during Week 105.

Table 1: Study Design in Rat Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Vehicle	60	60
2	10	Low	60	60
3	25	Med	60	60
4	75	High	60	60

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data were analyzed in accordance with current FDA guidelines (Food and Drug Administration, 2001). Tests to compare survival were performed, with a two-sided risk for increasing and decreasing mortality with dose. Tests were performed for dose response and for each dosed group against control using Kaplan-Meier product-limit estimates, along with log-rank and Wilcoxon tests. These were performed using the LIFETEST procedure in SAS.

Results of all pair-wise comparisons were reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings: Sponsor's analysis showed the numbers (percents) of death were 40 (66.7%), 45 (75%), 45 (75%), and 45 (75%) in vehicle control, 10 mg/kg/day, 25 mg/kg/day and 75 mg/kg/day dose groups, respectively in males and 42 (70%), 40 (66.7%), 46 (76.7%), and 45 (75%) in vehicle controls, 10 mg/kg/day, 25 mg/kg/day, and 75 mg/kg/day dose groups, respectively in females.

The sponsor concluded that,

1. For males, the test for trend was significant, $P = 0.0028$ and $P = 0.0026$ for the Log-Rank and Wilcoxon tests, respectively. The high-dose group (75 mg/kg/day) had higher mortality than control (45 out of 60 versus 40 of 60 in control), with $P = 0.0019$ for the Log-Rank test and $P = 0.0011$ for

the Wilcoxon test, respectively.

2. For females, there were no statistically significant differences in mortality.

3.1.2. Tumor data analysis

For each given tumor type, statistical analysis was performed if the incidence in at least one dosed group was increased by at least two occurrences over the control group. Tests to compare tumor incidence were performed, with a one-sided risk for increasing incidence with dose. Tests were performed for dose response and for each dosed group against control. Unadjusted P-values were reported for tumors. An indication of a possible treatment effect was assessed on the basis of rare or common tumor type, in line with the current FDA guidelines (Food and Drug Administration Draft Guidance for Industry, 2001).

Sponsor's findings: The sponsor's analyses showed a statistically significant increase in incidences in M-Carcinoma, basal cell in Skin/Subcutis (P-value=0.0478<0.05) in female rats when comparing the middle group to the vehicle control group.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on April 1, 2019 via NDA211280/0020.

3.2.1. Survival analysis

The survival distributions of animals in all four groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested for vehicle controls, low, medium and high dose groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 7 and 8 in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1 and 2 in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 9 and 10 in the appendix for males and females, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of death were 40 (67%), 45 (75%), 45 (75%), and 45 (75%) in vehicle control, 10 mg/kg/day, 25 mg/kg/day and 75 mg/kg/day dose groups, respectively in males and 42 (70%), 40 (67%), 46 (77%), and 45 (75%) in vehicle controls, 10 mg/kg/day, 25 mg/kg/day, and 75 mg/kg/day dose groups, respectively in females.

For male rats, the survival analyses showed a statistically significant dose response relationship in mortality across the vehicle control group and treated groups. The p-value of likelihood ratio test is 0.0495(<0.05). The pairwise comparisons showed a statistically significant difference in mortality between the vehicle control group and the high dose groups. The p-values for Likelihood Ratio test is 0.0019 (<0.05) and the p-values for Log-Rank test is 0.0015 (<0.05).

For female rats, the survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle control group and treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and each of the treated groups.

3.2.2. Tumor data analysis

The tumor data were analyzed for the positive dose response relationships and the positive pairwise comparison increases between each of the treated groups with control group. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies

at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group

size is defined as $\sum s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N . These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k , which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of $k=3$ is suggested in the literature. Hence, this reviewer used $k=3$ for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons are listed in Tables 11 and 12 in the appendix for male and female rats, respectively.

Adjustment for multiple testing: For the chronic study in rats, the adjustment of multiple testing of the dose response relationship for a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for the chronic rat study. For pairwise comparisons for the chronic rat study in the above type of submission with one chronic rat study and one transgenic mouse study, the same guidance document suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for the chronic rat study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 in either tests for dose response relationship or for pairwise comparisons between the vehicle control group and each of the treated groups.

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicles (N=60) P-Value Trend	10 mg/kg/day Low (N=60) P-Value – Vehicles vs. Low	25 mg/kg/day Med (N=60) P-Value – Vehicles vs. Medium	75 mg/kg/day High (N=60) P-Value – Vehicles vs. High
SKIN/SUBCUTIS	M-FIBROSARCOMA	0/60 (40) 0.8128	4/60 (36) 0.0459	0/60 (35) NC	0/60 (25) NC
	C_Fibrosarcoma+Sarcoma	0/60 (40) 0.8128	4/60 (36) 0.0459	0/60 (35) NC	2/60 (26) 0.1515
ZYMBAL GLAND	M-CARCINOMA	0/60 (40) 0.0070	0/60 (35) NC	0/60 (35) NC	3/60 (27) 0.0611
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.					

Reviewer's findings: Based on the above criterion for multiple testing adjustment, we make the following conclusions,

1. For male rats, the trend test showed a statistically significant positive trend in incidence in M-Carcinoma in Zymbal Gland (P-value=0.007 < 0.025).
2. For male rats, the pairwise comparisons between the vehicle controls and the treated groups showed a statistically significant increase in incidence in M-Fibrosarcoma in Skin/Subcutis (P-value=0.0459 < 0.05) in the 10 mg/kg/day group and in combined tumor of Fibrosarcoma and Sarcoma in Skin/Subcutis (P-value=0.0459 < 0.05) in the 10 mg/kg/day group when compared with the vehicle control group.

4. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred CByB6F1-Tg(HRAS)2Jic mice of each sex were randomly assigned to the treated and vehicle control group in equal size of 25 mice per group. There are 10 mice of each sex in the positive control group. The dose levels for treated groups were 20, 50, and 150 mg/kg/day for male mice and 25, 80, and 250 mg/kg/day for female mice. The mice in the vehicle control group received the vehicle ((0.25% [w/v] methylcellulose [400 cps] in reverse osmosis water, pH 4.0 ± 0.05)). The study was designed to continue for up to 26 weeks for both sexes, however in accordance with study termination criteria, all surviving mice were sacrificed during Week 27. The mice in the positive control group received N-methyl-N-nitrosourea; MNU via intraperitoneal injection once on Day 1 at a volume of 10 mL/kg.

Table 3: Study Design in Mouse Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Vehicle	25	25
2	20/25	Low	25	25
3	50/80	Middle	25	25
4	150/250	High	25	25
5	MNU	Positive	10	10

4.1. Sponsor's analyses

4.1.1. Survival analysis

The sponsor used the same survival analysis methods used for the rats study in this mouse study.

Sponsor's findings: The sponsor's analysis showed 2 (8%), 0 (0%), 0 (0%), 1 (4%), and 5 (50%) mortalities in male mice, and 0 (0%), 2 (8%), 0 (0%), 1 (4%), and 8 (80%) mortalities in female mice in vehicle control, low, medium, high dose groups and positive control group, respectively.

There were no statistically significant differences in survival rates in either males or females in any treated groups when compared with the vehicle control group.

For both males and females, the positive control group showed a statistically significant increase in mortality over the vehicle control group (For males, $p=0.0066$ and $p=0.0104$ for the Log-Rank and Wilcoxon tests respectively. For females, $p<0.0001$ for both the Log-Rank and Wilcoxon tests).

4.1.2. Tumor data analysis

The sponsor used the same tumor data analysis methods used for the rat study in this mouse study

Sponsor's findings: For males, hemolymphoreticular system malignant lymphoma had a statistically significant increased incidence in the positive control group (Group 5) compared with vehicle control ($p=0.0038$).

For females, hemolymphoreticular system malignant lymphoma had a statistically significant increased incidence in the positive control group (Group 5) compared with vehicle control ($p=0.0003$).

4.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on April 1, 2019 via NDA211280/0020. The significance level for all statistical tests was set at 0.05.

4.2.1. Survival analysis

The survival distributions of three treated groups, one vehical control group, one water control group and one positive control group were estimated using the Kaplan-Meier product limit method. The dose response relationship in survival was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 3 and 4 in the appendix for male and female mice, respectively. The intercurrent mortality data are given in Tables 13 and 14 in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals among the vehicle control and three treated groups are given in Tables 15 and 16 in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of death 2 (8%), 0 (0%), 0 (0%), 1 (4%), and 5 (50%) mortalities in male mice, and 0 (0%), 2 (8%), 0 (0%), 1 (4%), and 8 (80%) mortalities in female mice in vehicol control, low, medium, high dose groups and positive control group, respectively.

The survival analyses did not show a statistically significant dose response relationship in mortality across vehicle control and treated groups for either males or females. The pairwise comparisons did not show statistically significant differences in mortality between the vehicle control and each of the treated groups for either males or females.

The pairwise comparisons showed a statistically significant increase in mortality in the positive control group when compared to the vehicle control for the male and female mice. The p-values for Likelihood Ratio test are <0.0001 and <0.0001 and the p-values for Log-Rank test are <0.0001 and <0.0001, respectively.

4.2.2. Tumor data analysis

The reviewer used the same tumor data analysis methods for the rat study in this mouse study.

The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons between vehicle control and three treated groups, and between vehicle control and positive control are listed in Tables 17, 18, 19, 20 in the appendix for male and female mice, respectively.

Adjustment for multiple testing: For the adjustment of multiple testing of dose response relationship for the transgenic mouse study in a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.05$ for both common tumors and rare tumors for the mouse study. For pairwise, the same guidance document suggests the use of test levels $\alpha = 0.05$ for both common tumors and rare tumors for the mouse study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: The tumor types in Tables 4 (both trend tests and pairwise comparison using data of vehicle control and treated groups for female mice); and 5 and 6 (pairwise comparisons between vehicle and positive control groups for male mice and female mice, respectively) below showed p-values less than or equal to 0.05 in the tests for trend and for pairwise comparisons between the vehicle control group and each of the treated groups; and in comparison tests between the vehicle control group and the positive control group.

Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	25 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	80 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	250 mg/kg/day High (N=25) P-value - Vehicle vs. High
LUNG	M-CARCINOMA, BRONCHIOLO-ALV*	0/25 (25) 0.0186	0/25 (24) NC	1/25 (25) 0.5000	3/25 (25) 0.1173
	C_bronchiolo-alveo Adeno+Carcin	0/25 (25) 0.0138	1/25 (24) 0.4898	1/25 (25) 0.5000	4/25 (25) 0.0549
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.					

Table 5: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (23)	4/10 (9) 0.0035
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (23)	5/10 (8) <0.001
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (23)	7/10 (9) <0.001
	M-CARCINOMA, SQUAMOUS CELL	0/25 (23)	3/10 (8) 0.0125

Table 6: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and Positive Control-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (25)	7/10 (10) <0.001
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	7/10 (9) <0.001
	M-CARCINOMA, SQUAMOUS CELL	0/25 (25)	2/10 (6) 0.0323
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	5/10 (7) <0.001

Reviewer's findings: Based on the criteria of adjustment for multiple testing discussed in the mouse data analysis section, we make the following conclusions:

1. For female mice, the trend test showed statistically significant positive dose-responses in incidence in M-Carcinoma, Bronchiolo-Alv in Lung (P-value=0.0186 < 0.05), and in combined tumor of Carcinoma and Adenoma, Bronchiolo-Alv in Lung (P-value=0.0138 < 0.05).
2. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of M-Malignant Lymphoma in Hemolympho-Reticu (P-value=0.0035), of B-Papilloma, Squamous Cell in Skin/Subcutis (P-value<0.001), of B-Papilloma, Squamous Cell in Stomach, Nonglandu (P-value<0.001), of B-Carcinoma, Squamous Cell in Stomach, Nonglandu (P-value=0.0125), of Adenoma, Bronchiolar Alveolar in Lung (P-value=0.0108), of Lymphoma in Multicentric Neopl (P-value=0.0136), of combined tumor of Adenoma, Bronchiolar Alveolar and Carcinoma in Lung (P-value=0.0423), and of Papilloma, Squamous Cell in Skin (P-value=0.0431) in male mice.
3. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of M-Malignant Lymphoma in Hemolympho-Reticu (P-value<0.001), of B-Papilloma, Squamous Cell in Skin/Subcutis (P-value<0.001), of M-Carcinoma, Squamous Cell in Skin/Subcutis (P-value=0.0323), and of B-Papilloma, Squamous Cell in Stomach, Nonglandu (P-value<0.001) in female mice.

5. Conclusion

In this submission the sponsor included reports of two animal carcinogenicity studies, one in CrI:CD(SD) rats and one in CByB6F1-Tg(HRAS)2Jic hemizygous transgenic mice. These studies were intended to assess the carcinogenic potential of lasmiditan when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study: Two hundred and forty CrI:CD(SD) rats of each sex were randomly assigned to the treated and vehicle control group in equal size of 60 rats per group. The dose levels for treated groups were 10, 25, and 75 mg/kg/day. The rats in the vehicle control group received the vehicle (0.25% (w/v) methylcellulose (400 cps) in reverse osmosis water, pH 4.0 $\pm$ 0.05).

Survival analysis: For male rats, the survival analyses showed a statistically significant dose response relationship in mortality across the vehicle control group and treated groups. The pairwise comparisons showed a statistically significant differences in mortality between the vehicle control group and the high dose group.

Tumor analysis: For male rats, the trend test showed a statistically significant positive dose response in incidence in M-Carcinoma in Zymbal Gland (P-value=0.007 < 0.025). For male rats, the pairwise comparisons between the vehicle control and the individual treated groups showed a statistically significant increase in incidence in M-Fibrosarcoma in Skin/Subcutis (P-value=0.0459 < 0.05) in the 10 mg/kg/day group and in combined tumor of Fibrosarcoma and Sarcoma in Skin/Subcutis (P-value=0.0459 < 0.05) in the 10 mg/kg/day group when compared with the vehicle control group.

Mouse Study: One hundred CByB6F1-Tg(HRAS)2Jic mice of each sex were randomly assigned to the treated and vehicle control group in equal size of 25 mice per group. There are 10 mice of each sex in the positive control group. The dose levels for treated groups were 20, 50, and 150 mg/kg/day for male mice and 25, 80, and 250 mg/kg/day for female mice.

Survival analysis: The pairwise comparisons showed a statistically significant increase in mortality in the positive control group when compared to the vehicle control for the male and female mice.

Tumor analysis:

1. For female mice, the trend test showed statistically significant positive trends in incidence in M-Carcinoma, Bronchiolo-Alv in Lung (P-value=0.0186 < 0.05) and in combined tumor of Carcinoma and Adenoma, Bronchiolo-Alv in Lung (P-value=0.0138 < 0.05).
2. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of M-Malignant Lymphoma in Hemolympho-Reticu (P-value=0.0035), in B-Papilloma, Squamous Cell in Skin/Subcutis (P-value<0.001), in B-Papilloma, Squamous Cell in Stomach, Nonglandu (P-value<0.001), B-Carcinoma, Squamous Cell in Stomach, Nonglandu (P-value=0.0125), in Adenoma, Bronchiolar Alveolar in Lung (P-value=0.0108), Lymphoma in Multicentric Neopl (P-value=0.0136), in combined tumor of Adenoma, Bronchiolar Alveolar and Carcinoma in Lung (P-value=0.0423), and in Papilloma, Squamous Cell in Skin (P-value=0.0431) in male mice.
3. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of M-Malignant Lymphoma in Hemolympho-Reticu (P-value<0.001), of B-Papilloma, Squamous Cell in Skin/Subcutis (P-value<0.001), of M-Carcinoma, Squamous Cell in Skin/Subcutis (P-value=0.0323), and of B-Papilloma, Squamous Cell in Stomach, Nonglandu (P-value<0.001) in female mice.

Zhuang Miao, Ph.D.

NDA211280

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Mathematical Statistician

Concur:
Feng Zhou, MS
Mathematical Statistician, Biometrics-6

Karl Lin, Ph.D.
Mathematical Statistician, Team Leader, Biometrics-6

cc:
Archival NDA 211280
Yi Tsong, Ph.D.
Edmund Nesti, Ph.D.
Papanastasiou, Emilios

6. Appendix
Table 7: Intercurrent Mortality Rate -Male Rats

	Vehicle Control 0 mg/kg/day (N=60)		10 mg/kg/day (N=60)		25 mg/kg/day (N=60)		75 mg/kg/day (N=60)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	2	3.33	5	8.33	6	10.00	3	5.00
53 - 78	13	25.00	22	45.00	15	35.00	32	58.33
79 - 91	14	48.33	6	55.00	13	56.67	9	73.33
92 - 103	11	66.67	12	75.00	11	75.00	1	75.00
Ter. Sac.	20	33.33	15	25.00	15	25.00	15	25.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 8: Intercurrent Mortality Rate -Female Rats

	Vehicle Control 0 mg/kg/day (N=60)		10 mg/kg/day (N=60)		25 mg/kg/day (N=60)		75 mg/kg/day (N=60)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	2	3.33	2	3.33	5	8.33	7	11.67
53 - 78	22	40.00	19	35.00	27	53.33	20	45.00
79 - 91	13	61.67	16	61.67	11	71.67	17	73.33
92 - 103	5	70.00	3	66.67	3	76.67	1	75.00
Ter. Sac.	18	30.00	20	33.33	14	23.33	15	25.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 9: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Male Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.0495	0.2026	0.1981	0.0019
Homogeneity	Log-Rank	0.1652	0.1966	0.1914	0.0015

Table 10: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Female Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicles vs. Low	P_Value Vehicles vs. Medium	P_Value Vehicles vs. High
Dose-Response	Likelihood Ratio	0.1846	0.6533	0.1114	0.1376
Homogeneity	Log-Rank	0.2738	0.6470	0.1042	0.1303

Table 11: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=60) P-value - Trend	10 mg/kg/day Low (N=60) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=60) P-value - Vehicle vs. Med	75 mg/kg/day High (N=60) P-value - Vehicle vs. High
ADRENAL, CORTEX	B-ADENOMA	3/60 (41) 0.9852	3/60 (36) 0.5982	0/60 (35) 1.0000	0/60 (25) 1.0000
	M-CARCINOMA	0/60 (40) 0.7037	1/60 (35) 0.4667	0/60 (35) NC	0/60 (25) NC
ADRENAL, MEDULLA	B-PHEOCHROMOCYTOMA	10/60 (42) 0.7185	4/60 (36) 0.9624	3/60 (35) 0.9839	4/60 (26) 0.8747
	M-MALIGNANT PHEOCHROMOCYTOMA	1/60 (40) 0.7635	1/60 (35) 0.7189	1/60 (35) 0.7189	0/60 (25) 1.0000
Adrenals Medulla	C_Pheochromocytoma B+M	11/60 (42) 0.8004	5/60 (36) 0.9494	4/60 (35) 0.9746	4/60 (26) 0.9132
Adrenals Cortex	C_Adenoma+Carcinoma	3/60 (41) 0.9839	4/60 (36) 0.4263	0/60 (35) 1.0000	0/60 (25) 1.0000
BONE, OTHER	M-OSTEOSARCOMA	0/60 (40) 0.7582	2/60 (36) 0.2211	0/60 (35) NC	0/60 (25) NC
BRAIN	B-GRANULAR CELL TUMOR	1/60 (40) 0.3372	0/60 (35) 1.0000	0/60 (35) 1.0000	1/59 (25) 0.6250
	M-MALIGNANT GLIOMA	0/60 (40) 0.4765	0/60 (35) NC	3/60 (36) 0.1016	0/59 (25) NC
EPIDIDYMIS	M-MALIGNANT MESOTHELIOMA	1/60 (41) 1.0000	0/60 (35) 1.0000	0/60 (35) 1.0000	0/60 (25) 1.0000
EYE	M-MELANOMA, AMELANOTIC	0/60 (40) 0.4444	0/60 (35) NC	1/58 (35) 0.4667	0/60 (25) NC
HEART	M-ENDOCARDIAL SCHWANNOMA	0/60 (40) 0.5275	1/60 (36) 0.4737	2/60 (36) 0.2211	0/60 (25) NC
HEMOLYMPHO- RETICU	M-HISTIOCYTIC SARCOMA	1/60 (40) 0.9150	1/60 (36) 0.7263	0/60 (35) 1.0000	0/60 (25) 1.0000
	M-LARGE GRANULAR CELL LEUKE*	1/60 (40) 1.0000	0/60 (35) 1.0000	0/60 (35) 1.0000	0/60 (25) 1.0000
	M-LEUKEMIA, GRANULOCYTIC	0/60 (40) 0.7059	1/60 (36) 0.4737	0/60 (35) NC	0/60 (25) NC
KIDNEY	B-LIPOMA	0/60 (40) 0.0377	0/60 (35) NC	0/60 (35) NC	2/60 (27) 0.1588
	M-LIPOSARCOMA	0/60 (40) 0.7037	1/60 (35) 0.4667	0/60 (35) NC	0/60 (25) NC
	M-NEPHROBLASTOMA	0/60 (40) 0.4485	0/60 (35) NC	1/60 (36) 0.4737	0/60 (25) NC
LIVER	M-CARCINOMA, HEPATOCELLULAR	0/60 (40) 0.4444	0/60 (35) NC	1/60 (35) 0.4667	0/60 (25) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=60) P-value - Trend	10 mg/kg/day Low (N=60) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=60) P-value - Vehicle vs. Med	75 mg/kg/day High (N=60) P-value - Vehicle vs. High
LYMPH NODE, MESENT	B-LYMPHANGIOMA	0/59 (40) 0.4444	0/60 (35) NC	1/60 (35) 0.4667	0/60 (25) NC
	M-HEMANGIOSARCOMA	1/59 (40) 0.2815	0/60 (35) 1.0000	3/60 (36) 0.2685	1/60 (26) 0.6364
MAMMARY GLAND	B-FIBROADENOMA	1/60 (40) 0.3929	1/60 (36) 0.7263	1/60 (35) 0.7189	1/60 (26) 0.6364
	M-CARCINOMA	0/60 (40) 0.4485	0/60 (35) NC	1/60 (36) 0.4737	0/60 (25) NC
MANDIBULAR SALIVAR	M-SARCOMA	0/59 (39) 0.7111	1/59 (36) 0.4800	0/60 (35) NC	0/60 (25) NC
MUSCLE, BICEPS FEM	B-GRANULAR CELL TUMOR	1/60 (40) 1.0000	0/60 (35) 1.0000	0/60 (35) 1.0000	0/60 (25) 1.0000
PANCREAS	B-ADENOMA, ACINAR CELL	0/60 (40) 0.7037	1/60 (35) 0.4667	0/60 (35) NC	0/60 (25) NC
	B-ADENOMA, ISLET CELL	3/60 (41) 0.7555	5/60 (36) 0.2846	7/60 (36) 0.1075	1/60 (26) 0.8679
	M-CARCINOMA, ISLET CELL	2/60 (40) 0.8158	1/60 (35) 0.8537	2/60 (35) 0.6403	0/60 (25) 1.0000
Pancreas	C_Islet cell Adenoma+Acinar cell Adenoma	3/60 (41) 0.7892	6/60 (36) 0.1794	7/60 (36) 0.1075	1/60 (26) 0.8679
	C_Islet cell Adenoma+Carcinoma	5/60 (41) 0.8735	6/60 (36) 0.4065	9/60 (37) 0.1361	1/60 (26) 0.9549
PARATHYROID	B-ADENOMA	1/56 (37) 0.2954	3/58 (35) 0.2863	4/57 (35) 0.1617	2/57 (25) 0.3543
PITUITARY	B-ADENOMA	39/60 (50) 0.1177	40/60 (50) 0.5000	43/60 (52) 0.3642	46/60 (53) 0.1803
	M-CARCINOMA	2/60 (41) 0.7452	0/60 (35) 1.0000	2/60 (36) 0.6416	0/60 (25) 1.0000
Pituitary	C_Adenoma+Carcinoma	41/60 (51) 0.1669	40/60 (50) 0.6175	45/60 (52) 0.2831	46/60 (53) 0.2688
PROSTATE	B-ADENOMA	0/60 (40) 0.4444	0/60 (35) NC	1/60 (35) 0.4667	0/60 (25) NC
	M-CARCINOMA	1/60 (41) 0.1504	1/60 (36) 0.7198	0/60 (35) 1.0000	2/60 (27) 0.3455
Prostate	C_Adenoma+Carcinoma	1/60 (41) 0.1604	1/60 (36) 0.7198	1/60 (35) 0.7123	2/60 (27) 0.3455
SKIN/SUBCUTIS	B-ADENOMA, SEBACEOUS	1/60 (40) 0.3929	1/60 (36) 0.7263	1/60 (35) 0.7189	1/60 (26) 0.6364
	B-BASAL CELL TUMOR	0/60 (40) 0.1912	0/60 (35) NC	0/60 (35) NC	1/60 (26) 0.3939
	B-FIBROMA	5/60 (42) 0.6551	4/60 (36) 0.6757	9/60 (40) 0.1634	2/60 (26) 0.8315

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=60) P-value - Trend	10 mg/kg/day Low (N=60) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=60) P-value - Vehicle vs. Med	75 mg/kg/day High (N=60) P-value - Vehicle vs. High
	B-KERATOACANTHOMA	2/60 (41) 0.7638	6/60 (38) 0.1085	3/60 (36) 0.4376	1/60 (26) 0.7775
	B-LIPOMA	0/60 (40) 0.6994	3/60 (36) 0.1016	2/60 (36) 0.2211	0/60 (25) NC
	B-MYXOMA	0/60 (40) 0.7037	1/60 (35) 0.4667	0/60 (35) NC	0/60 (25) NC
	B-PAPILLOMA, SQUAMOUS CELL	2/60 (41) 0.4600	0/60 (35) 1.0000	1/60 (36) 0.8543	1/60 (26) 0.7775
	B-PILOMATRICOMA	2/60 (41) 0.5113	1/60 (35) 0.8484	2/60 (35) 0.6303	1/60 (26) 0.7775
	M-CARCINOMA, BASAL CELL	1/60 (40) 0.3469	0/60 (35) 1.0000	0/60 (35) 1.0000	1/60 (26) 0.6364
	M-CARCINOMA, SEBACEOUS	0/60 (40) 0.1912	0/60 (35) NC	0/60 (35) NC	1/60 (26) 0.3939
	M-FIBROSARCOMA	0/60 (40) 0.8128	4/60 (36) 0.0459	0/60 (35) NC	0/60 (25) NC
	M-MELANOMA, AMELANOTIC	1/60 (40) 0.9150	1/60 (36) 0.7263	0/60 (35) 1.0000	0/60 (25) 1.0000
	M-SARCOMA	0/60 (40) 0.0354	0/60 (35) NC	0/60 (35) NC	2/60 (26) 0.1515
Skin Subcutis	C_Fibrosarcoma+Sarcoma	0/60 (40) 0.8128	4/60 (36) 0.0459	0/60 (35) NC	2/60 (26) 0.1515
	C_Keratoa+Papilloma+Carcinoma	4/60 (42) 0.3402	6/60 (38) 0.3057	3/60 (36) 0.7155	4/60 (27) 0.3810
SPINAL CORD	B-GLIOMA	1/59 (40) 1.0000	0/60 (35) 1.0000	0/60 (35) 1.0000	0/60 (25) 1.0000
SPLEEN	M-HEMANGIOSARCOMA	0/60 (40) 0.5384	1/60 (35) 0.4667	1/60 (35) 0.4667	0/60 (25) NC
STOMACH, GLANDULAR	M-LEIOMYOSARCOMA	0/60 (40) 0.4444	0/60 (35) NC	1/60 (35) 0.4667	0/60 (25) NC
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/60 (40) 0.4444	0/60 (35) NC	1/60 (35) 0.4667	0/60 (25) NC
	M-CARCINOMA, SQUAMOUS CELL	0/60 (40) 0.7059	1/60 (36) 0.4737	0/60 (35) NC	0/60 (25) NC
TESTIS	B-INTERSTITIAL CELL TUMOR	1/60 (40) 0.6932	0/60 (35) 1.0000	1/60 (35) 0.7189	0/60 (25) 1.0000
	M-MALIGNANT MESOTHELIOMA	1/60 (41) 1.0000	0/60 (35) 1.0000	0/60 (35) 1.0000	0/60 (25) 1.0000
THYMUS	M-MALIGNANT SCHWANNOMA	1/60 (41) 1.0000	0/56 (33) 1.0000	0/56 (32) 1.0000	0/57 (24) 1.0000
THYROID	B-ADENOMA, C-CELL	9/60 (42) 0.6263	9/60 (38) 0.5097	12/60 (37) 0.1978	5/60 (27) 0.7221

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=60) P-value - Trend	10 mg/kg/day Low (N=60) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=60) P-value - Vehicle vs. Med	75 mg/kg/day High (N=60) P-value - Vehicle vs. High
	B-GANGLIONEUROMA	0/60 (40) 0.1912	0/60 (35) NC	0/60 (35) NC	1/60 (26) 0.3939
	M-CARCINOMA, C-CELL	3/60 (41) 0.2993	3/60 (36) 0.5982	2/60 (35) 0.7676	3/60 (27) 0.4493
	M-CARCINOMA, FOLLICULAR CELL	1/60 (40) 0.4760	2/60 (36) 0.4600	1/60 (35) 0.7189	1/60 (26) 0.6364
Thyroid	C_C-cell Adenoma+Carcinoma	11/60 (43) 0.5783	12/60 (39) 0.3908	13/60 (37) 0.2465	7/60 (28) 0.6271
Whold Body	C_hemangiosarcoma	1/60 (41) 0.2776	0/60 (35) 1.0000	3/60 (36) 0.2598	1/60 (26) 0.6291
ZYMBAL GLAND	M-CARCINOMA	0/60 (40) 0.0070	0/60 (35) NC	0/60 (35) NC	3/60 (27) 0.0611

Table 12: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=60) P-value - Trend	10 mg/kg/day Low (N=60) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=60) P-value - Vehicle vs. Med	75 mg/kg/day High (N=60) P-value - Vehicle vs. High
ADRENAL, CORTEX	B-ADENOMA	1/60 (30) 0.5520	2/60 (32) 0.5246	1/60 (26) 0.7175	1/60 (26) 0.7175
ADRENAL, MEDULLA	B-PHEOCHROMOCYTOMA	3/59 (30) 0.7490	1/60 (32) 0.9509	1/60 (26) 0.9254	1/60 (26) 0.9254
	M-MALIGNANT PHEOCHROMOCYTOMA	1/59 (29) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/60 (25) 1.0000
Adrenals Medulla	C_Pheochromocytoma B+M	3/60 (31) 0.7426	1/60 (32) 0.9472	1/60 (26) 0.9203	1/60 (26) 0.9203
BRAIN	B-GRANULAR CELL TUMOR	0/60 (30) 0.2301	0/60 (31) NC	0/60 (26) NC	1/60 (26) 0.4643
	B-MENINGIOMA	0/60 (30) 0.4554	0/60 (31) NC	1/60 (26) 0.4643	0/60 (25) NC
	M-MALIGNANT GLIOMA	1/60 (31) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/60 (25) 1.0000
CERVIX	B-GRANULAR CELL TUMOR	1/60 (30) 0.7056	0/60 (31) 1.0000	1/60 (26) 0.7175	0/59 (25) 1.0000
	M-SARCOMA, STROMAL	1/60 (30) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/59 (25) 1.0000
HEMOLYMPHO- RETICU	M-HISTIOCYTIC SARCOMA	0/60 (30) 0.2301	0/60 (31) NC	0/60 (26) NC	1/60 (26) 0.4643
	M-MALIGNANT LYMPHOMA	1/60 (30) 0.9313	1/60 (32) 0.7700	0/60 (26) 1.0000	0/60 (25) 1.0000
KIDNEY	B-LIPOMA	0/60 (30) 0.7321	1/60 (31) 0.5082	0/60 (26) NC	0/60 (25) NC
	M-FIBROSARCOMA	1/60 (31) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/60 (25) 1.0000
LIVER	B-ADENOMA, HEPATOCELLULAR	1/60 (30) 1.0000	0/60 (31) 1.0000	0/59 (25) 1.0000	0/60 (25) 1.0000
MAMMARY GLAND	B-ADENOMA	0/59 (29) 0.3024	4/60 (33) 0.0734	1/60 (26) 0.4727	2/59 (26) 0.2189
	B-FIBROADENOMA	33/59 (44) 0.9834	30/60 (44) 0.8277	26/60 (39) 0.8595	17/59 (33) 0.9913
	M-CARCINOMA	14/59 (36) 0.6618	16/60 (39) 0.5190	16/60 (35) 0.3664	11/59 (31) 0.7050
Mammary Gland	C_Adenoma+carcinoma	14/60 (37) 0.5673	20/60 (41) 0.2285	17/60 (35) 0.2480	13/60 (32) 0.5038
OVARY	B-SERTOLI CELL TUMOR	0/60 (30) 0.7345	1/60 (32) 0.5161	0/60 (26) NC	0/59 (25) NC
	B-SEX CORD/STROMAL TUMOR	0/60 (30) 0.5801	1/60 (31) 0.5082	1/60 (26) 0.4643	0/59 (25) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=60) P-value - Trend	10 mg/kg/day Low (N=60) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=60) P-value - Vehicle vs. Med	75 mg/kg/day High (N=60) P-value - Vehicle vs. High
PANCREAS	B-ADENOMA, ISLET CELL	1/60 (30) 0.8089	2/60 (32) 0.5246	2/60 (26) 0.4455	0/60 (25) 1.0000
	M-CARCINOMA, ISLET CELL	1/60 (30) 0.6333	0/60 (31) 1.0000	2/60 (26) 0.4455	0/60 (25) 1.0000
Pancreas	C_Islet cell Adenoma+Carinoma	2/60 (30) 0.8689	2/60 (32) 0.7180	4/60 (27) 0.2853	0/60 (25) 1.0000
PITUITARY	B-ADENOMA	50/60 (55) 0.8831	49/60 (55) 0.7365	54/60 (57) 0.3383	43/60 (51) 0.9087
	M-CARCINOMA	3/60 (31) 0.5645	2/60 (32) 0.8326	1/60 (26) 0.9203	2/60 (27) 0.7775
Pituitary	C_Adenoma+Carcinoma	53/60 (56) 0.9336	51/60 (56) 0.8645	55/60 (57) 0.4916	45/60 (52) 0.9643
SKIN/SUBCUTIS	B-FIBROMA	2/59 (30) 0.5294	0/60 (31) 1.0000	1/60 (26) 0.8535	1/60 (26) 0.8535
	B-KERATOACANTHOMA	0/59 (29) 0.7854	2/60 (32) 0.2710	0/60 (26) NC	0/60 (25) NC
	B-LIPOMA	1/59 (30) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/60 (25) 1.0000
	M-CARCINOMA, BASAL CELL	0/59 (29) 0.4545	0/60 (31) NC	2/60 (26) 0.2189	0/60 (25) NC
	M-FIBROSARCOMA	1/59 (29) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/60 (25) 1.0000
	M-LIPOSARCOMA	1/59 (29) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/60 (25) 1.0000
	M-MALIGNANT SCHWANNOMA	0/59 (29) 0.2321	0/60 (31) NC	0/60 (26) NC	1/60 (26) 0.4727
Skin Subcutis	C_Fibrosarcoma+Liposarcoma	2/60 (30) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/60 (25) 1.0000
	C_Keratoacanthoma+Carcinoma	0/60 (30) 0.6902	2/60 (32) 0.2623	2/60 (26) 0.2110	0/60 (25) NC
SPLEEN	M-HEMANGIOSARCOMA	0/60 (30) 0.2301	0/60 (31) NC	0/60 (26) NC	1/60 (26) 0.4643
THYMUS	B-THYMOMA	0/55 (27) 0.7453	1/56 (30) 0.5263	0/58 (25) NC	0/58 (24) NC
	M-MALIGNANT THYMOMA	1/55 (27) 1.0000	0/56 (29) 1.0000	0/58 (25) 1.0000	0/58 (24) 1.0000
Thymus	C_Thymoma B+M	1/60 (30) 0.9300	1/60 (31) 0.7623	0/60 (26) 1.0000	0/60 (25) 1.0000
THYROID	B-ADENOMA, C-CELL	6/60 (31) 0.7146	7/60 (34) 0.5747	4/60 (28) 0.8057	4/60 (27) 0.7882
	B-ADENOMA, FOLLICULAR CELL	0/60 (30) 0.2575	1/60 (31) 0.5082	1/60 (26) 0.4643	1/60 (26) 0.4643

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=60) P-value - Trend	10 mg/kg/day Low (N=60) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=60) P-value - Vehicle vs. Med	75 mg/kg/day High (N=60) P-value - Vehicle vs. High
	B-GANGLIONEUROMA	0/60 (30) 0.7321	1/60 (31) 0.5082	0/60 (26) NC	0/60 (25) NC
	M-CARCINOMA, C-CELL	1/60 (30) 0.9232	2/60 (32) 0.5246	0/60 (26) 1.0000	0/60 (25) 1.0000
	M-CARCINOMA, FOLLICULAR CELL	1/60 (30) 0.4088	0/60 (31) 1.0000	0/60 (26) 1.0000	1/60 (26) 0.7175
Thyroid	C_C cell Adenoma+Carcinoma	1/60 (30) 0.9232	2/60 (32) 0.5246	0/60 (26) 1.0000	0/60 (25) 1.0000
	C_Follicular cell Adenoma+Carcinoma	1/60 (30) 0.2149	1/60 (31) 0.7623	1/60 (26) 0.7175	2/60 (26) 0.4455
TONGUE	B-GRANULAR CELL TUMOR	1/60 (30) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/60 (25) 1.0000
UTERUS	B-GRANULAR CELL TUMOR	0/60 (30) 0.7321	1/60 (31) 0.5082	0/60 (26) NC	0/59 (25) NC
	B-POLYP, ENDOMETRIAL STROMAL	2/60 (31) 0.1122	2/60 (32) 0.7057	2/60 (27) 0.6398	4/59 (27) 0.2708
	M-LEIOMYOSARCOMA	0/60 (30) 0.2301	0/60 (31) NC	0/60 (26) NC	1/59 (26) 0.4643
	M-MALIGNANT SCHWANNOMA	1/60 (30) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/59 (25) 1.0000
	M-SARCOMA, ENDOMETRIAL STRO*	0/60 (30) 0.2301	0/60 (31) NC	0/60 (26) NC	1/59 (26) 0.4643
Uterus	C_Polyp+Sarcoma	2/60 (31) 0.0539	2/60 (32) 0.7057	2/60 (27) 0.6398	5/60 (28) 0.1717
ZYMBAL GLAND	B-ADENOMA	1/60 (30) 1.0000	0/60 (31) 1.0000	0/60 (26) 1.0000	0/60 (25) 1.0000
	M-CARCINOMA	0/60 (30) 0.2301	0/60 (31) NC	0/60 (26) NC	1/60 (26) 0.4643

Table 13: Intercurrent Mortality Rate -Male Mice

Week	Vehicle 0 mg/kg/day (N=25)		Low 20 mg/kg/day (N=25)		Middle 50 mg/kg/day (N=25)		High 150 mg/kg/day (N=25)		Positive (N=10)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	.	.	.	.	.	.
14 - 26	2	8.00	.	.	.	.	1	4.00	5	50.00
Ter. Sac.	23	92.00	25	100.00	25	100.00	24	96.00	5	50.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 14: Intercurrent Mortality Rate -Female Mice

Week	Vehicle 0 mg/kg/day (N=25)		Low 25 mg/kg/day (N=25)		Middle 80 mg/kg/day (N=25)		High 250 mg/kg/day (N=25)		Positive (N=10)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	.	.	.	.	.	.
14 - 26	.	.	2	8.00	.	.	1	4.00	8	80.00
Ter. Sac.	25	100.00	23	92.00	25	100.00	24	96.00	2	20.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 15: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control, Positive Control and Vehicle Control -Male Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.8655	0.0935	0.0935	0.5362	<0.0001
Homogeneity	Log-Rank	0.2814	0.1531	0.1531	0.5396	<0.0001

Table 16: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control, Positive Control and Vehicle Control --Female Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.8500	0.0935	.	0.2390	<0.0001
Homogeneity	Log-Rank	0.2846	0.1531	.	0.3173	<0.0001

Table 17: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	20 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	50 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	150 mg/kg/day High (N=25) P-value - Vehicle vs. High
BRAIN	M-HEMANGIOSARCOMA	1/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000
HARDERIAN GLAND	B-ADENOMA	0/25 (23) 0.5102	0/25 (25) NC	1/25 (25) 0.5208	0/25 (25) NC
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (23) 0.7653	1/25 (25) 0.5208	0/25 (25) NC	0/25 (25) NC
KIDNEY	M-HEMANGIOSARCOMA	0/25 (23) 0.7653	1/25 (25) 0.5208	0/25 (25) NC	0/25 (25) NC
LUNG	B-ADENOMA, BRONCHIOLO- ALVEO*	2/25 (23) 0.9560	2/25 (25) 0.7270	1/25 (25) 0.8976	0/25 (25) 1.0000
	M-CARCINOMA, BRONCHIOLO- ALV*	0/25 (23) 0.1946	0/25 (25) NC	1/25 (25) 0.5208	1/25 (25) 0.5208
Lung	C_bronchiolo-alveo Adeno+Carcin	2/25 (23) 0.7581	2/25 (25) 0.7270	2/25 (25) 0.7270	1/25 (25) 0.8976
SPLEEN	M-HEMANGIOSARCOMA	2/25 (24) 0.7724	2/25 (25) 0.7110	0/25 (25) 1.0000	1/25 (25) 0.8901
STOMACH, GLANDULAR	B-ADENOMA	0/25 (23) 0.5102	0/25 (25) NC	1/25 (25) 0.5208	0/25 (25) NC
TESTIS	M-HEMANGIOSARCOMA	1/25 (23) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000
THORACIC CAVITY	M-MALIGNANT MESOTHELIOMA	0/25 (23) 0.2551	0/25 (25) NC	0/25 (25) NC	1/25 (25) 0.5208
Whole Body	C_Hemangiosarcoma	4/25 (25) 0.9410	3/25 (25) 0.7913	0/25 (25) 1.0000	1/25 (25) 0.9749

Table 18: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
BRAIN	M-HEMANGIOSARCOMA	1/25 (24)	0/10 (7) 1.0000
HARDERIAN GLAND	B-ADENOMA	0/25 (23)	0/10 (7) NC
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (23)	4/10 (9) 0.0035
JEJUNUM	M-CARCINOMA	0/25 (23)	1/10 (7) 0.2333
KIDNEY	M-HEMANGIOSARCOMA	0/25 (23)	0/10 (7) NC
LUNG	B-ADENOMA, BRONCHIOLO- ALVEO*	2/25 (23)	0/10 (7) 1.0000
	M-CARCINOMA, BRONCHIOLO- ALV*	0/25 (23)	0/10 (7) NC
Lung	C_bronchiolo-alveo Adeno+Carcin	2/25 (23)	0/10 (7) 1.0000
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (23)	5/10 (8) <0.001
SPLEEN	M-HEMANGIOSARCOMA	2/25 (24)	0/10 (7) 1.0000
STOMACH, GLANDULAR	B-ADENOMA	0/25 (23)	0/10 (7) NC
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (23)	7/10 (9) <0.001
	M-CARCINOMA, SQUAMOUS CELL	0/25 (23)	3/10 (8) 0.0125
TESTIS	M-HEMANGIOSARCOMA	1/25 (23)	0/10 (7) 1.0000
Whole Body	C_Hemangiosarcoma	4/25 (25)	0/10 (7) 1.0000

Table 19: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	25 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	80 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	250 mg/kg/day High (N=25) P-value - Vehicle vs. High
BRAIN	M-HEMANGIOSARCOMA	0/25 (25) 0.7500	1/25 (25) 0.5000	0/25 (25) NC	0/25 (25) NC
HARDERIAN GLAND	B-ADENOMA	0/25 (25) 0.2525	0/25 (24) NC	0/25 (25) NC	1/25 (25) 0.5000
	M-HEMANGIOSARCOMA	0/25 (25) 0.7500	1/25 (25) 0.5000	0/25 (25) NC	0/25 (25) NC
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (25) 0.8131	2/25 (25) 0.2449	0/25 (25) NC	0/25 (25) NC
LUNG	B-ADENOMA, BRONCHIOLO- ALVEO*	0/25 (25) 0.3144	1/25 (24) 0.4898	0/25 (25) NC	1/25 (25) 0.5000
	M-CARCINOMA, BRONCHIOLO- ALV*	0/25 (25) 0.0186	0/25 (24) NC	1/25 (25) 0.5000	3/25 (25) 0.1173
Lung	C_bronchiolo-alveo Adeno+Carcin	0/25 (25) 0.0138	1/25 (24) 0.4898	1/25 (25) 0.5000	4/25 (25) 0.0549
SPLEEN	M-HEMANGIOSARCOMA	0/25 (25) 0.8173	3/25 (25) 0.1173	2/25 (25) 0.2449	0/24 (24) NC
THORACIC CAVITY	M-HEMANGIOSARCOMA	0/25 (25) 0.2525	0/25 (24) NC	0/25 (25) NC	1/25 (25) 0.5000
THYMUS	B-THYMOMA	3/25 (25) 0.9957	1/22 (22) 0.9291	0/25 (25) 1.0000	0/21 (21) 1.0000
UTERUS	B-POLYP, ENDOMETRIAL STROMAL	2/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000
	M-HEMANGIOSARCOMA	1/25 (25) 0.9382	1/25 (24) 0.7449	0/25 (25) 1.0000	0/25 (25) 1.0000
Whole Body	C_Hemangiosarcoma	1/25 (25) 0.8260	5/25 (25) 0.0947	2/25 (25) 0.5000	1/25 (25) 0.7551

Table 20: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control -Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
BRAIN	M-HEMANGIOSARCOMA	0/25 (25)	0/10 (5) NC
HARDERIAN GLAND	M-HEMANGIOSARCOMA	0/25 (25)	0/10 (5) NC
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (25)	7/10 (10) <0.001
	M-MAST CELL TUMOR	0/25 (25)	1/10 (5) 0.1667
LUNG	B-ADENOMA, BRONCHIOLO- ALVEO*	0/25 (25)	0/10 (5) NC
	M-CARCINOMA, BRONCHIOLO- ALV*	0/25 (25)	0/10 (5) NC
Lung	C_bronchiolo-alveo Adeno+Carcin	0/25 (25)	0/10 (5) NC
MAMMARY GLAND	M-CARCINOMA	0/23 (23)	1/10 (6) 0.2069
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	7/10 (9) <0.001
	M-CARCINOMA, SQUAMOUS CELL	0/25 (25)	2/10 (6) 0.0323
SPLEEN	M-HEMANGIOSARCOMA	0/25 (25)	0/10 (5) NC
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	5/10 (7) <0.001
	M-CARCINOMA, SQUAMOUS CELL	0/25 (25)	1/10 (6) 0.1935
THYMUS	B-THYMOMA	3/25 (25)	0/10 (5) 1.0000
	M-HEMANGIOSARCOMA	0/25 (25)	1/10 (6) 0.1935
UTERUS	B-POLYP, ENDOMETRIAL STROMAL	2/25 (25)	0/10 (5) 1.0000
	M-HEMANGIOSARCOMA	1/25 (25)	0/10 (5) 1.0000
Whole Body	C_Hemangiosarcoma	1/25 (25)	1/10 (6) 0.3548

Figure 1: Kaplan-Meier Survival Functions for Male Rats

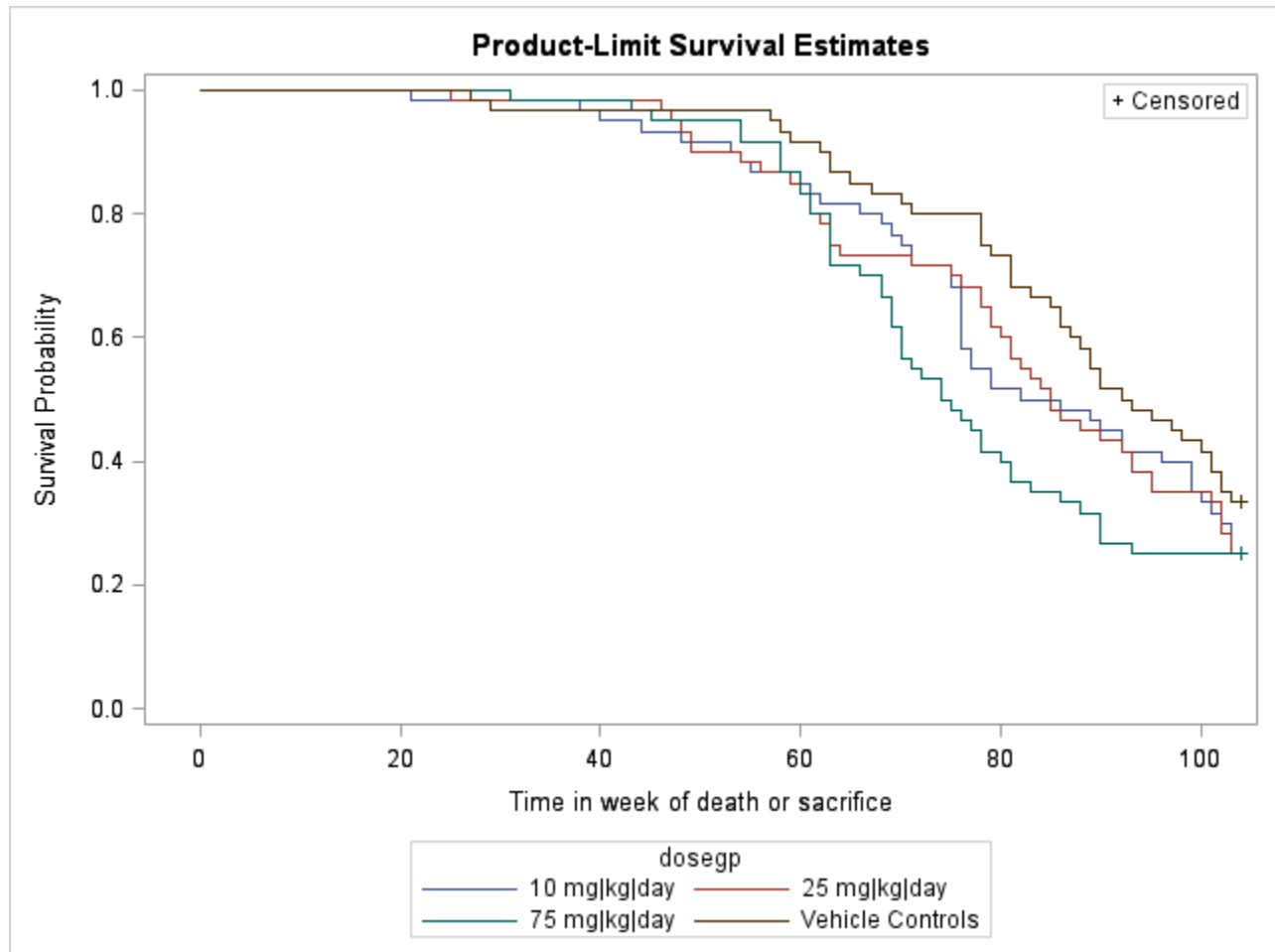
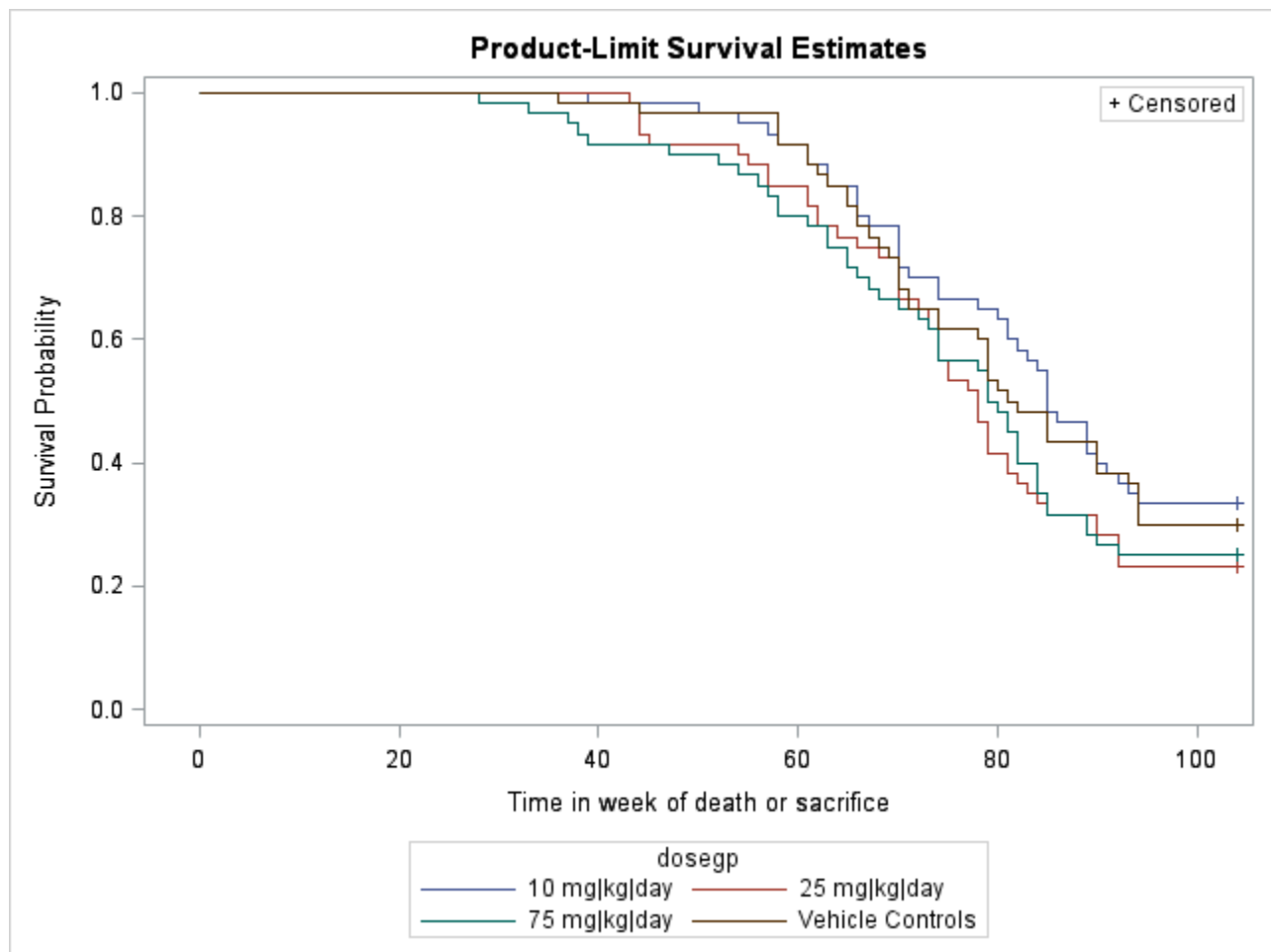


Figure 2: Kaplan-Meier Survival Functions for Female Rats



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Figure 3: Kaplan-Meier Survival Functions for Male Mice

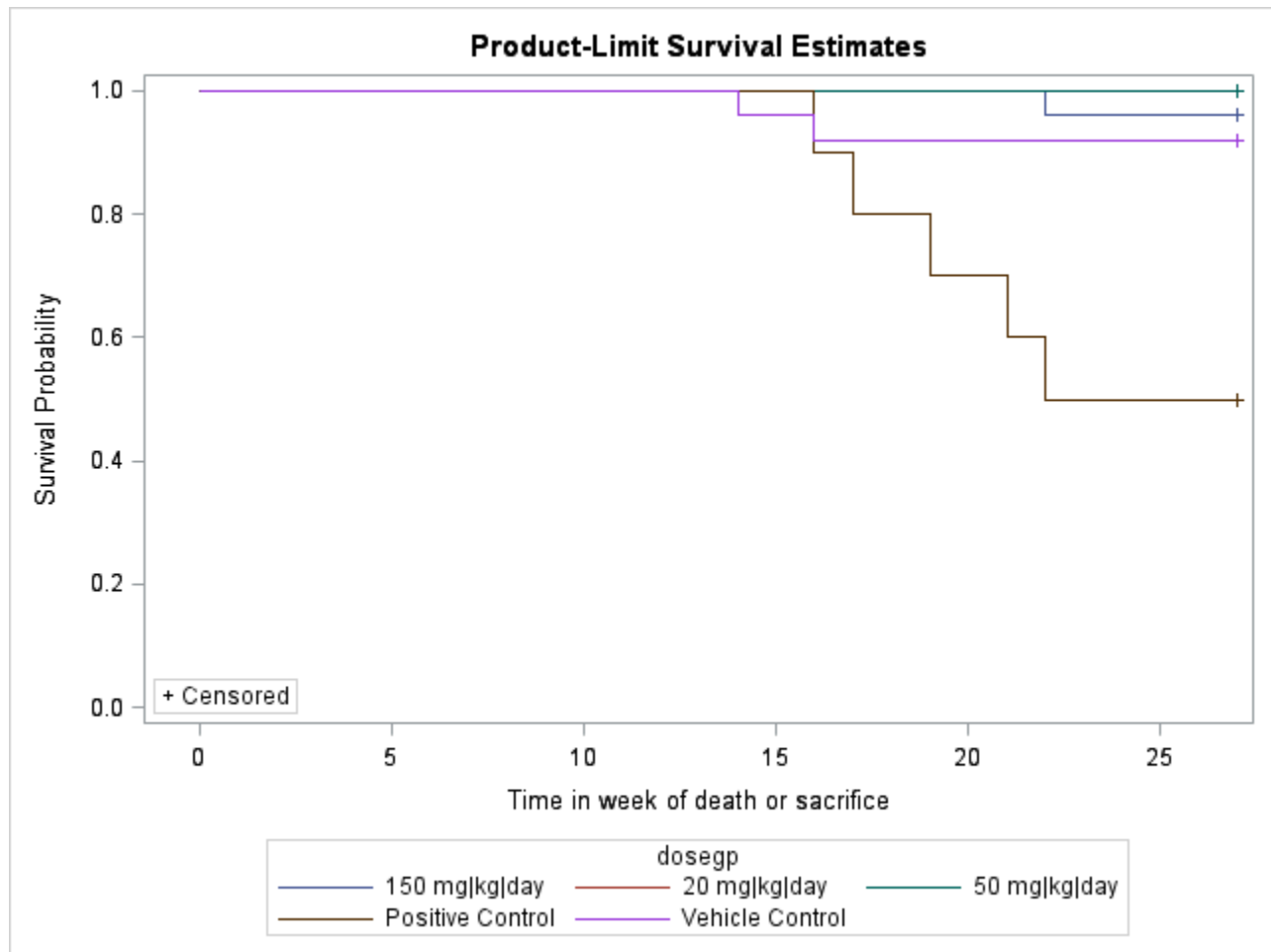
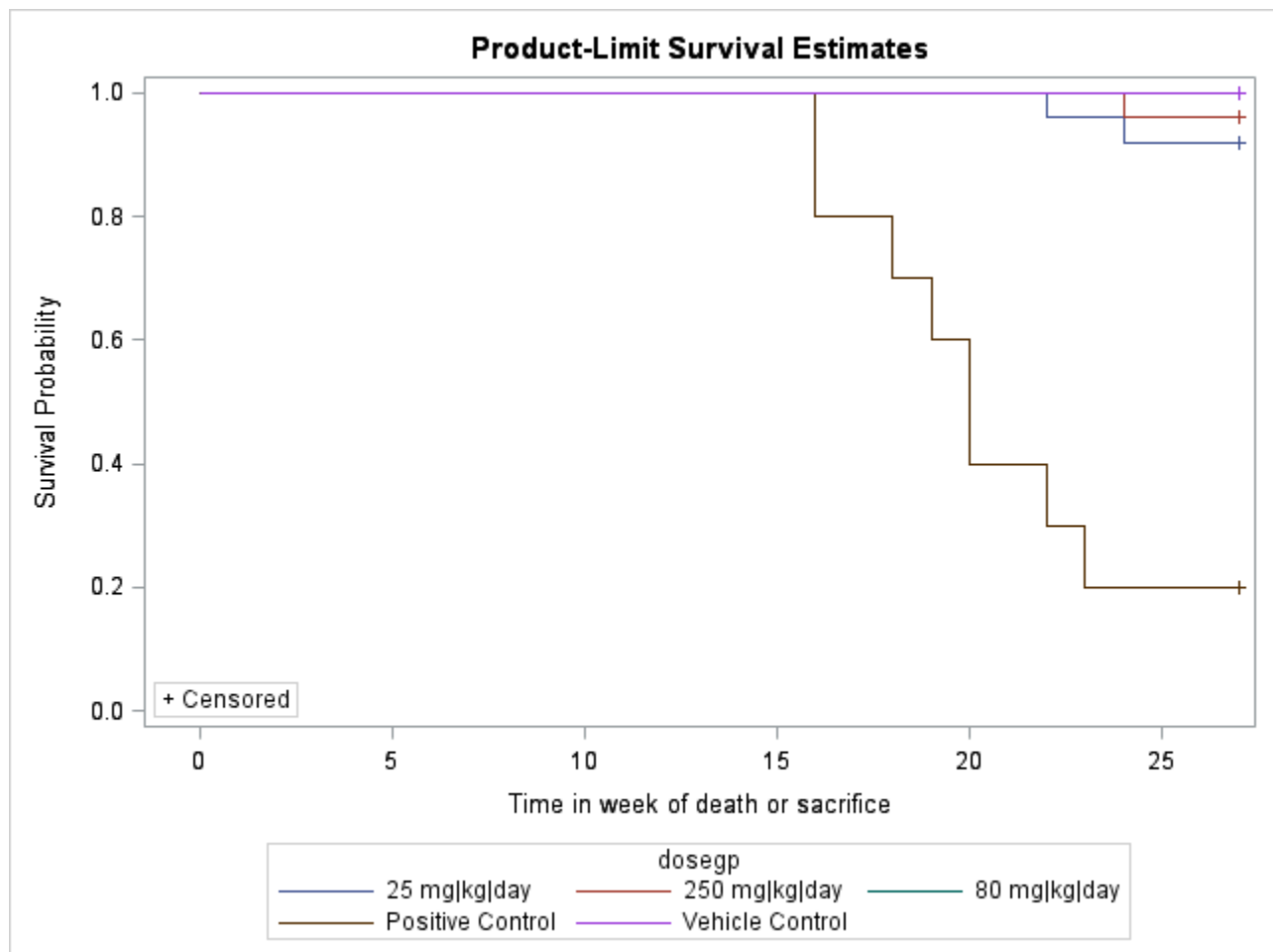


Figure 4: Kaplan-Meier Survival Functions for Female Mice



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