

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 211765 / Serial Number 0001 -

Drug Name: Ubrogepant (AGN 241668; MK-1602)
25 mg, 50 mg, or 100 mg tablets to be taken orally

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

Applicant: Allergan

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1 EXECUTIVE SUMMARY

This NDA submission is to obtain marketing authorization for Ubrogepant in the treatment of acute migraine in adults. The study doses are 25 mg, 50 mg and 100 mg tablet.

The pivotal efficacy evidence is from two Phase III studies UBR-MD-01 and UBR-MD-02.

1.1 Conclusions and Recommendations

The two pivotal studies in patients with acute migraine presented statistical evidence that Ubrogepant, at 50 mg or 100 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 Ubrogepant treated groups show an efficacy result better than that of the placebo control group.

1.2 Brief Overview of Clinical Study UBR-MD-01 and UBR-MD-02

Study 1 (UBR-MD-01) is a study for acute migraine with two dose levels 50 mg and 100 mg. Study 2 (UBR-MD-02) is a study for acute migraine with two dose levels 25 mg and 50 mg,

Both studies are multi-center, randomized, double-blinded, parallel group and placebo controlled.

1.3 Statistical Issues and Findings

No major statistical issues were found.

2 INTRODUCTION

Two studies: Study 1 (UBR-MD-01) and Study 2 (UBR-MD-02) are included in this statistical review for the efficacy evaluation.

2.1 Overview

Ubrogepant is being developed as a novel CGRP receptor antagonist that is chemically distinct from both telcagepant and MK-3207, for the acute treatment of migraine. Preclinical and clinical studies conducted to date for ubrogepant have shown no evidence of hepatotoxicity.

Table 1 Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
Study 1 UBR-MD-01	MC, R, DB, PG, PC	Placebo/ 456 Drug 50 mg/ 423 Drug 100 mg/448	Free from headache pain at 2 hours post initial dose	21.2% in 100 mg 19.2% in 50 mg 11.8% in placebo with p-values 0.0003, and 0.0023 versus placebo
			Most Bothersome Symptom free at 2 hours post initial dose	37.7% in 100 mg 38.6% in 50 mg 27.8% in placebo with p-values 0.0023, and 0.0023 versus placebo
Study 2 UBR-MD-02	MC, R, DB, PG, PC	Placebo/456 Drug 25 mg/ 435 Drug 50 mg/ 464	Free from headache pain at 2 hours post initial dose	21.8% in 50 mg 20.7% in 25 mg 14.3% in placebo with p-values 0.0129, and 0.0285 versus placebo
			Most Bothersome Symptom free at 2 hours post initial dose	38.9% in 50 mg 34.1% in 25 mg 27.4% in placebo with p-values 0.0129, and 0.0711 versus placebo

MC: multi-center, R: randomized, DB: double-blinded, PG: parallel group, PC: placebo controlled.
(Source: Sponsor' result at the Filing review, replicated but not verified by the reviewer.)

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\NDA211765\0001>

The corrected ADAM datasets for study 2 were resubmitted in this link:

<\\CDSESUB1\evsprod\NDA211765\0005>

The sponsor has resubmitted all 14 ADAM datasets for study 2 which was received by CDER on 2/7/2019 as response to our IR on 1/31/2019. The sponsor has stated that a data transfer error happened on their side which caused the patient counts in the ADEFF dataset to be 9 less than in the study report for the primary endpoints. The CSR (clinical study report) was not affected.

The corrected ADSL datasets for study 1 and study 2 were resubmitted in this link:

<\\CDSESUB1\evsprod\NDA211765\0010>

As response to our IR dated 09 April 2019 seeking clarification of 31 patients' dosing status in study 1, the sponsor has resubmitted the ADSL dataset with variable EXCRSN1 to include the dosing information from the EDC in addition to the e-diary, the define.xml file and the Listing 16.2.3-1.1 in the CSR.

Similar issue also affected study 2 and 25 patients' dosing status were inconsistent between the mITT population and the safety population. The sponsor also resubmitted the ADSL dataset with variable EXCRSN1 to include the dosing information from the EDC in addition to the e-diary, the define.xml file and the Listing 16.2.3-1.1 in the CSR.

The SAS codes for the sensitivity analyses for the two co-primary endpoints for study 1 and study 2 to account for missing data were not included initially but were submitted at our request in this link:

<\\CDSESUB1\evsprod\NDA211765\0028>

The corrected ADSL datasets for study 1 and study 2 were resubmitted in this link:

<\\CDSESUB1\evsprod\NDA211765\0030>

The format and length of the core variables including USUBJID in the corrected ADSL dataset submitted in SN 10 was inconsistent with the ADEFF dataset which caused SAS warnings when the two datasets needed to be merged by USUBJID for review purposes. The sponsor stated that the truncating of the variable length was caused by a utility converting SAS data files to xpt files. The sponsor has resubmitted the ADSL datasets for study 1 and study 2 without any truncation this time.

The rescue medication use flag prior to the 2-hour time point was clarified in this IR also.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are some minor issues with the data quality and analysis in both study 1 and study 2.

(1) Study 2:

There were 9 patients less in the submitted efficacy datasets than what was stated in the study report. We have sent an IR and the sponsor has responded that the reason was a file transfer error from their side and was able to resubmit all efficacy (ADAM) datasets prior to the filing decision. The study report was not affected.

(2) Study 1 and Study 2:

There were 31 patients in study 1 listed with reason for exclusion from mITT as not taking any dose but were still included in the safety population which indicates that they were dosed. We have sent an IR and the sponsor has responded that the 31 patients were in fact dosed and have resubmitted datasets, define files, and listings in the study report that were affected by this oversight.

There were 25 patients in study 2 with similar issue. The sponsor was able to resubmit the datasets, define files, and listings in the study report that were affected by this oversight.

The primary efficacy results were not affected. The 31 patients in study 1 and 25 patients in study 2 took the drug but did not provide any post dose efficacy measurement, therefore could not be included in the efficacy analyses.

The patient level rescue medication use flag was not clear, and the sponsor provided clarification in SN 30. The reviewer was able to perform sensitivity analyses and the primary efficacy results were not affected.

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

3.2 Evaluation of Efficacy Study – UBR-MD-01

3.2.1 Description of the Study

This study had its first subject enrolled on 22 July 2016, last subject completed on 14 December 2017.

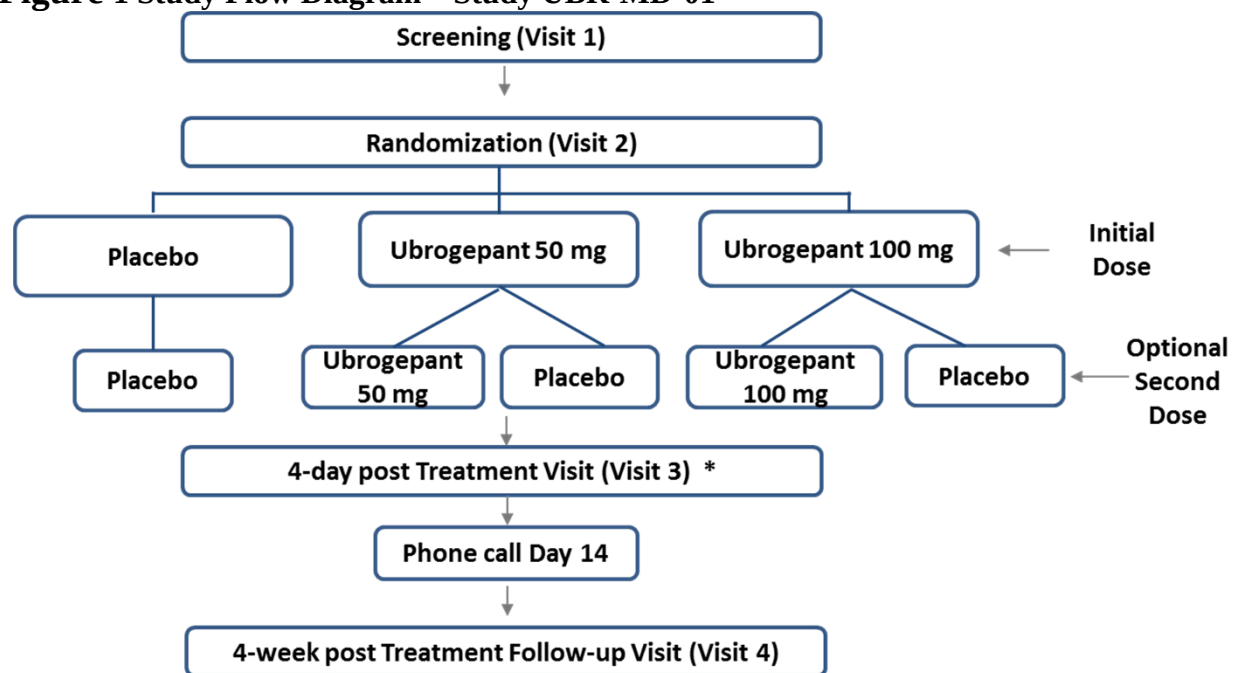
The primary objective was to evaluate the effect of Ubrogepant compared to placebo on the rates of pain free at 2 hours and MBS free at 2 hours in subjects with acute migraine.

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study of subjects with acute migraine. The study was conducted at 89 centers in the United States. Patients were randomized (1:1:1) to 1 of the 3 treatment groups: placebo, 50 mg, or 100 mg. Randomized study patients had up to 60 days to treat a single qualifying migraine attack of moderate or severe intensity at home.

Eligible subjects were adults 18 to 75 years of age with history of migraine for ≥ 12 months who experienced 2 to 8 migraine attacks per month with moderate to severe pain in each of the 3 months before screening, with migraine onset before the age of 50 years.

Sample size was planned as 550 per group to detect with power $> 85\%$ a difference in pain free response rates of 10% and 24% between placebo, and drug groups assuming a 20% drop out rate and a 10% missing data rate. These rates were taken from the Phase 2b studies.

Figure 1 Study Flow Diagram – Study UBR-MD-01



(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 initial dose treating a qualifying acute migraine attack during the double-blind treatment phase.

3.2.2.2 Secondary Endpoints

The secondary efficacy endpoints were:

- 1) Pain relief (PR) at 2 hours.
- 2) Sustained pain relief (SPR) from 2 to 24 hours.
- 3) Sustained pain freedom (SPF) from 2 to 24 hours.
- 4) Absence of photophobia at 2 hours.
- 5) Absence of phonophobia at 2 hours.
- 6) Absence of nausea at 2 hours.

3.2.3 Statistical Analysis Methods

Efficacy analyses were based on the 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 initial dose.

The primary efficacy variable of PF (Pain Free) at 2 hours after the initial dose was analyzed using a logistic regression model with treatment group, and historical triptan response (triptan responder, triptan insufficient responder, or triptan naïve), use of medication for migraine prevention (yes/no), baseline headache severity (moderate or severe) as covariates.

The missing data were imputed using LOCF approach. We generally don't allow imputing for an acute migraine study. However, this is pre-specified by the sponsor in the study document at which time LOCF approach was not un-acceptable as a LAV (Last Available Value) method.

The primary efficacy variable of absence of the MBS (most bothersome symptom) at 2 hours after the initial dose was analyzed using a similar logistic regression model with an additional categorical term for the underlying symptom that was identified as the most bothersome.

The respective comparisons of the Ubrogepant doses versus placebo, which are the formal tests of the efficacy hypotheses, were conducted using the appropriate pairwise contrasts within the logistic regression model.

3.2.3.1 Multiplicity Adjustment

The multiplicity adjustment method was pre-specified by the sponsor as the following:

A graphical approach with closed testing procedure was used to control the overall type I error rate for multiple comparisons across the Ubrogepant doses and the primary and secondary efficacy endpoints. The coprimary efficacy endpoints served as the gatekeepers of the secondary endpoints.

The overall Type 1 error was controlled by this pre-specified method.

However, it may render the outcome of “Low dose wins while High dose loses” which would make the study results difficult to interpret clinically. We usually provide such comments at IND stage, in this case, we did provide such comments to this sponsor for another similar drug trial but not this product.

On the other hand, for this study 1 (MD-01), both high dose (100 mg) and low dose (50 mg) won using the sponsor pre-specified multiplicity adjustment plan.

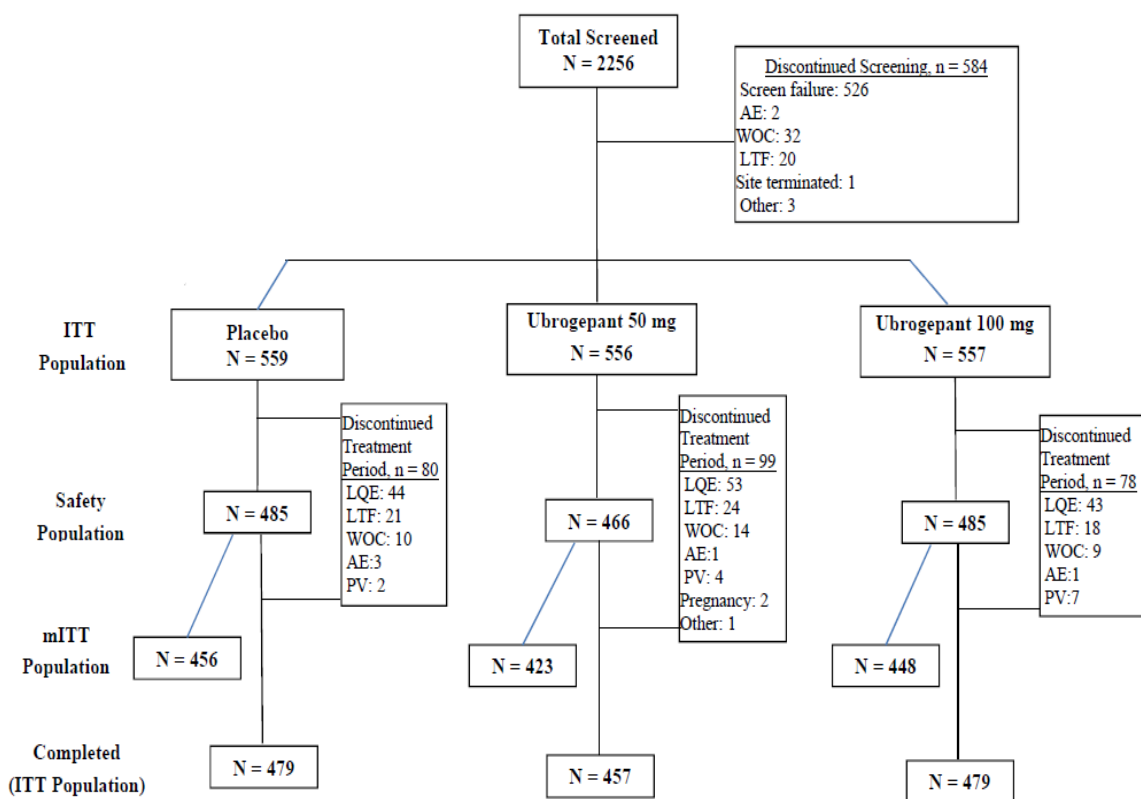
3.2.4 Patient Results

3.2.4.1 Patient Disposition

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

Of the 2256 patients who were screened for eligibility, 584 patients were discontinued from the screening period and not randomized to a treatment assignment. Screen failure (patient failed to meet eligibility criteria) was the primary reason for discontinuation during screening (526 of 584 patients).

Figure 2 Patient Disposition Diagram – Study UBR-MD-01



AE = adverse event; ITT = intent to treat; LTF = lost to follow-up; LQE = lack of qualifying event; mITT = modified intent to treat; PV = protocol violation; WOC = withdrawal of consent
(Source: CSR)

A total of 1672 patients passed screening and were randomized (intent-to-treat [ITT] population): 559 to the placebo group, 556 to the 50 mg group and 557 to the 100 mg group.

Table 2 Patient Completion and Discontinuation – Study UBR-MD-01

Phase Disposition	Placebo (N=559) n (%)	Ubrogepant 50 mg (N=556) n (%)	Ubrogepant 100 mg (N=557) n (%)	Total (N=1672) n (%)
Treatment Period				
Entered phase	559 (100.0)	556 (100.0)	557 (100.0)	1672 (100.0)
Completed phase	479 (85.7)	457 (82.2)	479 (86.0)	1415 (84.6)
Discontinued phase	80 (14.3)	99 (17.8)	78 (14.0)	257 (15.4)
Reason for phase discontinuation				
Adverse Event	3 (0.5)	1 (0.2)	1 (0.2)	5 (0.3)
Withdrawal of Consent	10 (1.8)	14 (2.5)	9 (1.6)	33 (2.0)
Lost to Follow-Up	21 (3.8)	24 (4.3)	18 (3.2)	63 (3.8)
Lack of Qualifying Event	44 (7.9)	53 (9.5)	43 (7.7)	140 (8.4)
Pregnancy	0	2 (0.4)	0	2 (0.1)
Protocol Violation	2 (0.4)	4 (0.7)	7 (1.3)	13 (0.8)
Other	0	1 (0.2)	0	1 (0.1)
Entered Safety Follow-up Phase	480 (85.9)	458 (82.4)	480 (86.2)	1418 (84.8)
Completed safety follow-up phase	460 (82.3)	440 (79.1)	461 (82.8)	1361 (81.4)

(Source: modified from the Table 10-1 in the sponsor's study report, verified by the statistical reviewer.)

Overall, 1415 (84.6%) of patients in the ITT population completed the treatment period and 257 (15.4%) subjects discontinued the study for the following reasons: lack of qualifying event, lost to follow-up, withdraw of consent, protocol violation, adverse event, pregnancy, and other.

Table 3 Analysis Populations - Study UBR-MD-01

Analysis Populations, n	Placebo	U50mg	U100mg	Total
ITT Population	559	556	557	1672
Safety Population	485	466	485	1436
mITT Population	456	423	448	1327

Intent-to-treat (ITT) population = Patients randomized to a study treatment group.

Safety population = Patients who took ≥ 1 dose of investigational product.

Modified ITT (mITT) population = Randomized patients who received at least 1 dose of investigational product, recorded a baseline migraine headache severity measurement, with ≥ 1 post dose headache severity or migraine associated symptom measurement at or before the 2-hour timepoint.

(Source: modified from the Table 10-4 in the sponsor's study report, verified by the statistical reviewer.)

3.2.4.2 Patient Demographics

Of the 1327 subjects in the mITT population, majority were women (88.39%), white (83.80%), and the mean age was 40.29 (18 to 75) years. The treatment groups were balanced for these baseline demographic characteristics.

Table 4 Patient Baseline Demographics – mITT – Study UBR-MD-01

	Placebo	U50mg	U100mg	Total
Age (years), n	456	423	448	1327
Mean (SD)	40.77 (11.70)	39.71 (11.61)	40.34 (12.08)	40.29 (11.80)
Median	40.00	38.00	40.00	39.00
Minimum	18	18	18	18
Maximum	74	70	75	75
Gender, n (%)	456	423	448	1327
Female	407 (89.25)	380 (89.83)	386 (86.16)	1173 (88.39)
Male	49 (10.75)	43 (10.17)	62 (13.84)	154 (11.61)
Race, n (%)	456	423	448	1327
Black or African	51 (11.18)	58 (13.71)	63 (14.06)	172 (12.96)
White	391 (85.75)	349 (82.51)	372 (83.04)	1112 (83.80)
Other	14 (3.07)	16 (3.78)	13 (2.90)	53 (3.24)
BMI (kg/m²), n	456	423	447	1326
Mean (SD)	29.93(7.48)	30.06(7.96)	30.53 (8.08)	30.18 (7.84)
Median	28.54	28.67	28.74	28.69
Minimum	17.54	14.86	17.38	14.86
Maximum	63.51	59.68	61.85	63.51

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.

In the mITT population, 22.76% of patients reported current use of prophylactic medication for migraine. Based on historical triptan response, 40.39% of patients were triptan responders, 27.20% were triptan insufficient-responders, and 32.40% were triptan naïve.

The mean (SD) duration of years with migraine at baseline was 19.01(12.34), 17.60 (11.66), and 18.87(12.31) years in the placebo, 50 mg, and 100 mg groups, respectively.

The mean (SD) migraine per month in the past 3 months at baseline was 4.39 (1.73), 4.59 (1.88), and 4.62 (1.76) in the placebo, 50 mg, and 100 mg groups, respectively.

Table 5 Patient Baseline Disease Characteristics -mITT - Study UBR-MD-01

	Placebo	U50mg	U100mg	Total
Concomitant Prophylactic Migraine Medication, n (%)	456	423	448	1327
Yes	106 (23.25)	96 (22.70)	100 (22.32)	302 (22.76)
No	350 (76.75)	327 (77.30)	348 (77.68)	1025 (77.24)
Historical Triptan Response, n (%)	456	423	448	1327
Triptan Responder	191 (41.89)	172 (40.66)	173 (38.62)	536 (40.39)
Triptan Insufficient-Responder	117 (25.66)	118 (27.90)	126 (28.13)	361 (27.20)
Triptan Naïve	148 (32.46)	133 (31.44)	149 (33.26)	430 (32.40)
Migraine Disorder Duration in Years	456	422	448	1326
Mean (SD)	19.01 (12.34)	17.60 (11.66)	18.87 (12.31)	18.52 (12.13)
Median	16.00	15.00	17.00	16.00
Min, Max	1.00, 58.00	1.00, 65.00	1.00, 65.00	1.00, 65.00
Migraines/Month in Past 3 Months	456	423	448	1327
Mean (SD)	4.39 (1.73)	4.59 (1.88)	4.62 (1.76)	4.53 (1.79)
Median	4.00	4.00	4.00	4.00
Min, Max	2.00, 8.00	2.00, 8.00	2.00, 8.00	2.00, 8.00

(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 confirmed. Both the 50 mg and 100 mg won.

Table 6 Primary Endpoint Analyses- mITT-Study UBR-MD-01

	Placebo	Ubrogepant	
		50 mg	100 mg
Pain Moderate to Severe at time of dosing	456	422	448
Pain Free at 2 hours	54	81	95
%	11.8%	19.2%	21.2%
p-value	-	.0017	.0001
MBS recorded at time of dosing	454	420	448
MBS Free at 2 hours	126	162	169
%	27.8%	38.6%	37.7%
p-value	-	.0003	.0008

P-values were from a logistic regression model with treatment group and historical triptan response, use of medication for migraine prevention, and baseline headache severity (or the underlying symptom) as explanatory variables.

(Source: reviewer's own analysis and sponsor's analysis verified by the reviewer.)

The primary analysis for Pain free status at 2 hours included 1326 patients. There was a statistically significant increase in the rate of pain free at 2 hours from 11.8% in the placebo group to 19.2% in the 50 mg group and 21.2% in the 100 mg group. The p-values versus placebo were .0017 and .0001.

The primary analysis for MBS free status at 2 hours included 1322 patients. There was a statistically significant increase in the rate of MBS free at 2 hours from 27.8% in the placebo group to 38.6% in the 50 mg group and 37.7% in the 100 mg group. The p-values versus placebo were .0003 and .0008.

Patients with missing data at 2-hour time point were imputed using LOCF. The LOCF method is considered problematic in general, but this drug development program has been in existence for a quite long time that the LOCF method was considered acceptable back then and was pre-specified in the study document. Therefore, we would like to follow the pre-specified method. A separate section on missing data and various sensitivity analyses was presented next (Table 9, 10 and 11).

As a clinical rule, patients with rescue medication use prior to the 2-hour time point should be considered as treatment failures. However, the sponsor did not provide clear patient level flag and did not follow such rule in the analyses.

We have sent IR (Information Request) and in the response under SN 30 the sponsor clarified how to identify such patients. Based on the additional information and clarification, the reviewer was able to apply this rule and found that: the change of responder counts was small and did not alter the efficacy conclusion. For example, for PF2H, the change was -1/-1/0 for the placebo group, the 50 mg group and the 100 mg group respectively if we use the time window of -5

minutes as suggested by the sponsor. If we use +5 minutes time window, or the +35 minutes time window, the change was -3/-5/-1, and -3/-7/-2. Please see below Table 7 and 8 for more details.

Table 7 PF2H ResMeds Time Window Sensitivity Analyses- mITT-Study UBR-MD-01

Study MD-01	Without consideration for resmed			AVAL<=115/60*			AVAL<=125/60			AVAL<=155/60		
mITT	456	422	448	456	422	448	456	422	448	456	422	448
pf2h	placebo	u50	u100	placebo	u50	u100	placebo	u50	u100	placebo	u50	u100
responder	54	81	95	53	80	95	51	76	94	51	74	93
%	11.84%	19.19%	21.21%	11.62%	18.96%	21.21%	11.18%	18.01%	20.98%	11.18%	17.54%	20.76%
p value versus placebo		0.0017	0.0001		0.0017	<.0001		0.003	<.0001		0.0054	<.0001
increase from placebo		7.35%	9.36%		7.33%	9.58%		6.83%	9.80%		6.35%	9.57%

(Sponsor's analysis and reviewer's own analysis)

- AVAL<=115/60: 5 minutes before the 2-hour time point
- AVAL<=125/60: 5 minutes after the 2-hour time point
- AVAL <=155/60: 35 minutes after the 2-hour time point

*In SN 30 submission, the sponsor was recommending the use of the time window of "5 minutes before the 2-hour time point".

Table 8 MBS2H ResMeds Time Window Sensitivity Analyses- mITT-Study UBR-MD-01

Study MD-01	Without consideration for resmed			AVAL<=115/60			AVAL<=125/60			AVAL<=155/60		
mITT	454	420	448	454	420	448	454	420	448	454	420	448
mbs2h	placebo	u50	u100	placebo	u50	u100	placebo	u50	u100	placebo	u50	u100
responder	126	162	169	121	160	168	103	138	147	93	129	140
%	27.75%	38.57%	37.72%	26.54%	37.91%	37.50%	22.59%	32.70%	32.81%	20.39%	30.57%	31.25%
p value versus placebo		0.0003	0.0008		0.0003	0.0008		0.0006	0.0007		0.0002	0.0004
increase from placebo		10.82%	9.97%		11.38%	10.96%		10.11%	10.22%		10.17%	10.86%

(Sponsor's analysis and reviewer's own analysis)

- AVAL<=115/60: 5 minutes before the 2-hour time point
- AVAL<=125/60: 5 minutes after the 2-hour time point
- AVAL <=155/60: 35 minutes after the 2-hour time point

*In SN 30 submission, the sponsor was recommending the use of the time window of "5 minutes before the 2-hour time point".

In conclusion, we consider the efficacy result presented in Table 6 (same as the sponsor's result in the study report) as adequate.

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 9 Patient Counts at Time of Dosing and Two Hours (rescue*= failure)– Study UBR-MD-01

	Pain at Time 0	Pain at 2 Hours	Missing n	Missing %	MBS at Time 0	MBS at 2 Hours	Missing n	Missing %
placebo	456	430	26	5.70%	454	429	25	5.51%
50 mg	422	404	18	4.27%	420	404	16	3.81%
100 mg	448	419	29	6.47%	448	418	30	6.70%

(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.

In the primary efficacy analysis, subjects with missing data at 2 hours timepoint were imputed using LOCF.

Table 10 shows how the breakdown of patient counts with or without actual efficacy measurements at 2 hours (Yes/No/Missing), and the patient efficacy results after applying the LOCF imputation.

Table 10 Descriptive Patient Counts for Data Status at 2 Hours – mITT- Study UBR-MD-01

	Pain		MBS	
Placebo	50	Yes	120	Yes
	380	No	309	No
	26	2-Hour missing (LOCF: 4 Yes; 22 No)	25	2-Hour missing (LOCF: 6 Yes; 19 No)
50 mg	76	Yes	155	Yes
	328	No	249	No
	18	2-Hour missing (LOCF: 5 Yes; 13 No)	16	2-Hour missing (LOCF: 7 Yes; 9 No)
100 mg	90	Yes	157	Yes
	329	No	261	No
	29	2-Hour missing (LOCF: 5 Yes; 24 No)	30	2-Hour missing (LOCF: 12 Yes; 18 No)

(Source: Reviewer's own analysis.)

In the sensitivity analysis performed by the sponsor the missing was imputed as non-responders. Additional sensitivity analysis performed by the sponsor used GLMM assuming missing at random.

Results for both sensitivity analyses were consistent with those observed for the primary analysis. Results from the “semi -worst case scenario” analysis were also consistent with the primary analysis, where the missing data from placebo group were excluded and the missing data from the drug group were assigned as treatment failures.

Table 11 Sensitivity Analyses – Study UBR-MD-01

	mITT using Missing as Non-responders			mITT using GLMM			mITT using Missing as Semi-Worst Case*		
	Ubrogapant			Ubrogapant			Ubrogapant		
	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg
Pain Moderate to Severe at time of dosing	456	422	448	456	422	448	430	422	448
Pain Free at 2 hours	50	76	90	-	-	-	50	76	90
%	11.0	18.0	20.1	9.5	16.4	18.1	11.6	18.0	20.1
p-value		.0021	.0001		.0016	.0001		.0067	.0006
MBS recorded at time of dosing	454	420	448	454	420	448	429	420	448
MBS Free at 2 hours	120	155	157	-	-	-	120	155	157
%	26.4	36.9	35.0	27.8	39.9	38.8	28.0	36.9	35.04
p-value		.0005	.0031		.0003	.0009		.0184	.0035

*Semi-WorstCase = missing from placebo group excluded while missing from drug group assigned as failures
(Source: reviewer’s analysis and sponsor’s analysis, verified by the reviewer.)

3.2.5.3 Efficacy Results of the Secondary Endpoints

The pre-specified secondary efficacy endpoints were:

- 1) Pain relief (PR) at 2 hours.
- 2) Sustained pain relief (SPR) from 2 to 24 hours.
- 3) Sustained pain freedom (SPF) from 2 to 24 hours.
- 4) Absence of photophobia at 2 hours.
- 5) Absence of phonophobia at 2 hours.
- 6) Absence of nausea at 2 hours.

The nominal p-values reported by the sponsor were confirmed.

Pain relief (PR) 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), at the indicated assessment time. The mITT population was used for the analysis. The proportions of subjects with pain relief at 2 hours were 49.1%, 60.7%, and 61.4% for the placebo, 50 mg, and 100 mg groups, respectively (p as versus placebo).

The sponsor's analysis result was confirmed. Missing data at 2-hours timepoint was minimal and LOCF method was used.

Table 12 Responder Rate: Pain Relief at 2 Hours - Study UBR-MD-01

	Placebo	U50	U100
Moderate, or Severe Headache Recorded at Time of Dosing	456	422	448
Headache Relief 2 hours post-dose, n (%)	224(49.1)	256 (60.7)	275 (61.4)
p-value* vs Placebo		.0002	.0002

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

Sustained pain relief from 2 to 24 hours

The proportions of subjects with sustained pain relief from 2 to 24 hours were 20.8%, 36.3%, and 38.0% for the placebo, 50 mg, and 100 mg groups, respectively (p as versus placebo).

Table 13 Responder Rate: Sustained Pain Relief from 2 to 24 Hours –Study UBR-MD-01

	Placebo	U50	U100
Determinable from 2 to 24 hours after dosing	447	413	434
Headache Relief 24 hours post-dose, n (%)	93 (20.8)	150 (36.3)	165 (38.0)
p-value* vs Placebo		<.0001	<.0001

Determinable cases = patients for whom sustained pain relief from 2 to 24 hours status can be determined based on the observed headache severity at scheduled time points, use of rescue medication or optional second dose between 2 and 24 hours, and the answer to the headache recurrence question at 24 or 48 hours.

P-value* = nominal significant only.

(Source: sponsor's analysis verified by the reviewer).

Sustained pain free from 2 to 24 hours

Table 14 Responder Rate: Sustained Pain Free from 2 to 24 Hours - Study UBR-MD-01

	Placebo	U50	U100
Determinable from 2 to 24 hours after dosing	452	418	441
Headache Free 24 hours post-dose, n (%)	39 (8.6)	53 (12.7)	68 (15.4)
p-value* vs Placebo		.0436	.0018

Determinable cases = patients for whom sustained pain freedom from 2 to 24 hours status can be determined based on the observed headache severity at scheduled time points, use of rescue medication or optional second dose between 2 and 24 hours, and the answer to the headache recurrence question at 24 or 48 hours.

P-value* = nominal significant only.

(Source: sponsor's analysis verified by the reviewer).

Absence of Photophobia at 2 hours

Table 15 Responder Rate: Absence of photophobia at 2 hours - Study UBR-MD-01

	Placebo	U50	U100
Recorded at Time of Dosing	456	423	448
Photophobia Free 2 hours post-dose, n (%)	143 (31.4)	172 (40.7)	205 (45.8)
p-value* vs Placebo		.0011	<.0001

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

Absence of Phonophobia at 2 hours

Table 16 Responder Rate: Absence of phonophobia at 2 hours - Study UBR-MD-01

	Placebo	U50	U100
Recorded at Time of Dosing	456	423	448
Phonophobia Free 2 hours post-dose, n (%)	215 (47.1)	245 (57.9)	244 (54.5)
p-value* vs Placebo		.0033	.0091

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

Absence of Nausea at 2 hours

Table 17 Responder Rate: Absence of nausea at 2 hours - Study UBR-MD-01

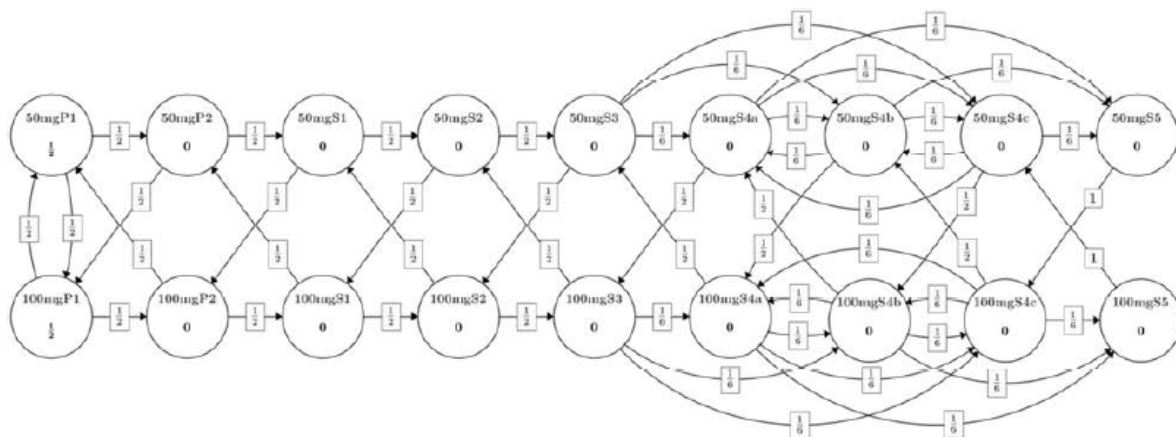
	Placebo	U50	U100
Recorded at Time of Dosing	456	423	448
Nausea Free 2 hours post-dose, n (%)	284 (62.3)	297 (70.2)	310 (69.2)
p-value* vs Placebo		.0833	.0481

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

3.2.5.4 Summary Efficacy Result After Multiplicity Adjustment

A graphical approach with the weighted Bonferroni-based closed test procedure was used to control the overall type I error rate at $\alpha=0.05$ for multiple comparisons across 2 ubrogepant doses versus placebo and the primary and secondary efficacy endpoints.

Figure 3 Multiple Comparisons Procedure – Study UBR- MD-01



(Source: Study SAP)

Statistically significant higher response rates were observed for the ubrogepant 50 and 100 mg doses compared with placebo for both coprimary efficacy endpoints: PF at 2 hours after the initial dose of IP and absence of the most bothersome migraine associated symptom at 2 hours after the initial dose of IP.

Table 18 Summary of Hypotheses Tests for the Two Co-Primary Endpoints – Study UBR-MD-01

			Study 1 (MD-01)		
			Placebo	U50	U100
Two co-primary endpoints	1 pf2h	N	456	422	448
		%	11.8%	19.2%	21.2%
		p		.0017	.0001
		p adjusted		.0023	.0003
		Significant (Yes/No)		Yes	Yes
	2 mbs f2h	N	454	420	448
		%	27.8%	38.6%	37.7%
		p		.0003	.0008
		p adjusted		.0023	.0023
		Significant (Yes/No)		Yes	Yes

(Source: sponsor's analysis verified by the reviewer).

Table 19 Summary of Hypotheses Tests for the Six Secondary Endpoints – Study UBR-MD-01

			Study 1 (MD-01)		
			Placebo	U50	U100
Six Secondary Endpoints	1 PR at 2h	N	456	422	448
		%	49.1%	60.7%	61.4%
		p		.0002	.0002
		p adjusted		.0023	.0023
		Significant (Yes/No)		Yes	Yes
	2 SPR 2 to 24	N	447	413	434
		%	20.8%	36.3%	38.0%
		p		<.0001	<.0001
		p adjusted		.0023	.0023
		Significant (Yes/No)		Yes	Yes
	3 SPF 2 to 24	N	452	418	441
		%	8.6%	12.7%	15.4%
		p		.0436	.0018
		p adjusted		.0577	.0037
		Significant (Yes/No)		No	Yes
	4 AofPhoto at 2h	N	456	423	448
		%	31.4%	40.7%	45.8%
		p		.0011	<.0001
		p adjusted		.0577	.0037
		Significant (Yes/No)		No	Yes
	5 AofPhono at 2h	N	456	423	448
		%	47.1%	57.9%	54.5%
		p		.0033	.0091
		p adjusted		.0577	.0577
		Significant (Yes/No)		No	No
	6 AofNausea at 2h	N	456	423	448
		%	62.3%	70.2%	69.2%
		p		.0833	.0481
		p adjusted		.0962	.0962
		Significant (Yes/No)		No	No

(Source: sponsor's analysis verified by the reviewer).

Ubrogepant 100 mg demonstrated statistically significant higher response rates compared with placebo for 4 of 6 secondary endpoints: PR at 2 hours after the initial dose, SPR from 2 to 24 hours and SPF from 2 to 24 hours after the initial dose, and absence of photophobia at 2 hours after the initial dose.

Ubrogepant 50 mg demonstrated statistically significant higher response rates compared with placebo for 2 of 6 secondary endpoints: PR at 2 hours after the initial dose and SPR from 2 to 24 hours after the initial dose.

3.3 Evaluation of Efficacy Study – UBR-MD-02

3.3.1 Description of the Study

This study had its first subject enrolled on 26 August 2016, last subject completed on 26 February 2018.

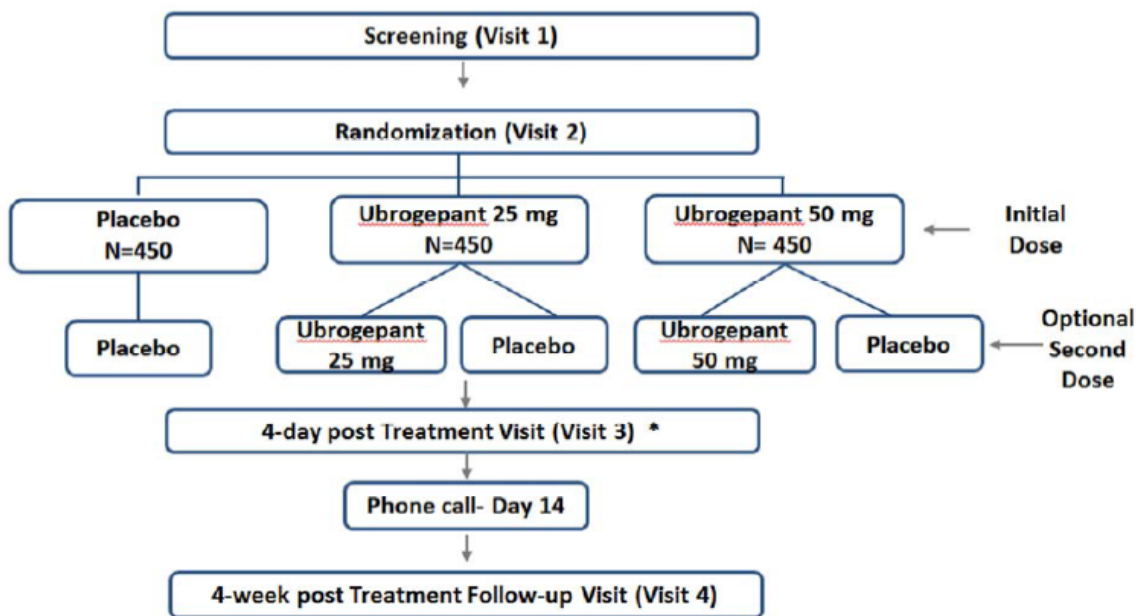
The primary objective was to evaluate the effect of Ubrogepant compared to placebo on the rates of pain free at 2 hours and MBS free at 2 hours in subjects with acute migraine.

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study of subjects with acute migraine. The study was conducted at 100 centers in the United States. Patients were randomized (1:1:1) to 1 of the 3 treatment groups: placebo, 25 mg, or 50 mg. Randomized study patients had up to 60 days to treat a single qualifying migraine attack of moderate or severe intensity at home.

Eligible subjects were adults 18 to 75 years of age with history of migraine for ≥ 12 months who experienced 2 to 8 migraine attacks per month with moderate to severe pain in each of the 3 months before screening, with migraine onset before the age of 50 years.

A sample size of 550 per group were needed to detect with power $> 85\%$ a difference in pain free response rates of 10% and 24% between placebo, and drug groups assuming a 20% drop out rate and a 10% missing data rate. These rates were taken from the Phase 2b studies.

Figure 4 Study Flow Diagram – Study UBR-MD-02



(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 initial dose treating a qualifying acute migraine attack during the double-blind treatment phase.

3.3.2.2 Secondary Endpoints

The secondary efficacy endpoints were:

- 1) Pain relief (PR) at 2 hours.
- 2) Sustained pain relief (SPR) from 2 to 24 hours.
- 3) Sustained pain freedom (SPF) from 2 to 24 hours.
- 4) Absence of photophobia at 2 hours.
- 5) Absence of phonophobia at 2 hours.
- 6) Absence of nausea at 2 hours.

3.3.3 Statistical Analysis Methods

Efficacy analyses were based on the 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 initial dose.

The primary efficacy variable of PF at 2 hours after the initial dose was analyzed using a logistic regression model with treatment group, and historical triptan response (triptan responder, triptan insufficient responder, or triptan naïve), use of medication for migraine prevention (yes/no), baseline headache severity (moderate or severe) as covariates.

The missing data were imputed using LOCF approach. This LOCF is considered problematic but was acceptable back when this drug development program started quite a few years ago and was pre-specified in the study document. A separate section on missing data and sensitivity analyses was written in this review, please see Table 27, 28 and 29 for more details.

The primary efficacy variable of absence of the most bothersome symptom at 2 hours after the initial dose was analyzed using a similar logistic regression model with an additional categorical term for the underlying symptom that was identified as the most bothersome.

The respective comparisons of the Ubrogepant doses versus placebo, which are the formal tests of the efficacy hypotheses, were conducted using the appropriate pairwise contrasts within the logistic regression model.

3.3.3.1 Multiplicity Adjustment

The multiplicity adjustment method was pre-specified by the sponsor as the following:

A graphical approach with closed testing procedure was used to control the overall type I error rate for multiple comparisons across the Ubrogepant doses and the primary and secondary efficacy endpoints. The coprimary efficacy endpoints served as the gatekeepers of the secondary endpoints.

The overall Type 1 error was controlled by this pre-specified method.

However, it may render the outcome of “Low dose wins while High dose loses” which would make the study results difficult to interpret clinically.

For this study 2 (MD-02) under review, the high dose (50 mg) won and the low dose (25 mg) lost using the sponsor pre-specified multiplicity adjustment plan.

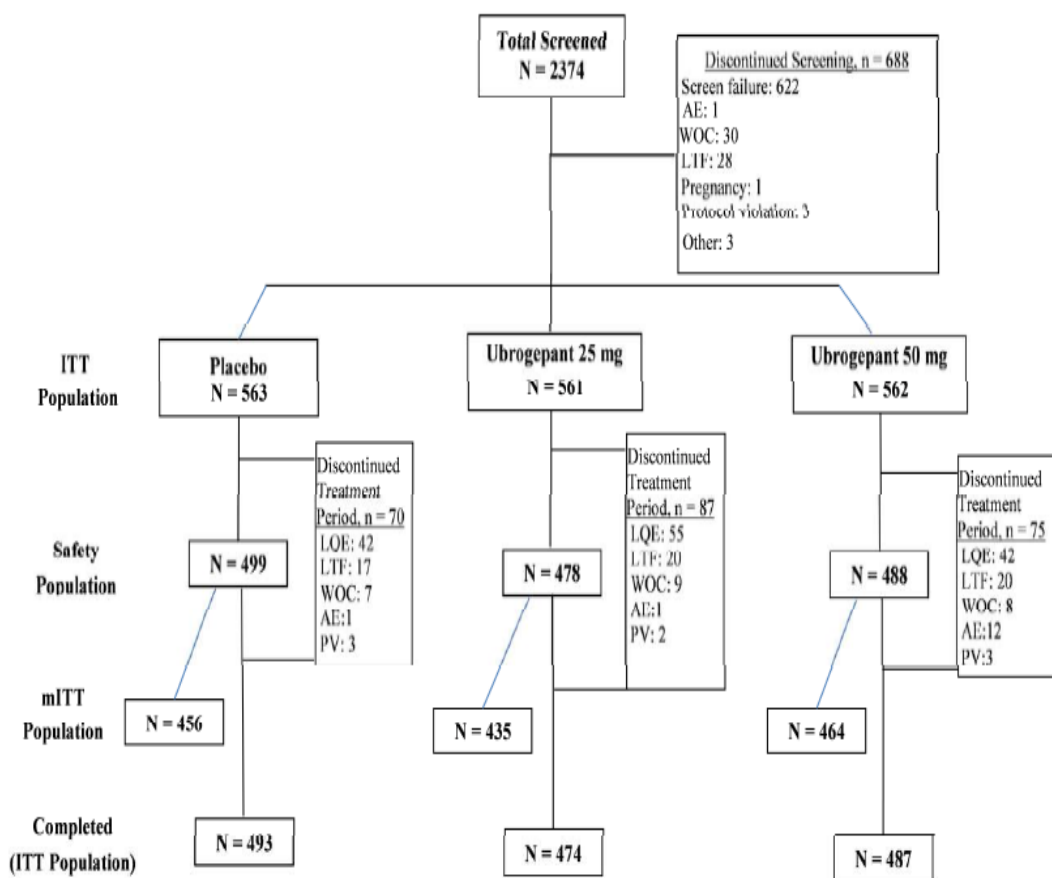
3.3.4 Patient Results

3.3.4.1 Patient Disposition

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

Of the 2374 patients who were screened for eligibility, 688 patients were discontinued from the screening period and not randomized to a treatment assignment. Screen failure (patient failed to meet eligibility criteria) was the primary reason for discontinuation during screening (622 of 688 patients).

Figure 5 Patient Disposition Diagram – Study UBR-MD-02



AE = adverse event; ITT = intent to treat; LTF = lost to follow-up; LQE = lack of qualifying event; mITT = modified intent to treat; PV = protocol violation; WOC = withdrawal of consent
(Source: CSR)

A total of 1686 patients passed screening and were randomized (intent-to-treat [ITT] population): 563 to the placebo group, 561 to the 25 mg group and 562 to the 50 mg group.

Table 20 Patient Completion and Discontinuation - Study UBR-MD-02

Phase Disposition	Placebo (N=563) n (%)	Ubrogepant 25 mg (N=561) n (%)	Ubrogepant 50 mg (N=562) n (%)	Total (N=1686) n (%)
Treatment Period				
Entered phase	563 (100.0)	561 (100.0)	562 (100.0)	1686 (100.0)
Completed phase	493 (87.6)	474 (84.5)	487 (86.7)	1454 (86.2)
Discontinued phase	70 (12.4)	87 (15.5)	75 (13.3)	232 (13.8)
Reason for phase discontinuation				
Adverse Event	1 (0.2)	1 (0.2)	2 (0.4)	4 (0.2)
Withdrawal of Consent	7 (1.2)	9 (1.6)	8 (1.4)	24 (1.4)
Lost to Follow-Up	17 (3.0)	20 (3.6)	20 (3.6)	57 (3.4)
Lack of Qualifying Event	42 (7.5)	55 (9.8)	42 (7.5)	139 (8.2)
Protocol Violation	3 (0.5)	2 (0.4)	3 (0.5)	8 (0.5)
Entered Safety Follow-up Phase	493 (87.6)	474 (84.5)	487 (86.7)	1454 (86.2)
Completed Safety Follow-up phase	482 (85.6)	459 (81.8)	473 (84.2)	1414 (83.9)

(Source: modified from the Table 10-1 in the sponsor's study report, verified by the statistical reviewer.)

Overall, 1454 (86.2%) of patients in the ITT population completed the treatment period and 232 (13.8%) subjects discontinued the study for the following reasons: lack of qualifying event, lost to follow-up, withdraw of consent, protocol violation, adverse event, pregnancy, and other.

Table 21 Analysis Populations - Study UBR-MD-02

Analysis Populations, n	Placebo	U25mg	U50mg	Total
ITT Population	563	561	562	1686
Safety Population	499	478	488	1465
mITT Population	456	435	464	1355

Intent-to-treat (ITT) population = Patients randomized to a study treatment group.

Safety population = Patients who took ≥ 1 dose of investigational product.

Modified ITT (mITT) population = Randomized patients who received at least 1 dose of investigational product, recorded a baseline migraine headache severity measurement, with ≥ 1 post dose headache severity or migraine associated symptom measurement at or before the 2-hour timepoint.

(Source: modified from the Table 10-4 in the sponsor's study report, verified by the statistical reviewer.)

3.3.4.2 Patient Demographics

Of the 1355 subjects in the mITT population, majority were women (89.89%), white (81.70%), and the mean age was 41.21 (18 to 75) years. The treatment groups were balanced for these baseline demographic characteristics.

Table 22 Patient Baseline Demographics – mITT – Study UBR-MD-02

	Placebo	U25mg	U50mg	Total
Age (years), n	456	435	464	1355
Mean (SD)	41.45 (12.13)	41.11 (12.29)	41.06 (12.42)	41.21 (12.28)
Median	41.00	40.00	41.00	41.00
Minimum	18	18	18	18
Maximum	73	71	75	75
Gender, n (%)	456	435	464	1355
Female	402 (88.16)	393 (90.34)	423 (91.16)	1218 (89.89)
Male	54 (11.84)	42 (9.66)	41 (8.84)	137 (10.11)
Race, n (%)	456	435	464	1355
Black or African	75 (16.45)	60 (13.79)	77 (16.59)	212 (15.65)
White	363 (79.61)	365 (83.91)	379 (81.68)	1107 (81.70)
Other	18 (3.95)	10 (2.30)	8 (1.72)	36 (2.66)
BMI (kg/m2), n	456	435	464	1355
Mean (SD)	29.88(7.72)	29.68(7.14)	30.59 (7.59)	30.06 (7.50)
Median	28.49	28.69	29.49	28.93
Minimum	15.94	16.72	15.91	15.91
Maximum	73.83	63.35	67.10	73.83

BMI = body mass index

(Source: Reviewer's own analysis.)

3.3.4.3 Patient Baseline Disease Characteristics

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

In the mITT population, 24.13% of patients reported current use of prophylactic medication for migraine. Based on historical triptan response, 34.69% of patients were triptan responders, 23.32% were triptan insufficient-responders, and 41.99% were triptan naïve.

The mean (SD) duration of years with migraine at baseline was 19.01(12.63), 18.60(12.25), and 18.05(12.38) years in the placebo, 25 mg, and 50 mg groups, respectively.

The mean (SD) migraine per month in the past 3 months at baseline was 4.57(1.85), 4.77(1.81), and 4.42(1.84) in the placebo, 25 mg, and 50 mg groups, respectively.

Table 23 Patient Baseline Disease Characteristics -mITT - Study UBR-MD-02

	Placebo	U25mg	U50mg	Total
Concomitant Prophylactic Migraine Medication, n (%)	456	435	464	1355
Yes	111 (24.34)	100 (22.99)	116 (25.00)	327 (24.13)
No	345 (75.66)	335 (77.01)	348 (75.00)	1028 (75.87)
Historical Triptan Response, n	456	435	464	1355
Triptan Responder	159 (34.87)	151 (34.71)	160 (34.48)	470 (34.69)
Triptan Insufficient-Responder	106 (23.25)	100 (22.99)	110 (23.71)	316 (23.32)
Triptan Naïve	191 (41.89)	184 (42.30)	194 (41.81)	569 (41.99)
Migraine Disorder Duration in Years	456	434	464	1354
Mean (SD)	19.01(12.63)	18.60(12.25)	18.05(12.38)	18.55(12.42)
Median	17.00	16.50	16.00	17.00
Min, Max	1.00, 57.00	1.00, 60.00	1.00, 56.00	1.00, 60.00
Migraines/Month in Past 3 Months	456	435	464	1355
Mean (SD)	4.57(1.85)	4.77(1.81)	4.42(1.84)	4.58(1.84)
Median	4.00	4.00	4.00	4.00
Min, Max	2.00, 8.00	2.00, 8.00	2.00, 8.00	2.00, 8.00

(Source: Reviewer's own analysis.)

3.3.5 Results and Conclusion

3.3.5.1 Efficacy Results of the Primary Endpoints

The results reported by the sponsor were confirmed.

The 50 mg won but the 25 mg did not win.

Table 24 Primary Endpoint Analyses – Study UBR-MD-02

	Placebo	Ubrogepant	
		25 mg	50 mg
Pain Moderate to Severe at time of dosing	456	435	464
Pain Free at 2 hours	65	90	101
%	14.3%	20.7%	21.8%
p-value	-	.0143	.0065
MBS recorded at time of dosing	456	435	464
MBS Free at 2 hours	125	148	180
%	27.4%	34.1%	38.9%
p-value	-	.0355*	.0005

P-values were from a logistic regression model with treatment group and historical triptan response, use of medication for migraine prevention, and baseline headache severity (or the underlying symptom) as explanatory variables.

*P value for the 25 mg versus placebo for MBS endpoint was not significant after multiplicity adjustment.

(Source: reviewer's own analysis and sponsor's analysis verified by the reviewer.)

The primary analysis for Pain free status at 2 hours included 1355 patients. There was a statistically significant increase in the rate of pain free at 2 hours from 14.3% in the placebo group to 20.7% in the 25 mg group and 21.8% in the 50 mg group.

The p-values versus placebo were .0143 and .0065.

Both p-values achieved statistical significance under the pre-specified multiplicity adjustment plan.

The primary analysis for MBS free status at 2 hours included 1355 patients. There was an increase in the rate of MBS free at 2 hours from 27.4% in the placebo group to 34.1% in the 25 mg group and 38.9% in the 50 mg group.

The p-values versus placebo were .0355 and .0005.

But only the 50 mg group achieved statistical significance after adjusting for multiplicity. The 25 mg group did not achieve statistical significance with a nominal p-value at .0355.

Patients with missing data at 2-hour time point were imputed using LOCF. The LOCF method is considered problematic in general, but this drug development program has been in existence for a quite long time that the LOCF method was considered acceptable back then and was pre-specified in the study document. Therefore, we would like to follow the pre-specified method. A separate section on missing data and various sensitivity analyses was presented next (Table 27, 28 and 29).

As a clinical rule, patients with rescue medication use prior to the 2-hour time point were considered as treatment failures. However, the sponsor did not provide clear patient level flag and did not follow such rule in the analyses.

We have sent IR (Information Request) and in the response under SN 30 the sponsor clarified how to identify such patients. Based on the additional information and clarification, the reviewer was able to apply this rule and found that: the change of responder counts was small and did not alter the efficacy conclusion. For example, for PF2H, the change was 0/-1/0 for the placebo group, the 25 mg group and the 50 mg group respectively if we use the time window of -5 minutes as suggested by the sponsor. If we use +5 minutes time window, or the +35 minutes time window, the change was -1/-7/-2, and -1/-9/-5. Please see below Table 25 and 26 for more details.

Please note that the 25 mg group versus placebo for the “MBS Free at 2 Hours” endpoint showed a change in p value from 0.0355 to 0.0514 using the sponsor’s own result of “5 minutes before Time Window” as in the response to our IR in SN 30.

Due to this design feature of the e-Dairy which allowed patients to enter data for the 2-hour timepoint during the 40 minutes time window from 5 minutes before to 35 minutes later, we really have no way of knowing exactly which one is the more accurate (closer to the true data).

Even without imposing any penalty from a multiplicity adjustment, 25 mg group produced a p value larger than the .05 if we use the “5 minute before Time Window”.

Table 25 PF2H ResMeds Time Window Sensitivity Analyses- mITT-Study UBR-MD-02

Study MD-02	Without consideration for resmed			AVAL<=115/60			AVAL<=125/60			AVAL<=155/60		
mITT	456	435	464	456	435	464	456	435	464	456	435	464
pf2h	placebo	u25	u50	placebo	u25	u50	placebo	u25	u50	placebo	u25	u50
responder	65	90	101	65	89	101	64	83	99	64	81	96
%	14.25%	20.69%	21.77%	14.25%	20.46%	21.77%	14.04%	19.08%	21.34%	14.04%	18.62%	20.69%
p value versus placebo		0.0143	0.0065		0.018	0.0065		0.0513	0.0082		0.0757	0.0157
increase from placebo		6.44%	7.51%		6.21%	7.51%		5.05%	7.30%		4.59%	6.65%

(Sponsor’s analysis and review’s own analysis)

- AVAL<=115/60: 5 minutes before the 2-hour time point
- AVAL<=125/60: 5 minutes after the 2-hour time point
- AVAL <=155/60: 35 minutes after the 2-hour time point

*In SN 30 submission, the sponsor was recommending the use of the time window of “5 minutes before the 2-hour time point”.

Table 26 MBS2H ResMeds Time Window Sensitivity Analyses- mITT-Study UBR-MD-02

Study MD-02	Without consideration for resmed			AVAL<=115/60			AVAL<=125/60			AVAL<=155/60		
	456	434	463	456	434	463	456	434	463	456	434	463
mITT	456	434	463	456	434	463	456	434	463	456	434	463
mbs2h	placebo	u25	u50	placebo	u25	u50	placebo	u25	u50	placebo	u25	u50
responder	125	148	180	125	146	180	101	123	155	91	104	148
%	27.41%	34.10%	38.88%	27.41%	33.64%	38.88%	22.15%	28.34%	33.48%	19.96%	23.96%	31.97%
p value versus placebo		0.0355	0.0005		0.0514	0.0005		0.0398	0.0003		0.1761	<.0001
increase from placebo		6.69%	11.46%		6.23%	11.46%		6.19%	11.33%		4.01%	12.01%

(Sponsor's analysis and review's own analysis)

- AVAL<=115/60: 5 minutes before the 2-hour time point
- AVAL<=125/60: 5 minutes after the 2-hour time point
- AVAL <=155/60: 35 minutes after the 2-hour time point

*In SN 30 submission, the sponsor was recommending the use of the time window of "5 minutes before the 2-hour time point".

In conclusion, we consider the efficacy result presented in Table 24 (same as the sponsor's result in the study report) as adequate.

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 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 27 Patient Counts at Time of Dosing and Two Hours - Study UBR-MD-02

	Pain at Time 0	Pain at 2 Hours	Missing n	Missing %	MBS at Time 0	MBS at 2 Hours	Missing n	Missing %
placebo	456	429	27	5.92%	456	429	27	5.92%
25 mg	435	401	34	7.82%	434	401	33	7.60%
50 mg	464	433	31	6.68%	463	432	31	6.70%

(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 included in the MBS analysis.

In the primary efficacy analysis, subjects with missing data at 2 hours timepoint were imputed using LOCF.

Table 28 shows the breakdown of patient counts with or without actual efficacy measurements at 2 hours (Yes/No/Missing), and the patient efficacy results after applying the LOCF imputation.

Table 28 Descriptive Patient Counts for Data Status at 2 Hours – mITT- Study UBR-MD-02

	Pain		MBS	
Placebo	59	Yes	115	Yes
	370	No	314	No
	27	2-Hour missing (LOCF: 6 Yes; 21 No)	27	2-Hour missing (LOCF: 10 Yes; 17 No)
25 mg	85	Yes	143	Yes
	316	No	258	No
	34	2-Hour missing (LOCF: 5 Yes; 29 No)	33	2-Hour missing (LOCF: 5 Yes; 28 No)
50 mg	97	Yes	172	Yes
	336	No	260	No
	31	2-Hour missing (LOCF: 4 Yes; 27 No)	31	2-Hour missing (LOCF: 8 Yes; 23 No)

(Source: Reviewer's own analysis.)

In the sensitivity analysis performed by the sponsor the missing was imputed as non-responders. Additional sensitivity analysis performed by the sponsor used GLMM assuming missing at random.

Results for both sensitivity analyses were consistent with those observed for the primary analysis.

Results from the “Semi Worst Case” analysis were also consistent with the primary analysis.

Table 29 Sensitivity Analyses – Study UBR-MD-02

	mITT using Missing as Non-responders			mITT using GLMM			mITT using Missing as Semi Worst Case		
	Ubrogapant			Ubrogapant			Ubrogapant		
	Placebo	25 mg	50 mg	Placebo	25 mg	50 mg	Placebo	25 mg	50 mg
Pain Moderate to Severe at time of dosing	456	435	464	456	435	464	429	435	464
Pain Free at 2 hours	59	85	97	-	-	-	59	85	97
%	12.9	19.5	20.9	12.1	18.1	18.8	13.8	19.5	20.9
p-value		.0095	.0029		.0103	.0041		.0319	.0117
MBS recorded at time of dosing	456	434	463	456	434	463	429	434	463
MBS Free at 2 hours	115	143	172	-	-	-	115	143	172
%	25.2	32.9	37.1	29.0	37.1	41.3	26.8	33.0	37.2
p-value		.0138	.0002		.0156	.0003		.0643	.0024

*Semi-Worst Case = missing from placebo group excluded while missing from drug group assigned as failures

(Source: reviewer's analysis and sponsor's analysis, verified by the reviewer.)

3.3.5.3 Efficacy Results of the Secondary Endpoints

The pre-specified secondary efficacy endpoints were:

- 1) Pain relief (PR) at 2 hours.
- 2) Sustained pain relief (SPR) from 2 to 24 hours.
- 3) Sustained pain freedom (SPF) from 2 to 24 hours.
- 4) Absence of photophobia at 2 hours.
- 5) Absence of phonophobia at 2 hours.
- 6) Absence of nausea at 2 hours.

The nominal p-values reported by the sponsor were confirmed.

Pain relief (PR) 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) at the indicated assessment time. The mITT population was used for the analysis. The proportions of subjects with pain relief at 2 hours were 48.2%, 60.5%, and 62.7% for the placebo, 25 mg, and 50 mg groups, respectively (p as versus placebo). The sponsor's analysis result was confirmed. Missing data at 2-hours timepoint was minimal and LOCF method was used.

Table 30 Responder Rate: Pain Relief at 2 Hours – mITT Population - Study UBR-MD-02

	Placebo	U25	U50
Moderate, or Severe Headache Recorded at Time of Dosing	456	435	464
Headache Relief 2 hours post-dose, n (%)	220(48.2)	263 (60.5)	291 (62.7)
p-value* vs Placebo		.0004	<.0001

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

Sustained pain relief from 2 to 24 hours

The proportions of subjects with sustained pain relief from 2 to 24 hours were 21.0%, 32.5%, and 36.7% for the placebo, 25 mg, and 50 mg groups, respectively (p as versus placebo).

Table 31 Responder Rate: Sustained Pain Relief from 2 to 24 Hours – mITT - Study UBR-MD-02

	Placebo	U25	U50
Determinable from 2 to 24 hours after dosing	443	424	449
Headache Relief 24 hours post-dose, n (%)	93 (21.0)	138 (32.5)	165 (36.7)
p-value* vs Placebo		.0002	<.0001

Determinable cases = patients for whom sustained pain relief from 2 to 24 hours status can be determined based on the observed headache severity at scheduled time points, use of rescue medication or optional second dose between 2 and 24 hours, and the answer to the headache recurrence question at 24 or 48 hours.

P-value* = nominal significant only.

(Source: sponsor's analysis verified by the reviewer).

Sustained pain free from 2 to 24 hours

Table 32 Responder Rate: Sustained Pain Free from 2 to 24 Hours - Study UBR-MD-02

	Placebo	U25	U50
Determinable from 2 to 24 hours after dosing	451	432	457
Headache Free 24 hours post-dose, n (%)	37 (8.2)	55 (12.7)	66 (14.4)
p-value* vs Placebo		.0317	.0051

Determinable cases = patients for whom sustained pain freedom from 2 to 24 hours status can be determined based on the observed headache severity at scheduled time points, use of rescue medication or optional second dose between 2 and 24 hours, and the answer to the headache recurrence question at 24 or 48 hours.

P-value* = nominal significant only.

(Source: sponsor's analysis verified by the reviewer).

Absence of Photophobia at 2 hours

Table 33 Responder Rate: Absence of photophobia at 2 hours - Study UBR-MD-02

	Placebo	U25	U50
Recorded at Time of Dosing	456	435	464
Photophobia Free 2 hours post-dose, n (%)	162 (35.5)	171 (39.3)	203 (43.8)
p-value* vs Placebo		.0917	.0042

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

Absence of Phonophobia at 2 hours

Table 34 Responder Rate: Absence of phonophobia at 2 hours - Study UBR-MD-02

	Placebo	U25	U50
Recorded at Time of Dosing	456	435	464
Phonophobia Free 2 hours post-dose, n (%)	211 (46.3)	233 (53.6)	251 (54.1)
p-value* vs Placebo		.0266	.0220

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

Absence of Nausea at 2 hours

Table 35 Responder Rate: Absence of nausea at 2 hours - Study UBR-MD-02

	Placebo	U25	U50
Recorded at Time of Dosing	456	435	464
Nausea Free 2 hours post-dose, n (%)	319 (70.0)	307 (70.6)	331 (71.3)
p-value* vs Placebo		.5410	.4761

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

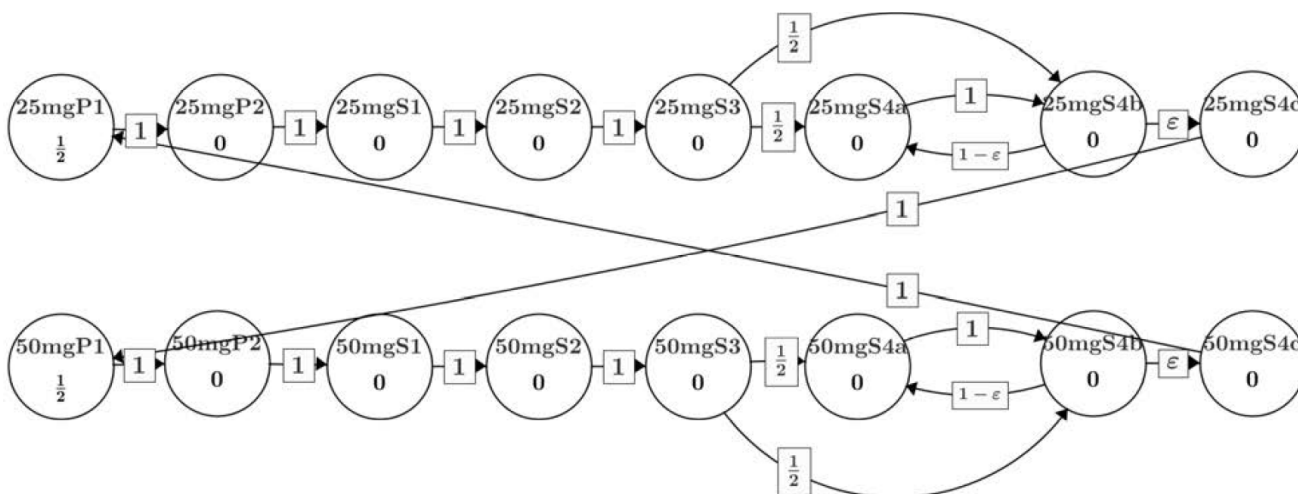
3.3.5.4 Summary Efficacy Result After Multiplicity Adjustment

A graphical approach with the weighted Bonferroni-based closed test procedure was used to control the overall type I error rate at $\alpha=0.05$ for multiple comparisons across 2 ubrogepant doses versus placebo and the primary and secondary efficacy endpoints.

The two coprimary efficacy endpoints will serve as the gatekeepers of the secondary endpoints.

Using graphical approach with the weighted Bonferroni-based closed test procedure, the endpoints are represented by circles with associated weights inside the circle. The weight is the fraction of α , representing local significance levels. The fraction in the rectangle, associated with a line connecting two circles, indicates the fraction of the local significance level of the circle at the beginning of the line which is added to the local significance level of the circle at the end of the line, if the null hypothesis at the beginning circle is rejected.

Figure 6 Multiple Comparisons Procedure – Study UBR-MD-02



(Source: Study SAP)

For the 2 coprimary endpoints: PF at 2 hours after the initial dose of IP and absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose of IP), statistically significant higher response rates compared with placebo were observed for the ubrogepant 50 mg dose.

For the ubrogepant 25 mg dose, statistically significant higher response rates compared with placebo were observed for the coprimary endpoint PF at 2 hours; however, statistical significance was not achieved for the coprimary endpoint of absence of the most bothersome migraine-associated symptom at 2 hours.

In addition, the sensitivity analyses using the “5-minute before time window” at the 2-hour time point for rescue medication use produced a p value of .0514 (larger than .05) for the 25 mg versus placebo for the co-primary endpoint of “MBS Free at 2 hours”.

Table 36 Summary of Hypotheses Tests for the Two Co-Primary Endpoints – Study UBR-MD-02

			Study 2 (MD-02)		
			Placebo	U25	U50
Two co-primary endpoints	1 pf2h	N	456	435	464
		%	14.3%	20.7%	21.8%
		p		.0143	.0065
		p adjusted		.0285	.0129
		Significant (Yes/No)		Yes	Yes
	2 mbs f2h	N	456	434	463
		%	27.4%	34.1%	38.9%
		p		.0355	.0005
		p adjusted		.0711	.0129
		Significant (Yes/No)		No	Yes

(Source: sponsor’s analysis verified by the reviewer).

Ubrogepant 50 mg demonstrated statistically significant higher response rates compared with placebo for 5 of 6 secondary endpoints: PR at 2 hours after the initial dose, SPR from 2 to 24 hours, SPF from 2 to 24 hours after the initial dose, absence of photophobia at 2 hours after the initial dose, and absence of phonophobia at 2 hours after the initial dose.

For the ubrogepant 25 mg group, multiplicity adjustments for the secondary endpoints were not conducted because it did not achieve statistical significance on both coprimary endpoints.

Table 37 Summary of Hypotheses Tests for the Six Secondary Endpoints – Study UBR-MD-02

			Study 2 (MD-02)		
			Placebo	U25	U50
Six Secondary Endpoints	1 PR at 2h	N	456	435	464
		%	48.2%	60.5%	62.7%
		p		.0004	<.0001
		p adjusted		.0711	.0129
		Significant (Yes/No)		No	Yes
	2 SPR 2 to 24	N	443	424	449
		%	21.0%	32.5%	36.7%
		p		.0002	<.0001
		p adjusted		.0711	.0129
		Significant (Yes/No)		No	Yes
	3 SPF 2 to 24	N	451	432	457
		%	8.2%	12.7%	14.4%
		p		.0317	.0051
		p adjusted		.0711	.0129
		Significant (Yes/No)		No	Yes
	4 AofPhoto at 2h	N	456	435	464
		%	35.5%	39.3%	43.8%
		p		.0917	.0042
		p adjusted		.1833	.0167
		Significant (Yes/No)		No	Yes
	5 AofPhono at 2h	N	456	435	464
		%	46.3%	53.6%	54.1%
		p		.0266	.0220
		p adjusted		.1066	.0440
		Significant (Yes/No)		No	Yes
	6 AofNausea at 2h	N	456	435	464
		%	70.0%	70.6%	71.3%
		p		.5410	.4761
		p adjusted		.9522	.9522
		Significant (Yes/No)		No	No

(Source: sponsor's analysis verified by the reviewer).

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region – Study UBR-MD-01

In the study 1 (UBR-MD-01), the median age of the subjects was about 38 to 40 years, with the percentage of female as 89% in the placebo group, 90% in the 50 mg group and 86% in the 100 mg drug group, and the majority being either black or white, with the percentage of being white 86%, 83% and 83%, being black as 11%, 14% and 14%.

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

Table 38 Age, Gender, and Race Summaries by Treatment Group - Study UBR-MD-01

	Age (Median)	Gender (%F)	Race (%White)	Race (%Black)
Placebo	40	89.25	85.75	11.18
50 mg	38	89.83	82.51	13.71
100 mg	40	86.16	83.04	14.06
Overall	40	88.39	83.80	12.96

(Reviewer's result.)

For study 1 (UBR-MD-01), 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 39 Findings in Subgroup Populations – Age, Gender and Race – Study UBR-MD-01

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					
Placebo	224	25	11.16%	232	29	12.50%			
50 mg	202	41	20.30%	220	40	18.18%			
100 mg	217	51	23.50%	231	44	19.05%			
	Gender = Female			Gender = Male					
Placebo	407	44	10.81%	49	10	20.41%			
50 mg	379	75	19.79%	43	6	13.95%			
100 mg	386	83	21.50%	62	12	19.35%			
	Race = White			Race = Black			Race = All Other		
Placebo	391	40	10.23%	51	11	21.57%	14	3	21.43%
50 mg	348	62	17.82%	58	17	29.31%	16	2	12.50%
100 mg	372	80	21.51%	63	12	19.05%	13	3	23.08%
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					
Placebo	223	57	25.56%	231	69	29.87%			
50 mg	201	83	36.87%	219	79	36.07%			
100 mg	217	80	41.29%	231	89	38.53%			
	Gender = Female			Gender = Male					
Placebo	405	105	25.93%	49	21	42.86%			
50 mg	378	145	38.36%	42	17	40.48%			
100 mg	386	147	38.08%	62	22	35.48%			
	Race = White			Race = Black			Race = All Other		
Placebo	390	99	25.38%	51	21	41.18%	13	6	46.15%
50 mg	347	131	37.75%	57	27	42.86%	16	4	25.00%
100 mg	372	139	37.37%	63	27	47.37%	13	3	23.08%

(Reviewer's result)

4.2 Gender, Race, Age and Geographic Region – Study UBR-MD-02

In the study 2 (UBR-MD-02), the median age of the subjects was about 40 to 41 years, with the percentage of female as 89% in the placebo group, 90% in the 25 mg group and 91% in the 50 mg drug group, and the majority being either black or white, with the percentage of being white 80%, 84% and 82%, being black as 17%, 14% and 17%.

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

Table 40 Age, Gender, Race and Country Summaries by Treatment Group - Study UBR-MD-02

	Age (Median)	Gender (%F)	Race (%White)	Race (%Black)
Placebo	41	88.16	79.61	16.45
25 mg	40	90.34	83.91	13.79
50 mg	41	91.16	81.68	16.59
Overall	41	89.89	81.70	15.65

(Reviewer's result.)

For study UBR-MD-02, 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 41 Findings in Subgroup Populations – Age, Gender, Race and Country – Study UBR-MD-02

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					
Placebo	219	34	15.53%	237	31	13.08%			
25 mg	211	46	21.80%	224	44	19.64%			
50 mg	230	54	23.48%	234	47	20.09%			
	Gender = Female			Gender = Male					
Placebo	402	58	14.43%	54	7	12.96%			
25 mg	393	86	21.88%	42	4	9.52%			
50 mg	423	93	21.99%	41	8	19.51%			
	Race = White			Race = Black			Race = All Other		
Placebo	363	41	11.29%	75	22	29.33%	18	2	11.11%
25 mg	365	71	19.45%	60	16	26.67%	10	3	30.00%
50 mg	379	86	22.69%	77	15	19.48%	8	0	0.00%
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					
Placebo	219	57	26.03%	237	68	28.69%			
25 mg	211	75	35.55%	223	73	32.74%			
50 mg	230	91	39.57%	233	89	38.20%			
	Gender = Female			Gender = Male					
Placebo	402	112	27.86%	54	13	24.07%			
25 mg	392	140	35.71%	42	8	19.05%			
50 mg	422	169	40.05%	41	11	26.83%			
	Race = White			Race = Black			Race = All Other		
Placebo	363	92	25.34%	75	29	38.67%	18	4	22.22%
25 mg	364	118	32.42%	60	25	41.67%	10	5	50.00%
50 mg	379	147	38.79%	76	32	42.11%	8	1	12.50%

(Reviewer's result)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

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

Study 1 (MD-01) provided evidence that ubrogepant 50 mg and 100 mg won on both co-primary endpoints, 50 mg also won on secondary endpoints 1 and 2, 100 mg won on secondary endpoints 1 to 4.

Study 2 (MD-02) provided evidence that ubrogepant 50 mg won on both co-primary endpoints, 50 mg also won on secondary endpoints 1 to 5. The 25 mg did not win the two co-primary endpoints by failing to produce a p value for “the MBS Free at 2 hours” that was reliably below .05 to be even nominally significant.

5.2 Conclusions and Recommendations

The following tables may be used for labeling purposes.

5.3 Labeling Recommendations

Table 42 Efficacy Result from Study UBR-MD-01 – mITT population

	Placebo	Ubrogepant	
		50 mg	100 mg
Pain Moderate to Severe at time of dosing	456	422	448
Pain Free at 2 hours	54	81	95
%	11.8%	19.2%	21.2%
p-value	-	.0017	.0001
MBS recorded at time of dosing	454	420	448
MBS Free at 2 hours	126	162	169
%	27.8%	38.6%	37.7%
p-value	-	.0003	.0008

Table 43 Efficacy Result from Study UBR-MD-02 – mITT population

	Placebo	Ubrogepant	
		25 mg	50 mg
Pain Moderate to Severe at time of dosing	456	435	464
Pain Free at 2 hours	65	90	101
%	14.3%	20.7%	21.8%
p-value	-	.0143	.0065
MBS recorded at time of dosing	456	435	464
MBS Free at 2 hours	125	148	180
%	27.4%	34.1%	38.9%
p-value	-	.0355*	.0005

p-value = 0.0355* nominal only, did not achieve statistical significance.

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>

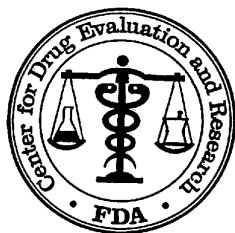
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/s/

JINNAN LIU
12/10/2019 03:51:43 PM

KUN JIN
12/10/2019 04:27:49 PM
I concur with the review.

HSIEN MING J HUNG
12/11/2019 10:18:37 AM



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 211765
Drug Name:	Ubrogepant (MK-1602)
Indication(s):	For the acute treatment of migraine with or without aura in adults
Studies	Two Year Oral Gavage Carcinogenicity Study in Rats and Mice.
Applicant:	Sponsor: Allergan Sales Llc. 2525 Dupont Dr. Irvine, California 92612, United States Test facility: Merck Research Laboratories West Point, Pennsylvania 19486 U.S.A.
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1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in regular mice. These studies were intended to assess the carcinogenic potential of Ubrogapant (MK-1602) a calcitonin gene-related peptide (CGRP) receptor antagonist, when administered to rats and mice by oral gavage once daily at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Nesti.

In this review, the phrase "dose response relationship" (trend) 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 dose increases.

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and two vehicle control groups. Two hundred and fifty Wistar Han rats of each sex were assigned to three treated groups and two vehicle control groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 50 animals, as indicated in Table 1. The dose levels for the three treated groups were 10, 30, and 100 mg/kg/day for male rats and 10, 30, 150 mg/kg/day for female rats, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control groups received each the vehicle only (100% Polyethylene Glycol 400), administered orally by gavage for about 104 weeks in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	50	50
Vehicle Control	2	0	0	50	50
Low	3	10	10	50	50
Medium	4	30	30	50	50
High	5	100	150	50	50

During the study period all animals were observed for general health/mortality and moribundity daily, abnormal findings were recorded throughout the study. Clinical sign observations were conducted for each carcinogenicity animal once per week from Study Week 1 through Study Week 104, except that salivation (observed post-dose) was generally not documented as a clinical sign beginning in Study Week 10 based on the established consistent pattern of salivation. Beginning in Study Week 26, all animals designated for carcinogenicity assessment were palpated for masses once every 4 weeks through Study Week 104 (except in Study Weeks 30 and 82, when palpations were performed in Study Weeks 31 and 81, respectively, instead). Additionally, unscheduled palpations were performed on individual animals found with masses during non-palpation weeks. Animals were palpated to provide information regarding the onset of possible neoplasms for use in statistical analyses. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity rats, were recorded weekly. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively was euthanized. Observations included, but were not limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the

experiment. Body weights were measured pretest, once per week during Study Weeks 1 through 22, and once every 4 weeks thereafter, and for each animal of that sex/group during the week of sacrifice.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's analysis, the tests for survival comparisons were performed with SAS® Proc LifeTest. This test is used to compute nonparametric estimates of the survivor function by the product-limit method (also called the Kaplan-Meier method). The sponsor tested whether the compound under investigation increased the unscheduled death by statistical comparison of the survival curves. A log-rank test based on censored-data generalizations of the Savage (exponential scores) test is used to test for homogeneity/equality of the survival functions across the dose groups.

The minimum P-value from an ordinal dose scale was reported. P-values were one-tailed for positive trend since the primary concern was in determining whether treatment with MK-1602 increased unscheduled death. However, when the observed trend was negative (decreasing unscheduled death with increasing dose), one-tailed negative trend P-values were calculated and appear below with the suffix "N" for negative trend in the sponsor's report .

The two vehicle control groups were also combined for comparisons against the dosed groups

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 66 (66%), 29 (58%), 33 (66%), and 31 (62%), in the combined vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 60 (60%), 30 (60%), 34 (68%), and 29 (58%) in combined vehicle control, low, medium, and high dose groups, in female rats, respectively. The sponsor's report concluded that, there was not a statistically significant increase in unscheduled death through the top dose of 100 mg/kg/day or 150 mg/kg/day of MK-1602, for males or for females respectively ($P=0.926$, or $= 0.633$, respectively).

2.1.2. Tumor data analysis

Tumor data of males and females were analyzed separately. For each organ and tumor combination site, the response variable of interest is the incidence of animals with tumor. Statistical analysis considered the context of observation of the tumor as well as survival differences among dose groups. The Peto method was used to analyze the palpable and nonpalpable tumor data. The significance level was set to 0.05.

The primary analysis of tumor incidence was by the trend test (an increase or decrease in tumor incidence with increasing dose of the test article). Both unadjusted and adjusted (for multiplicity of tests) p-values were calculated. For completeness, a supplementary analysis by comparing only the top dose group with the combined control groups was also conducted.

The analysis of tumors was based on the following fixed time intervals: Weeks 1-52, 53-65, 66-78, 79-91, 92-104, and terminal sacrifice for both male and female rats. The terminal necropsy was considered a single stratum, so all days of detection or death after day 728 were analyzed as if

occurring on day 729. The actual dose levels were used as the scores. All tumors in the scheduled terminal sacrifice interval were considered incidental for the statistical analysis.

Adjustment for the multiplicity:

Adjustment followed the recommendations made by Mantel, Heyse and Rom, and Harter. The procedure is as follows: Let $P_{(i)}$ be the smallest observed P-value from among all tumor types analyzed (males and females separated). Then the adjusted P-value of $P_{(i)}$ is $\text{Adj } P_{(i)} = 1 - \Pi(1 - P_i^*)$, where P_i^* is the largest possible P-value of the i -th parameter that is less than or equal to $P_{(i)}$. Note that P_i^* can be zero if P_i is discrete and $P_{(i)}$ is sufficiently small, so that many rare tumor types effectively drop out of the multiplicity adjustment. If $\text{Adj } P_{(i)}$ still shows a statistically significant effect, then the procedure is repeated for the remaining tumor type(s), omitting the type(s) that gave $P_{(i)}$.

Sponsor's findings:

The sponsor's report concluded that, there was not a statistically significant ($P > 0.05$) increase trend in tumor incidence for male rats. For female rats, there was a statistically significant increasing trend in tumor incidence of endometrial stromal sarcoma in uterus prior to multiplicity adjustment ($P = 0.043$). However, this increasing trend was not statistically significant after the adjustment for multiplicity ($\text{Adj. } P = 0.517$).

A statistically significant decreasing trend in tumor incidence through the top dose was found for adenoma in adrenal in female rats prior to multiplicity adjustment ($P = 0.009$ N). After adjustment for multiplicity, the decreasing trend was not statistically significant ($\text{Adj. } P = 0.073$ N).

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on October 11, 2019 via SN 0025.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

The two vehicle control groups were also compared using two-sided tests. As there were no statistically significant differences between the vehicle control groups, they were combined for comparisons against the dosed groups.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 66 (66%),

29 (58%), 33 (66%), and 31 (62%), in the combined vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 60 (60%), 30 (60%), 34 (68%), and 29 (58%) in combined vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant dose response relationship in the mortality of both male and female rats. The pairwise comparisons also showed no statistically significant increase or decrease in mortality between the individual treated groups, and the combined vehicle control group in either sex of rats.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups 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 with development of the tumor type being tested gets a score of $s_h = 1$. An animal that dies at Week w_h without development of the given tumor type 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 develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 10, 30, and 100 for male rats and 0, 10, 30, and 150 for female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA more recently revised draft guidance for the carcinogenicity study design and data analysis 2015, for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 2.

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons

Treated Groups and Control Group in Rats								
sex	Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC Comb. Veh. Cont (N=100) P - Trend	10 mg Low (N=50) P -VC vs. L	30 mg Med (N=50) P -VC vs. M	150 mg High (N=50) P -VC vs. H
Female	UTERUS	Endometrial Stromal sarcoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.0348 [@]	0/50 (41) NC	1/50 (45) 0.3571	2/50 (43) 0.1184

& 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.

[@]: not Statistically significant at 0.025 for rare tumor in dose response relationship test.

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased MK-1602 dose across the vehicle control and the treated groups dose in either sex of rats. The pairwise comparisons showed no tumor types with a statistically significant increase in tumor incidences in individual MK-1602 treated groups, when compare to the combined vehicle control group in either male or female rats.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups and two vehicle control groups. Two hundred and fifty Crl:CD1(ICR) mice of each sex were assigned to three treated groups and two vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 50 animals, as indicated in Table 3. The dose levels for the three treated groups were 5, 15, and 50 mg/kg/day for both male and female mice, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the daily oral vehicle control article only (10% polysorbate 80 in deionized water), administered orally by gavage for about 104 weeks in the same manner as the treated groups.

Table 3: Experimental Design in Mouse Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	50	50
Vehicle control	2	0	0	50	50
Low	3	5	5	50	50
Medium	4	15	15	50	50
High	5	50	50	50	50

During the study period all animals were observed for general health/mortality and moribundity daily, abnormal findings were recorded throughout the study. Clinical sign observations were conducted for each carcinogenicity animal once per week from Study Week 1 through Study Week 104. Beginning in Study Week 26, all animals designated for carcinogenicity assessment were palpated for masses once

every 4 weeks through Study Week 104. Additionally, unscheduled palpations were performed on individual animals found with masses during non-palpation weeks. Animals were palpated to provide information regarding the onset of possible neoplasms for use in statistical analyses. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity mice, were recorded weekly. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively was euthanized. Observations included, but were not limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights were measured pretest, once per week during Study Weeks 1 through 14, and once every 4 weeks thereafter.

3.1. Sponsor's analyses

3.1.1 Survival analysis

Males and females are analyzed separately. The analysis of unscheduled death is done by a statistical evaluation of survival curves, the product-limit method (also called the Kaplan-Meier method). A log-rank test is used to test for homogeneity and equality of the survival functions across the dose groups. The survival pattern among dose groups are compared by the Product Limit method. This method uses the censored observations as well as the uncensored observations. The significance level is set to 0.05.

Sponsor's findings:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 38 (38%), 26 (52%), 29 (58%), and 24 (48%), in the combined vehicle control group, low, medium, and high dose groups, in male mice, respectively, and 41 (41%), 22 (44%), 24 (48%), and 18 (36%) in combined vehicle control, low, medium, and high dose groups, in female mice, respectively. The sponsor's report concluded that, there was not a statistically significant increase in unscheduled death through the top dose of 100 mg/kg/day or 150 mg/kg/day of MK-1602, for males or for females respectively ($P=0.450$, or $= 0.511$, respectively).

3.1.2 Tumor data analysis

Data of males and females were analyzed separately. For each organ and tumor site, the response variable of interest was the incidence of animals with tumor. The statistical analysis considered the context of observation of the tumor as well as survival differences among dose groups. The Peto method was used to analyze the palpable and nonpalpable tumor data. The significance level was set to 0.05.

The primary analysis of tumor incidence was by the trend test (an increase or decrease in tumor incidence with increasing dose of the test article). Both unadjusted and adjusted (for multiplicity of tests) p-values are calculated. For completeness, a supplementary analysis by comparing only the top dose group with the combined control groups was also conducted.

The analysis of tumors was based on the following fixed time intervals: Weeks 1-52, 53-65, 66-78, 79-91, 92-104, and terminal sacrifice for both male and female mice. The terminal necropsy was considered a single stratum, so all days of detection or death after day 728 were analyzed as if occurring on day 729. The actual dose levels were used as the scores. All tumors in the scheduled terminal sacrifice interval were considered incidental for statistical analysis.

Multiple testing adjustment:

For multiplicity adjustment testing, the sponsor used the same method described in the rat's study.

Sponsor's findings:

For both males and females, there were no statistically significant increasing trend in tumor incidence.

A statistically significant decreasing trend in tumor incidence through the top dose tested was found for carcinoma in lung in male mice prior to multiplicity adjustment ($P=0.014N$). The Adj. P was 0.048N after adjustment for multiplicity, which indicated a statistically significant decreasing trend through the top dose. Accordingly, a step down analysis was performed. The step down analysis showed no statistically significant decreasing trend in tumor incidence through the mid dose ($P=0.397N$).

A statistically significant decreasing trend in tumor incidence through the top dose tested was found in female mice for Endometrial Stromal Sarcoma in Uterus in female mice prior to multiplicity adjustment ($P=0.024N$). The Adj. P was 0.122N after adjustment for multiplicity, which indicated no statistically significant decreasing trend.

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 38 (38%), 26 (52%), 29 (58%), and 24 (48%), in the combined vehicle control group, low, medium, and high dose groups, in male mice, respectively, and 41 (41%), 22 (44%), 24 (48%), and 18 (36%) in combined vehicle control, low, medium, and high dose groups, in female mice, respectively. This reviewer's analysis showed no statistically significant increase dose response relationship in the mortality of either male or female mice. The pairwise comparisons showed a statistically significant decrease in mortality between the medium dose group, and the combined vehicle control group in male mice ($p\text{-value} = 0.0232$).

3.2.2 Tumor data analysis

The tumor rates and the p -values of the tumor types tested for dose response relationship and the pairwise comparisons of vehicle control and individual treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

Following the same FDA more recently revised draft guidance for the carcinogenicity study design and data analysis 2015, for 2 years mouse study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Reviewer's findings:

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased MK-1602 dose across the combined vehicle control and the treated groups dose in either sex of mice. The pairwise comparisons showed no tumor types with a statistically significant increase in tumor incidences in MK-1602 individual treated groups, when compare to the combined vehicle control group in either male or female mice.

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in regular mice. These studies were intended to assess the carcinogenic potential of Ubrogapant (MK-1602) a calcitonin gene-related peptide (CGRP) receptor antagonist, when administered to rats and mice by oral gavage once daily at appropriate drug levels for about 104 weeks.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and two vehicle control groups. Two hundred and fifty Wistar Han rats of each sex were assigned to three treated groups and two vehicle control groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 50 animals, as indicated in Table 1. The dose levels for the three treated groups were 10, 30, and 100 mg/kg/day for male rats and 10, 30, 150 mg/kg/day for female rats, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle only (100% Polyethylene Glycol 400), administered orally by gavage for about 104 weeks in the same manner as the treated groups.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 66 (66%), 29 (58%), 33 (66%), and 31 (62%), in the combined vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 60 (60%), 30 (60%), 34 (68%), and 29 (58%) in combined vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant dose response relationship in the mortality of both male and female rats. The pairwise comparisons also showed no statistically significant increase or decrease in mortality between the treated groups, and the combined vehicle control group in either sex of rats.

For tumor data analysis, following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased MK-1602 dose across the combined vehicle control and the treated groups dose in either sex of rats. The pairwise comparisons showed no tumor types with a statistically significant increase in tumor incidences in MK-1602 treated groups, when compare to the combined vehicle control group in

either male or female rats.

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups and two vehicle control groups. Two hundred and fifty Crl:CD1(ICR) mice of each sex were assigned to three treated groups and two vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 50 animals, as indicated in Table 3. The dose levels for the three treated groups were 5, 15, and 50 mg/kg/day for both male and female mice, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the daily oral vehicle control article only (10% polysorbate 80 in deionized water), administered orally by gavage for about 104 weeks in the same manner as the treated groups.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 38 (38%), 26 (52%), 29 (58%), and 24 (48%), in the combined vehicle control group, low, medium, and high dose groups, in male mice, respectively, and 41 (41%), 22 (44%), 24 (48%), and 18 (36%) in combined vehicle control, low, medium, and high dose groups, in female mice, respectively. This reviewer's analysis showed no statistically significant increase dose response relationship in the mortality of either male or female mice. The pairwise comparisons showed statistically significant decrease in mortality between the medium dose group, and the combined vehicle control group in male mice (p-value = 0.0232).

For tumor data analysis, following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant positive dose response relationship in tumor incidences with increased MK-1602 dose across the vehicle control and the treated groups dose in either sex of mice. The pairwise comparisons showed no tumor types with a statistically significant increase in tumor incidences in MK-1602 treated groups, when compare to the combined vehicle control group in either male or female mice.

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cc:

Archival NDA 211765 - MK-1602

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5. Appendix

Table1A: Intercurrent Mortality Rate
Male Rats

Week	0 mg vehicle Cont 1		0 mg vehicle Cont 2		10mg Low		30mg Med		100mg High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	2	4.00	.	.	2	4.00	.	.	3	6.00
53 - 78	5	14.00	7	14.00	4	12.00	5	10.00	3	12.00
79 - 92	5	24.00	9	32.00	7	26.00	5	20.00	3	18.00
93 - 104	3	30.00	3	38.00	8	42.00	7	34.00	10	38.00
Ter. Sac.	35	70.00	31	62.00	29	58.00	33	66.00	31	62.00
Total	50	100.00	50	100.00	50	100.00	50	100.00	50	100.00

Table1B: Intercurrent Mortality Rate
Female Rats

Week	0 mg vehicle Cont 1		0 mg vehicle Cont 2		10mg Low		30mg Med		100mg High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	2	4.00	2	4.00	1	2.00	.	.	3	6.00
53 - 78	8	20.00	1	6.00	7	16.00	3	6.00	2	10.00
79 - 92	2	24.00	11	28.00	4	24.00	5	16.00	3	16.00
93 - 104	5	34.00	9	46.00	8	40.00	8	32.00	13	42.00
Ter. Sac.	33	66.00	27	54.00	30	60.00	34	68.00	29	58.00
Total	50	100.00	50	100.00	50	100.00	50	100.00	50	100.00

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	P-value for Comb. Veh Cont. Low, Med, high	P-value for Comb. Veh Cont. vs Low	P-value for Comb. Veh Cont. vs Med	P-value for Comb. Veh Cont. vs High
Dose-Response (Likelihood Ratio)	0.9491	0.4271	0.8664	0.7617
Homogeneity (Log-Rank)	0.8065	0.4199	0.8660	0.7597

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	P-value for Comb. Veh Cont. Low, Med, high	P-value for Comb. Veh Cont. vs Low	P-value for Comb. Veh Cont. vs Med	P-value for Comb. Veh Cont. vs High
Dose-Response (Likelihood Ratio)	0.9473	0.9329	0.2311	0.9552
Homogeneity (Log-Rank)	0.6780	0.9326	0.2367	0.9551

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Organ Name	Tumor Name	Male		Poly-3 test			
		0 mg vehicle Cont 1 (N=50)	0 mg vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	10 mg Low (N=50) P -VC vs. L	30 mg Med (N=50) P -VC vs. M	100 mg High (N=50) P -VC vs. H
Adipose Tissue, White	Lipoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Body Cavity / Mesentery	Hemangiosarcoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.6029	1/50 (41) 0.3306	0/50 (43) NC	0/50 (42) NC
Body Cavity / Thoracic Cavity	Hibernoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.6029	1/50 (41) 0.3306	0/50 (43) NC	0/50 (42) NC
Bone	Osteosarcoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 0.8434	1/50 (41) 0.5538	0/50 (43) 1.0000	0/50 (42) 1.0000
Brain	Astrocytoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 0.6525	0/50 (41) 1.0000	1/50 (44) 0.5747	0/50 (42) 1.0000
	Granular Cell Tumor	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.6029	1/50 (41) 0.3306	0/50 (43) NC	0/50 (42) NC
	Oligodendroglioma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.1262	0/50 (41) NC	1/50 (44) 0.3465	1/50 (43) 0.3413
Epididymis	Lipoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.4095	0/50 (41) NC	1/50 (44) 0.3465	0/50 (42) NC
	Mesothelioma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Eye	Leiomyoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
	Melanoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
	Schwannoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.6029	1/50 (41) 0.3306	0/50 (43) NC	0/50 (42) NC
Gland, Adrenal	Adenoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.4038	0/50 (41) NC	2/50 (43) 0.1147	0/50 (42) NC
	Carcinoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
	Adenoma / Carcinoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 0.5746	0/50 (41) 1.0000	2/50 (43) 0.2682	0/50 (42) 1.0000
	Pheochromocytoma	0/50 (50) NC	3/50 (50) NC	3/100 (83) 0.5905	1/50 (41) 0.8041	2/50 (43) 0.5576	1/50 (42) 0.8104
Gland, Harderian	Schwannoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Gland, Mammary	Carcinoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000

		Male		Poly-3 test			
Organ Name	Tumor Name	0 mg vehicle Cont 1 (N=50)	0 mg vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	10 mg Low (N=50) P -VC vs. L	30 mg Med (N=50) P -VC vs. M	100 mg High (N=50) P -VC vs. H
	Fibroadenoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Gland, Parathyroid	Adenoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.2010	0/50 (41) NC	0/50 (43) NC	1/50 (42) 0.3360
Gland, Pituitary / Pars Distalis	Adenoma	13/50 (50) NC	20/50 (50) NC	33/100 (92) 0.7973	23/50 (46) 0.0797	16/50 (47) 0.6537	15/50 (46) 0.7135
Gland, Pituitary / Pars Intermedia	Adenoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 0.6957	1/50 (41) 0.5538	1/50 (43) 0.5679	0/50 (42) 1.0000
Gland, Salivary	Carcinoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.4095	0/50 (41) NC	1/50 (44) 0.3465	0/50 (42) NC
	Squamous Cell Carcinoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Gland, Thyroid / Follicular Cell	Adenoma	2/50 (50) NC	0/50 (50) NC	2/100 (83) 0.5031	1/50 (41) 0.7037	1/50 (43) 0.7177	1/50 (42) 0.7108
	Carcinoma	1/50 (50) NC	3/50 (50) NC	4/100 (83) 0.6804	0/50 (41) 1.0000	1/50 (43) 0.8811	1/50 (42) 0.8762
	Adenoma / Carcinoma	3/50 (50) NC	3/50 (50) NC	6/100 (83) 0.6284	1/50 (41) 0.9448	2/50 (43) 0.8264	2/50 (42) 0.8182
Gland, Thyroid / Parafollicular Cell	Adenoma	2/50 (50) NC	2/50 (50) NC	4/100 (83) 0.9160	2/50 (41) 0.6489	3/50 (43) 0.4481	0/50 (42) 1.0000
	Carcinoma	1/50 (50) NC	2/50 (50) NC	3/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
	Adenoma / Carcinoma	3/50 (50) NC	4/50 (50) NC	7/100 (83) 0.9780	2/50 (41) 0.8629	3/50 (43) 0.7291	0/50 (42) 1.0000
Heart/Endocardium	Schwannoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.5246	1/50 (41) 0.3306	2/50 (43) 0.1147	0/50 (42) NC
Kidney	Liposarcoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Liver	Hepatocellular Adenoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 0.1652	1/50 (41) 0.5538	3/50 (43) 0.1147	2/50 (42) 0.2610
	Hepatocellular Carcinoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 0.8434	1/50 (41) 0.5538	0/50 (43) 1.0000	0/50 (42) 1.0000
	Hepatocellular Adenoma / Hepatocellular Carcinoma	0/50 (50) NC	2/50 (50) NC	2/100 (83) 0.3052	2/50 (41) 0.4026	3/50 (43) 0.2178	2/50 (42) 0.4122
Lung	Carcinoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.6029	1/50 (41) 0.3306	0/50 (43) NC	0/50 (42) NC
Lymph Node	Hemangioma	2/50 (50) NC	0/50 (50) NC	2/100 (83) 0.4917	0/50 (41) 1.0000	0/50 (43) 1.0000	1/50 (42) 0.7108

Organ Name	Tumor Name	Male Poly-3 test					
		0 mg vehicle Cont 1 (N=50)	0 mg vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	10 mg Low (N=50) P -VC vs. L	30 mg Med (N=50) P -VC vs. M	100 mg High (N=50) P -VC vs. H
	Hemangiosarcoma	1/50 (50) NC	1/50 (50) NC	2/100 (83) 0.0883	1/50 (41) 0.7037	0/50 (43) 1.0000	3/50 (42) 0.2098
Pancreas	Islet Cell Adenoma	0/50 (50) NC	2/50 (50) NC	2/100 (83) 0.1794	0/50 (41) 1.0000	3/50 (43) 0.2178	2/50 (42) 0.4122
	Islet Cell Carcinoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 0.6492	0/50 (41) 1.0000	1/50 (43) 0.5679	0/50 (42) 1.0000
	Islet Cell Adenoma / Islet Cell Carcinoma	0/50 (50) NC	3/50 (50) NC	3/100 (83) 0.2802	0/50 (41) 1.0000	4/50 (43) 0.1795	2/50 (42) 0.5471
	Lipoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.6029	1/50 (41) 0.3306	0/50 (43) NC	0/50 (42) NC
Pancreas/Acinus	Adenoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.6029	1/50 (41) 0.3306	0/50 (43) NC	0/50 (42) NC
Site, Uncertain Primary	Carcinoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
	Histiocytic Sarcoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 0.6492	0/50 (41) 1.0000	1/50 (43) 0.5679	0/50 (42) 1.0000
	Lymphoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 0.6957	1/50 (41) 0.5538	1/50 (43) 0.5679	0/50 (42) 1.0000
Skin	Fibroma	1/50 (50) NC	1/50 (50) NC	2/100 (83) 0.6942	4/50 (41) 0.0921	1/50 (43) 0.7177	1/50 (42) 0.7108
	Hemangiosarcoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
	Keratoacanthoma	3/50 (50) NC	3/50 (50) NC	6/100 (83) 0.8874	2/50 (41) 0.8095	1/50 (43) 0.9508	1/50 (42) 0.9479
	Leiomyoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
	Lipoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 0.3623	0/50 (41) 1.0000	0/50 (43) 1.0000	1/50 (42) 0.5609
	Papilloma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 0.3964	1/50 (41) 0.5538	0/50 (43) 1.0000	1/50 (42) 0.5609
	Schwannoma	0/50 (50) Nc	1/50 (50) Nc	1/100 (83) 0.5688	3/50 (41) 0.1051	0/50 (43) 1.0000	1/50 (42) 0.5609
	Sebaceous Adenoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.2010	0/50 (41) NC	0/50 (43) NC	1/50 (42) 0.3360
	Trichoepithelioma	2/50 (50) NC	1/50 (50) NC	3/100 (83) 0.9670	2/50 (41) 0.5364	0/50 (43) 1.0000	0/50 (42) 1.0000
Small Intestine	Carcinoma	0/50 (50) NC	0/50 (50) NC	0/100 (83) 0.4067	0/50 (41) NC	1/50 (43) 0.3413	0/50 (42) NC

		Male		Poly-3 test			
Organ Name	Tumor Name	0 mg vehicle Cont 1 (N=50)	0 mg vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	10 mg Low (N=50) P -VC vs. L	30 mg Med (N=50) P -VC vs. M	100 mg High (N=50) P -VC vs. H
	Leiomyosarcoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Spleen	Hemangiosarcoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Stomach	Squamous Cell Carcinoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Stomach/ Nonglandular Mucosa	Papilloma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000
Testis	Interstitial Cell Tumor	2/50 (50) NC	2/50 (50) NC	4/100 (83) 0.6942	1/50 (41) 0.8710	2/50 (43) 0.6699	1/50 (42) 0.8762
Thymus	Hemangiosarcoma	0/50 (50) NC	1/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/49 (42) 1.0000
	Thymoma	0/50 (50) NC	3/50 (50) NC	3/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/49 (42) 1.0000
Trachea	Schwannoma	1/50 (50) NC	0/50 (50) NC	1/100 (83) 1.0000	0/50 (41) 1.0000	0/50 (43) 1.0000	0/50 (42) 1.0000

& 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

Table3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

		Female Rats		Poly-3 test			
Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	10 mg Low (N=50) P -VC vs. L	30 mg Med (N=50) P -VC vs. M	150 mg High (N=50) P -VC vs. H
Body Cavity/Mesentery	Hemangioma	2/50 (50) NC	0/50 (49) NC	2/100 (81) 1.0000	0/50 (41) 1.0000	0/50 (45) 1.0000	0/50 (42) 1.0000
Brain	Astrocytoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.4920	1/50 (42) 0.3415	1/50 (45) 0.3571	0/50 (42) NC
	Granular Cell Tumor	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.1293	0/50 (41) NC	1/50 (45) 0.3571	1/50 (43) 0.3468
	Oligodendroglioma	0/50 (50) NC	1/50 (49) NC	1/100 (82) 0.6581	0/50 (41) 1.0000	1/50 (45) 0.5849	0/50 (42) 1.0000
Esophagus	Mesothelioma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.4163	0/50 (41) NC	1/50 (45) 0.3571	0/50 (42) NC
Gland, Adrenal	Adenoma	4/50 (50) NC	3/50 (49) NC	7/100 (82) 0.9944	1/50 (42) 0.9676	1/50 (45) 0.9734	0/50 (42) 1.0000
	Carcinoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.2010	0/50 (41) NC	0/50 (45) NC	1/50 (42) 0.3415
	Adenoma / Carcinoma	4/50 (50) NC	3/50 (49) NC	7/100 (82) 0.8879	1/50 (42) 0.9676	1/50 (45) 0.9734	1/50 (42) 0.9676
	Lipoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.6124	1/50 (41) 0.3361	0/50 (45) NC	0/50 (42) NC
Gland, Mammary	Adenoma	3/50 (50) NC	2/50 (49) NC	5/100 (83) 0.4345	0/50 (41) 1.0000	0/50 (45) 1.0000	2/50 (43) 0.7586
	Carcinoma	5/50 (50) NC	4/50 (49) NC	9/100 (83) 0.9257	1/50 (42) 0.9863	4/50 (46) 0.7510	1/50 (42) 0.9863
	Adenoma / Carcinoma	8/50 (50) NC	6/50 (49) NC	14/100 (85) 0.8542	1/50 (42) 0.9985	4/50 (46) 0.9376	3/50 (43) 0.9676
	Fibroadenoma	5/50 (50) NC	7/50 (49) NC	12/100 (83) 0.9236	8/50 (42) 0.3379	6/50 (45) 0.6640	3/50 (42) 0.9362
	Lipoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.2010	0/50 (41) NC	0/50 (45) NC	1/50 (42) 0.3415
Gland, Pituitary / Pars Distalis	Adenoma	41/50 (50) NC	26/50 (49) NC	67/100 (92) 0.5533	30/50 (47) 0.9004	34/50 (48) 0.6755	32/50 (46) 0.7282
Gland, Salivary	Carcinoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.6124	1/50 (41) 0.3361	0/50 (45) NC	0/49 (42) NC
Gland, Thyroid / Follicular Cell	Adenoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.0574	1/50 (42) 0.3415	1/50 (45) 0.3571	2/50 (42) 0.1148
	Carcinoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.4163	0/50 (41) NC	1/50 (45) 0.3571	0/50 (42) NC

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	10 mg Low (N=50) P -VC vs. L	30 mg Med (N=50) P -VC vs. M	150 mg High (N=50) P -VC vs. H
	Adenoma / Carcinoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.0705	1/50 (42) 0.3415	2/50 (45) 0.1257	2/50 (42) 0.1148
Gland, Thyroid / Parafollicular Cell	Adenoma	2/50 (50) NC	1/50 (49) NC	3/100 (81) 0.3790	5/50 (42) 0.0892	3/50 (45) 0.3656	3/50 (42) 0.3333
Kidney	Carcinoma	0/50 (50) NC	1/50 (49) NC	1/100 (81) 1.0000	0/50 (41) 1.0000	0/50 (45) 1.0000	0/50 (42) 1.0000
Liver	Hepatocellular Adenoma	1/50 (50) NC	0/50 (49) NC	1/100 (81) 0.1447	1/50 (41) 0.5610	0/50 (45) 1.0000	2/50 (42) 0.2684
Ovary	Granulosa Cell Tumor	1/50 (50) NC	1/50 (49) NC	2/100 (81) 0.4783	1/50 (41) 0.7110	2/50 (45) 0.4502	1/50 (42) 0.7181
	Hemangiosarcoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.4163	0/50 (41) NC	1/50 (45) 0.3571	0/50 (42) NC
	Luteoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.6124	1/50 (41) 0.3361	0/50 (45) NC	0/50 (42) NC
	Mesothelioma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.4163	0/50 (41) NC	1/50 (45) 0.3571	0/50 (42) NC
	Sertoli Cell Tumor	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.2058	1/50 (41) 0.3361	0/50 (45) NC	1/50 (42) 0.3415
Pancreas	Islet Cell Adenoma	1/50 (50) NC	0/50 (49) NC	1/100 (81) 1.0000	0/50 (41) 1.0000	0/50 (45) 1.0000	0/50 (42) 1.0000
	Mesothelioma	0/50 (50) NC	1/50 (49) NC	1/100 (82) 1.0000	0/50 (41) 1.0000	0/50 (45) 1.0000	0/50 (42) 1.0000
Site, Uncertain Primary	Carcinoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.6124	1/50 (41) 0.3361	0/50 (45) NC	0/50 (42) NC
	Lymphoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.2048	0/50 (41) NC	0/50 (45) NC	1/50 (43) 0.3468
	Mast Cell Tumor	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.2010	0/50 (41) NC	0/50 (45) NC	1/50 (42) 0.3415
Skin	Basal Cell Tumor	2/50 (50) NC	0/50 (49) NC	2/100 (81) 0.4917	0/50 (41) 1.0000	0/50 (45) 1.0000	1/50 (42) 0.7181
	Fibroma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.4927	1/50 (41) 0.3361	1/50 (45) 0.3571	0/50 (42) NC
	Fibrosarcoma	1/50 (50) NC	1/50 (49) NC	2/100 (82) 0.9426	1/50 (42) 0.7144	0/50 (45) 1.0000	0/50 (42) 1.0000
	Lipoma	0/50 (50) NC	1/50 (49) NC	1/100 (82) 1.0000	0/50 (41) 1.0000	0/50 (45) 1.0000	0/50 (42) 1.0000
	Papilloma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.6124	1/50 (41) 0.3361	0/50 (45) NC	0/50 (42) NC

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	10 mg Low (N=50) P -VC vs. L	30 mg Med (N=50) P -VC vs. M	150 mg High (N=50) P -VC vs. H
	Schwannoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.2010	0/50 (41) NC	0/50 (45) NC	1/50 (42) 0.3415
	Squamous Cell Carcinoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.1266	0/50 (41) NC	1/50 (45) 0.3571	1/50 (42) 0.3415
Small Intestine	Carcinoma	0/50 (50) NC	1/50 (49) NC	1/100 (82) 1.0000	0/50 (41) 1.0000	0/50 (45) 1.0000	0/50 (42) 1.0000
Thymus	Thymoma	0/50 (50) NC	3/50 (49) NC	3/99 (81) 0.9704	2/49 (41) 0.5473	0/50 (45) 1.0000	0/50 (42) 1.0000
Uterus	Carcinoma	4/50 (50) NC	0/50 (49) NC	4/100 (82) 0.2050	1/50 (41) 0.8737	0/50 (45) 1.0000	3/50 (43) 0.4545
	Endometrial Stromal Polyp	1/50 (50) NC	9/50 (49) NC	10/100 (82) 0.9206	5/50 (42) 0.6233	4/50 (45) 0.8044	2/50 (42) 0.9579
	Endometrial Stromal Sarcoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.0348	0/50 (41) NC	1/50 (45) 0.3571	2/50 (43) 0.1184
	Endometrial Stromal Polyp/Sarcoma	1/50 (50) NC	9/50 (49) NC	10/100 (82) 0.6841	5/50 (42) 0.6233	5/50 (45) 0.6732	4/50 (43) 0.7804
	Stromal Tumor	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.4163	0/50 (41) NC	1/50 (45) 0.3571	0/50 (42) NC
Uterus/Cervix	Adenoma	0/50 (50) NC	1/50 (49) NC	1/100 (81) 1.0000	0/50 (41) 1.0000	0/50 (45) 1.0000	0/50 (42) 1.0000
	Granular Cell Tumor	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.2010	0/50 (41) NC	0/50 (45) NC	1/50 (42) 0.3415
	Polyp	2/50 (50) NC	1/50 (49) NC	3/100 (81) 0.1622	1/50 (41) 0.8106	1/50 (45) 0.8338	3/50 (42) 0.3333
	Stromal Tumor	1/50 (50) NC	1/50 (49) NC	2/100 (83) 0.9413	1/50 (42) 0.7108	0/50 (45) 1.0000	0/50 (42) 1.0000
Vagina	Squamous Cell Carcinoma	0/50 (50) NC	0/50 (49) NC	0/100 (81) 0.4163	0/50 (41) NC	1/50 (45) 0.3571	0/49 (42) NC

& 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

Figure 1A: Kaplan-Meier Survival Curves for Male Rats

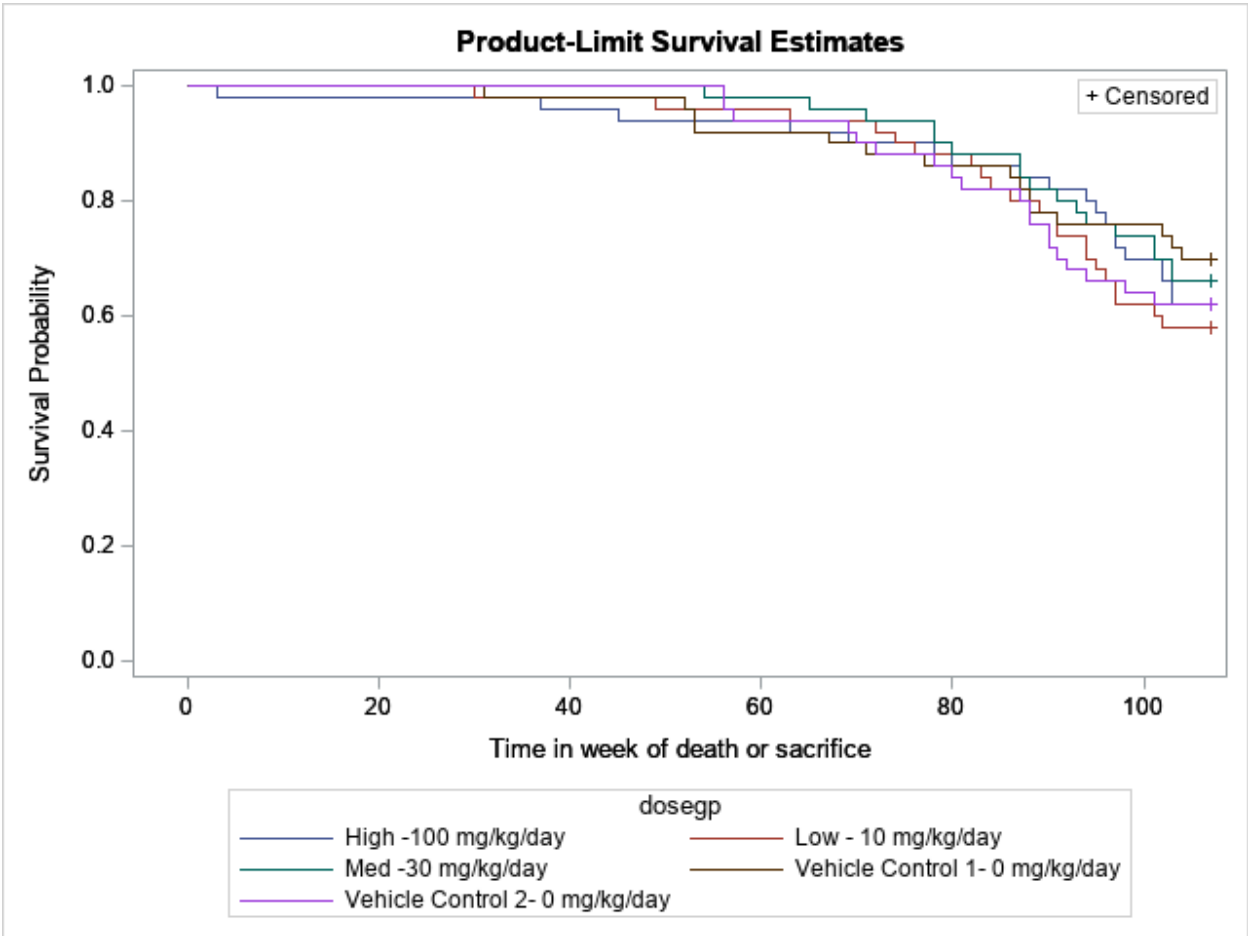


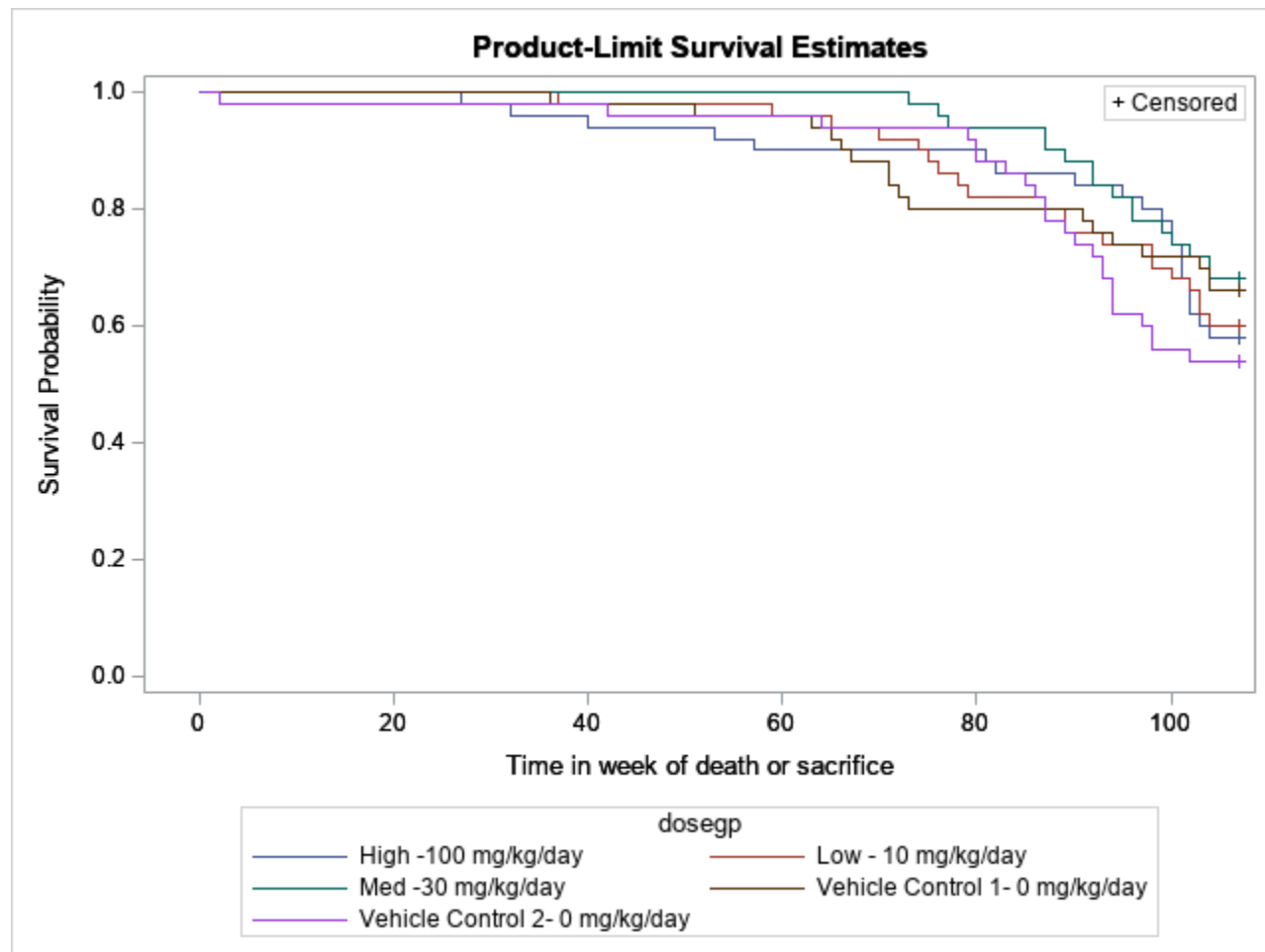
Figure 1B: Kaplan-Meier Survival Curves for
Female Rats

Table4A: Intercurrent Mortality Rate
Male Mice

Week	0 mg vehicle Cont 1		0 mg vehicle Cont 2		5mg Low		15mg Med		50mg High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	2	4.00	.	.	4	8.00	2	4.00	5	10.00
53 - 78	5	14.00	10	20.00	6	20.00	7	18.00	5	20.00
79 - 92	16	46.00	14	48.00	6	32.00	6	30.00	8	36.00
93 - 104	7	60.00	8	64.00	8	48.00	6	42.00	8	52.00
Ter. Sac.	20	40.00	18	36.00	26	52.00	29	58.00	24	48.00
Total	50	100.00	50	100.00	50	100.00	50	100.00	50	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded

Table4B: Intercurrent Mortality Rate
Female Mice

Week	0 mg vehicle Cont 1		0 mg vehicle Cont 2		10mg Low		30mg Med		100mg High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	1	2.00	7	14.00	4	8.00	.	.	4	8.00
53 - 78	5	12.00	9	32.00	7	22.00	5	10.00	9	26.00
79 - 92	10	32.00	8	48.00	7	36.00	5	20.00	9	44.00
93 - 105	11	54.00	8	64.00	10	56.00	16	52.00	10	64.00
Ter. Sac.	23	46.00	18	36.00	22	44.00	24	48.00	18	36.00
Total	50	100.00	50	100.00	50	100.00	50	100.00	50	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	P-value for Comb. Veh Cont. Low, Med, high	P-value for Comb. Veh Cont. vs Low	P-value for Comb. Veh Cont. vs Med	P-value for Comb. Veh Cont. vs High
Dose-Response (Likelihood Ratio)	0.4504	0.1411	0.0232*	0.3057
Homogeneity (Log-Rank)	0.1304	0.1454	0.0261*	0.3076

*: Statistically significant at level 0.05

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	P-value for Comb. Veh Cont. Low, Med, high	P-value for Comb. Veh Cont. vs Low	P-value for Comb. Veh Cont. vs Med	P-value for Comb. Veh Cont. vs High
Dose-Response (Likelihood Ratio)	0.5167	0.8177	0.2089	0.5469
Homogeneity (Log-Rank)	0.4344	0.8167	0.2112	0.5401

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise Comparisons

		Male Mice		Poly-3 test			
Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	5 mg Low (N=50) P - C vs. L	15 mg Med (N=50) P - C vs. M	50 mg High (N=50) P - C vs. H
Bone	Sarcoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.2011	0/50 (37) NC	0/50 (40) NC	1/50 (37) 0.3458
Brain	Astrocytoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.4153	0/50 (37) NC	1/50 (40) 0.3636	0/50 (36) NC
	Meningioma	1/50 (50) NC	0/50 (50) NC	1/100 (71) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000
	Schwannoma	1/50 (50) NC	0/50 (50) NC	1/100 (71) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000
Gland, Adrenal	Adenoma	1/50 (50) NC	0/50 (50) NC	1/100 (71) 0.6568	0/50 (37) 1.0000	1/50 (40) 0.5930	0/50 (36) 1.0000
	Adrenal Tumor, Subcapsular	2/50 (50) NC	1/50 (50) NC	3/100 (71) 0.6503	2/50 (37) 0.5607	2/50 (40) 0.5952	1/50 (36) 0.8117
	Pheochromocytoma	0/50 (50) NC	1/50 (50) NC	1/100 (70) 0.7063	1/50 (37) 0.5741	1/50 (40) 0.5972	0/50 (36) 1.0000
Gland, Harderian	Adenoma	4/50 (50) NC	6/50 (50) NC	10/100 (71) 0.8343	7/50 (38) 0.3691	11/50 (42) 0.0900	3/50 (37) 0.8914
Gland, Pituitary	Meningioma	1/50 (50) NC	0/50 (50) NC	1/100 (71) 1.0000	0/49 (37) 1.0000	0/50 (40) 1.0000	0/49 (36) 1.0000
Gland, Thyroid / Follicular Cell	Adenoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.4025	0/50 (37) NC	2/50 (40) 0.1301	0/50 (36) NC
Kidney	Adenoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.4913	1/50 (37) 0.3458	1/50 (40) 0.3636	0/50 (36) NC
Large Intestine	Carcinoma	1/50 (50) NC	0/50 (50) NC	1/100 (70) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000
	Polyp	0/50 (50) NC	1/50 (50) NC	1/100 (70) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000
Liver	Hemangiosarcoma	3/50 (50) NC	2/50 (50) NC	5/100 (71) 0.3261	1/50 (37) 0.9252	2/50 (40) 0.7922	3/50 (37) 0.5590
	Hepatocellular Adenoma	6/50 (50) NC	7/50 (50) NC	13/100 (73) 0.3816	5/50 (38) 0.8152	5/50 (41) 0.8551	7/50 (37) 0.5398
	Hepatocellular Carcinoma	3/50 (50) NC	2/50 (50) NC	5/100 (71) 0.1052	2/50 (38) 0.7727	3/50 (40) 0.6024	5/50 (37) 0.2228
	Hepatocellular Adenoma/Hepatocell Carcinoma	9/50 (50) NC	9/50 (50) NC	18/100 (74) 0.1487	7/50 (38) 0.8285	8/50 (41) 0.7935	12/50 (38) 0.2735
Lung	Adenoma	6/50 (50) NC	10/50 (50) NC	16/100 (75) 0.5319	8/50 (39) 0.6292	9/50 (41) 0.5578	8/50 (39) 0.6292

		Male Mice		Poly-3 test			
Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	5 mg Low (N=50) P - C vs. L	15 mg Med (N=50) P - C vs. M	50 mg High (N=50) P - C vs. H
	Carcinoma	15/50 (50) NC	6/50 (50) NC	21/100 (75) 0.9869	6/50 (38) 0.9559	12/50 (42) 0.5554	3/50 (37) 0.9977
	Adenoma / Carcinoma	21/50 (50) NC	16/50 (50) NC	37/100 (79) 0.9650	14/50 (40) 0.9241	21/50 (42) 0.4438	11/50 (40) 0.9880
Site, Uncertain Primary	Histiocytic Sarcoma	1/50 (50) NC	2/50 (50) NC	3/100 (71) 0.2860	0/50 (37) 1.0000	1/50 (40) 0.8378	2/50 (37) 0.5607
	Leukemia	1/50 (50) NC	0/50 (50) NC	1/100 (71) 0.4756	2/50 (39) 0.2861	0/50 (40) 1.0000	1/50 (37) 0.5699
	Lymphoma	4/50 (50) NC	2/50 (50) NC	6/100 (72) 0.5256	8/50 (40) 0.0702	7/50 (43) 0.1591	4/50 (37) 0.4581
	Mast Cell Tumor	0/50 (50) NC	1/50 (50) NC	1/100 (70) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000
Skin	Fibrosarcoma	1/50 (50) NC	4/50 (50) NC	5/100 (73) 0.3678	2/50 (38) 0.7616	2/50 (41) 0.7908	3/50 (37) 0.5433
	Hemangiosarcoma	1/50 (50) NC	1/50 (50) NC	2/100 (71) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000
	Keratoacanthoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.2011	0/50 (37) NC	0/50 (40) NC	1/50 (37) 0.3458
	Liposarcoma	1/50 (50) NC	0/50 (50) NC	1/100 (71) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000
	Papilloma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.6196	1/50 (38) 0.3519	0/50 (40) NC	0/50 (36) NC
Small Intestine	Adenoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.4905	1/50 (38) 0.3519	1/50 (40) 0.3636	0/50 (36) NC
Spleen	Hemangiosarcoma	1/50 (50) NC	1/50 (50) NC	2/100 (71) 0.4901	0/50 (37) 1.0000	0/50 (40) 1.0000	1/50 (37) 0.7200
Stomach	Adenoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.6175	1/50 (37) 0.3458	0/50 (40) NC	0/50 (36) NC
	Carcinoma	0/50 (50) NC	1/50 (50) NC	1/100 (70) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000
	Adenoma / Carcinoma	0/50 (50) NC	1/50 (50) NC	1/100 (70) 0.8550	1/50 (37) 0.5741	0/50 (40) 1.0000	0/50 (36) 1.0000
	Papilloma	0/50 (50) NC	2/50 (50) NC	2/100 (71) 0.5496	1/50 (38) 0.7277	0/50 (40) 1.0000	1/50 (37) 0.7200
Testis	Hemangioma	1/50 (50) NC	0/50 (50) NC	1/100 (70) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000
	Interstitial Cell Tumor	2/50 (50) NC	1/50 (50) NC	3/100 (70) 0.7144	2/50 (38) 0.5789	0/50 (40) 1.0000	1/50 (36) 0.8154

Male Mice

Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	5 mg Low (N=50) P - C vs. L	15 mg Med (N=50) P - C vs. M	50 mg High (N=50) P - C vs. H
Testis/Rete Testis	Adenoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.6175	1/50 (37) 0.3458	0/50 (40) NC	0/50 (36) NC
	Carcinoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.4153	0/50 (37) NC	1/50 (40) 0.3636	0/50 (36) NC
Urinary Bladder	Adenoma / Carcinoma	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.4913	1/50 (37) 0.3458	1/50 (40) 0.3636	0/50 (36) NC
	Mesenchymal Tumor	0/50 (50) NC	0/50 (50) NC	0/100 (70) 0.2011	0/50 (37) NC	0/50 (40) NC	1/50 (37) 0.3458
	Papilloma	1/50 (50) NC	0/50 (50) NC	1/100 (70) 1.0000	0/50 (37) 1.0000	0/50 (40) 1.0000	0/50 (36) 1.0000

& 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 6B: Tumor Rates and P-Values for Dose Response Relationship and The pairwise comparisons

		Female Mice Poly-3 test					
Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	5 mg Low (N=50) P -VC vs. L	15 mg Med (N=50) P -VC vs. M	50 mg High (N=50) P -VC vs. H
Gland, Adrenal	Adrenal Tumor, Subcapsular	3/50 (50) NC	1/50 (49) NC	4/100 (72) 0.3446	0/50 (36) 1.0000	2/50 (42) 0.7211	2/50 (34) 0.6296
	Pheochromocytoma	0/50 (50) NC	1/50 (49) NC	1/100 (72) 1.0000	0/50 (36) 1.0000	0/50 (41) 1.0000	0/50 (34) 1.0000
Gland, Harderian	Adenoma	7/50 (50) NC	3/50 (49) NC	10/100 (73) 0.8928	3/50 (36) 0.8721	2/50 (41) 0.9703	2/50 (34) 0.9438
	Carcinoma	0/50 (50) NC	1/50 (49) NC	1/100 (72) 0.2667	0/50 (36) 1.0000	1/50 (41) 0.5961	1/50 (34) 0.5407
	Adenoma / Carcinoma	7/50 (50) NC	4/50 (49) NC	11/100 (73) 0.7889	3/50 (36) 0.9061	3/50 (41) 0.9393	3/50 (34) 0.8880
Gland, Mammary	Adenoma	0/50 (50) NC	1/50 (49) NC	1/100 (72) 1.0000	0/50 (36) 1.0000	0/50 (41) 1.0000	0/50 (34) 1.0000
	Carcinoma	2/50 (50) NC	1/50 (49) NC	3/100 (73) 0.8778	2/50 (36) 0.5360	2/50 (42) 0.6043	0/50 (34) 1.0000
	Adenoma / Carcinoma	2/50 (50) NC	2/50 (49) NC	4/100 (73) 0.9248	2/50 (36) 0.6489	2/50 (42) 0.7153	0/50 (34) 1.0000
Gland, Pituitary	Adenoma	3/50 (50) NC	1/50 (49) NC	4/100 (72) 0.6757	1/50 (36) 0.8745	2/50 (41) 0.7111	1/50 (34) 0.8619
Gland, Pituitary/Pars Intermedia	Adenoma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.4130	0/50 (36) NC	1/50 (42) 0.3684	0/50 (34) NC
Liver	Hemangioma	1/50 (50) NC	0/50 (49) NC	1/100 (72) 0.3379	0/50 (36) 1.0000	0/50 (41) 1.0000	1/50 (34) 0.5407
	Hemangiosarcoma	1/50 (50) NC	0/50 (49) NC	1/100 (72) 0.3758	1/50 (36) 0.5576	0/50 (41) 1.0000	1/50 (34) 0.5407
	Hepatocellular Adenoma	0/50 (50) NC	1/50 (49) NC	1/100 (72) 0.3143	1/50 (36) 0.5576	2/50 (41) 0.2977	1/50 (34) 0.5407
	Hepatocellular Carcinoma	1/50 (50) NC	0/50 (49) NC	1/100 (72) 0.6530	0/50 (36) 1.0000	1/50 (41) 0.5961	0/50 (34) 1.0000
	Hepatocellular Adenoma / Hepatocellular Carcinoma	1/50 (50) NC	1/50 (49) NC	2/100 (72) 0.4480	1/50 (36) 0.7079	3/50 (41) 0.2514	1/50 (34) 0.6909
Lung	Adenoma	6/50 (50) NC	1/50 (49) NC	7/100 (74) 0.5887	4/50 (37) 0.5320	3/50 (42) 0.7752	3/50 (35) 0.6821
	Carcinoma	3/50 (50) NC	4/50 (49) NC	7/100 (74) 0.6436	6/50 (37) 0.2291	6/50 (42) 0.3082	3/50 (35) 0.6821
	Adenoma / Carcinoma	9/50 (50) NC	5/50 (49) NC	14/100 (76) 0.6738	10/50 (39) 0.2522	9/50 (43) 0.4582	6/50 (36) 0.6819

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	5 mg Low (N=50) P -VC vs. L	15 mg Med (N=50) P -VC vs. M	50 mg High (N=50) P -VC vs. H
Lymph Node	Hemangioma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.4130	0/50 (36) NC	1/50 (42) 0.3684	0/50 (34) NC
Ovary	Carcinoma	1/50 (50) NC	0/50 (49) NC	1/100 (72) 1.0000	0/50 (36) 1.0000	0/50 (41) 1.0000	0/50 (34) 1.0000
	Cystadenoma	1/50 (50) NC	2/50 (49) NC	3/100 (72) 0.3308	1/50 (36) 0.8080	1/50 (42) 0.8458	2/50 (35) 0.5297
	Granulosa Cell Tumor	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.6900	2/50 (37) 0.1131	0/50 (41) NC	0/50 (34) NC
	Hemangioma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.1174	0/50 (36) NC	1/50 (41) 0.3628	1/50 (34) 0.3208
	Luteoma	1/50 (50) NC	1/50 (49) NC	2/100 (72) 0.5212	1/50 (36) 0.7079	0/50 (41) 1.0000	1/50 (34) 0.6909
Pancreas	Islet Cell Adenoma	3/50 (50) NC	0/50 (49) NC	3/100 (72) 0.5838	0/50 (36) 1.0000	0/50 (41) 1.0000	1/50 (35) 0.8006
Site, Uncertain Primary	Histiocytic Sarcoma	4/50 (50) NC	3/50 (49) NC	7/100 (74) 0.4261	1/50 (36) 0.9632	7/50 (43) 0.2100	3/50 (35) 0.6821
	Leukemia	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.1213	0/50 (36) NC	1/50 (42) 0.3684	1/50 (35) 0.3271
	Lymphoma	10/50 (50) NC	6/50 (49) NC	16/100 (77) 0.4384	12/50 (41) 0.2093	9/50 (44) 0.6038	9/50 (37) 0.4201
Skin	Basal Cell Tumor	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.1902	0/50 (36) NC	0/50 (41) NC	1/50 (35) 0.3271
	Fibrosarcoma	0/50 (50) NC	4/50 (49) NC	4/100 (73) 0.7735	2/50 (36) 0.6489	0/50 (41) 1.0000	1/50 (34) 0.8587
	Hemangiosarcoma	0/50 (50) NC	1/50 (49) NC	1/100 (72) 1.0000	0/50 (36) 1.0000	0/50 (41) 1.0000	0/50 (34) 1.0000
	Myxosarcoma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.1858	0/50 (36) NC	0/50 (41) NC	1/50 (34) 0.3208
	Sarcoma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.4130	0/50 (36) NC	1/50 (42) 0.3684	0/50 (34) NC
	Squamous Cell Carcinoma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.1213	0/50 (36) NC	1/50 (42) 0.3684	1/50 (35) 0.3271
Spinal Cord	Meningioma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.6066	1/50 (36) 0.3333	0/50 (41) NC	0/50 (34) NC
Spleen	Hemangiosarcoma	1/50 (50) NC	1/50 (49) NC	2/100 (72) 0.5854	2/50 (37) 0.4184	0/50 (41) 1.0000	1/50 (34) 0.6909
Stomach	Papilloma	0/50 (50) NC	1/50 (49) NC	1/100 (72) 0.5610	0/50 (36) 1.0000	2/50 (41) 0.2977	0/50 (34) 1.0000

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont 1 (N=50)	0 mg Vehicle Cont 2 (N=50)	0 mg VC C1+C2(N=100) P - Trend	5 mg Low (N=50) P -VC vs. L	15 mg Med (N=50) P -VC vs. M	50 mg High (N=50) P -VC vs. H
Urinary Bladder	Hemangioma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.1902	0/50 (36) NC	0/49 (41) NC	1/49 (35) 0.3271
	Transitional Cell Carcinoma	1/50 (50) NC	0/50 (49) NC	1/100 (72) 1.0000	0/50 (36) 1.0000	0/49 (41) 1.0000	0/49 (34) 1.0000
Uterus	Carcinoma	1/50 (50) NC	0/50 (49) NC	1/100 (72) 1.0000	0/50 (36) 1.0000	0/50 (41) 1.0000	0/50 (34) 1.0000
	Endometrial Stromal Sarcoma	2/50 (50) NC	2/50 (49) NC	4/100 (72) 0.9869	3/50 (36) 0.4293	0/50 (41) 1.0000	0/50 (34) 1.0000
	Hemangioma	1/50 (50) NC	1/50 (49) NC	2/100 (72) 0.4855	1/50 (36) 0.7079	1/50 (42) 0.7520	1/50 (34) 0.6909
	Hemangiosarcoma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.6066	1/50 (36) 0.3333	0/50 (41) NC	0/50 (34) NC
	Leiomyoma	0/50 (50) NC	0/50 (49) NC	0/100 (72) 0.4758	1/50 (36) 0.3333	1/50 (41) 0.3628	0/50 (34) NC
	Leiomyosarcoma	0/50 (50) NC	1/50 (49) NC	1/100 (72) 0.2667	0/50 (36) 1.0000	1/50 (41) 0.5961	1/50 (34) 0.5407
	Leiomyoma / Leiomyosarcoma	0/50 (50) NC	1/50 (49) NC	1/100 (72) 0.3143	1/50 (36) 0.5576	2/50 (41) 0.2977	1/50 (34) 0.5407
	Polyp	6/50 (50) NC	3/50 (49) NC	9/100 (73) 0.1155	3/50 (36) 0.8283	4/50 (42) 0.7737	7/50 (36) 0.2388
Uterus/Cervix	Leiomyoma	1/50 (50) NC	0/50 (49) NC	1/100 (72) 0.8465	1/50 (36) 0.5576	0/50 (41) 1.0000	0/50 (34) 1.0000
	Leiomyosarcoma	1/50 (50) NC	0/50 (49) NC	1/100 (72) 1.0000	0/50 (36) 1.0000	0/50 (41) 1.0000	0/50 (34) 1.0000
	Leiomyoma / Leiomyosarcoma	2/50 (50) NC	0/50 (49) NC	2/100 (72) 0.9406	1/50 (36) 0.7079	0/50 (41) 1.0000	0/50 (34) 1.0000
	Polyp	1/50 (50) NC	0/50 (49) NC	1/100 (72) 1.0000	0/50 (36) 1.0000	0/50 (41) 1.0000	0/50 (34) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ= total number of animals observed;
NC = Not calculable;

Figure 2A: Kaplan-Meier Survival Curves for
Male Mice

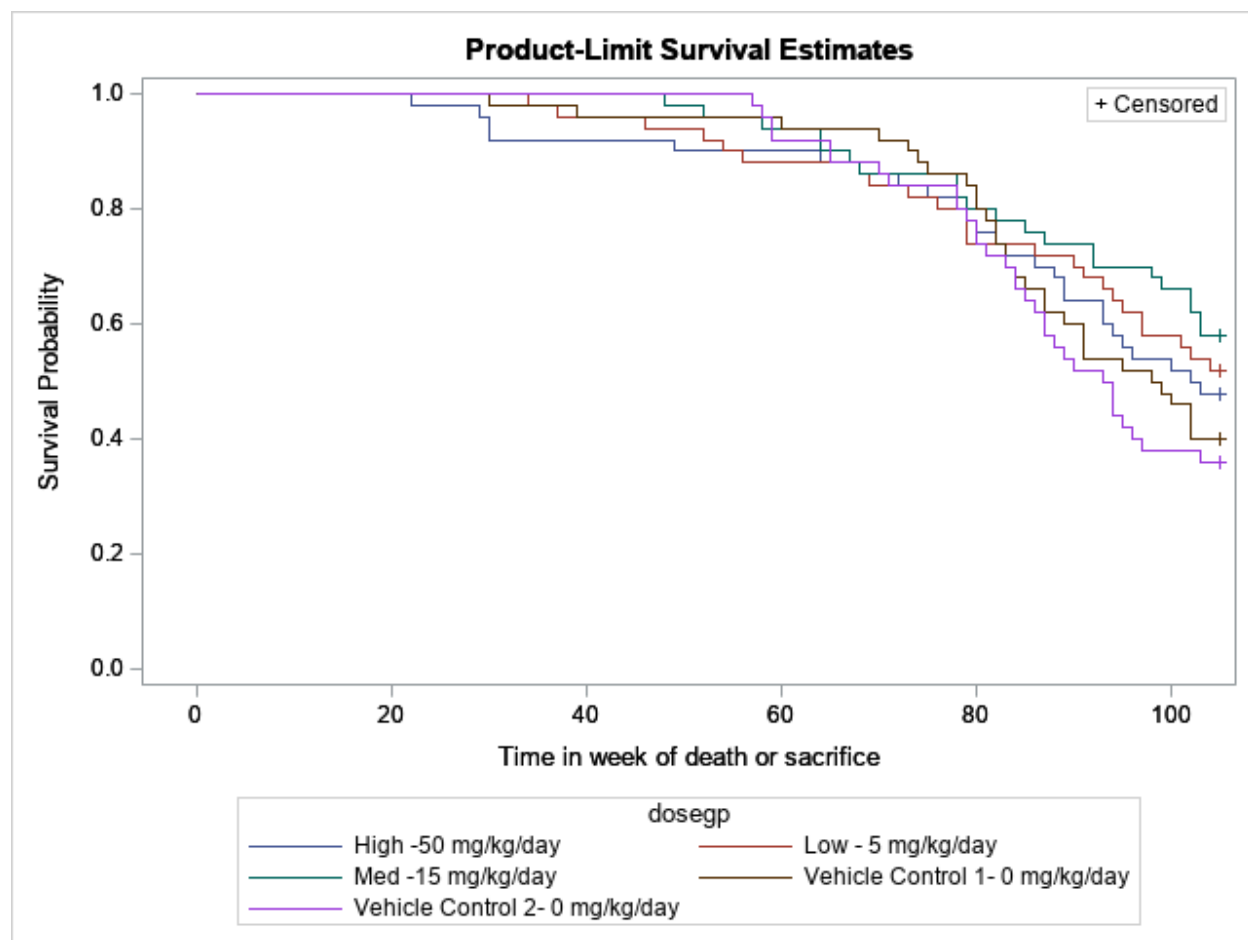
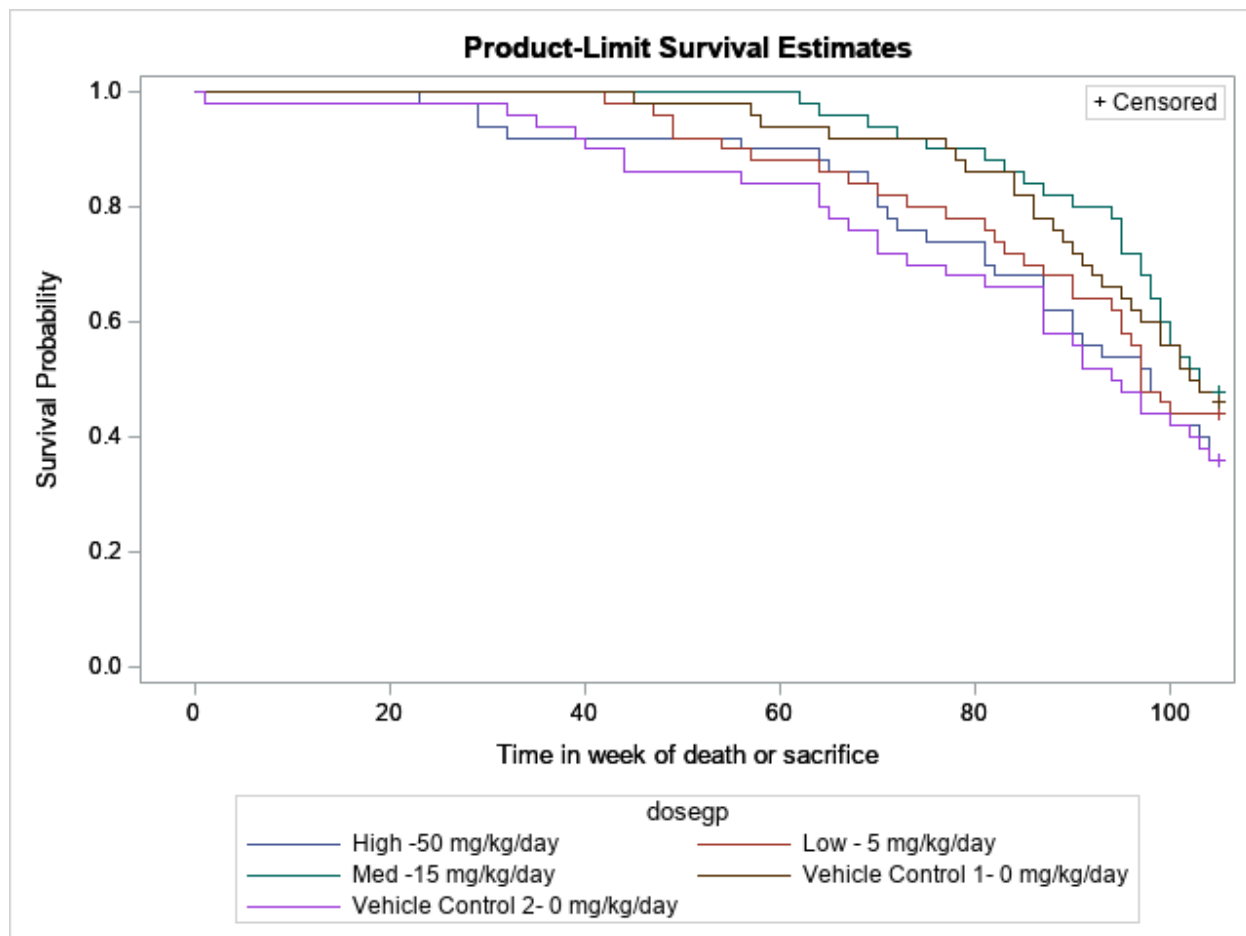


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice

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Concur with review.