CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207988Orig1s000

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/BLA #:	207988
Drug Name:	Zurampic (lesinurad)
Indication:	Treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor
Applicant:	Ardea Biosciences, Inc.
Dates:	Stamp date: December 29, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Gregory Levin, PhD
Concurring Reviewers:	Thomas Permutt, PhD Ruthanna Davi, PhD
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
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Keywords: NDA review, clinical studies, missing data, surrogate outcomes, safety, benefit-risk

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1 INTRODUCTION

Gout is a chronic disease typically characterized by reduced clearance or overproduction of uric acid, with the hyperuricemia leading to acute arthritis flares associated with substantial pain. It is estimated that approximately eight million adults in the United States suffer from gout. Treatment typically consists of medications such as colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids for the symptoms of acute attacks, short-term (e.g., 3–6 month) medications such as colchicine or an NSAID to prevent flares, and chronic medications to lower the serum uric acid level and improve long-term outcomes. The commonly used xanthine oxidase inhibitors (XOIs) allopurinol and febuxostat lower serum uric acid levels by lowering uric acid production. In contrast, uricosurics such as the approved drug probenecid lower uric acid levels by increasing urinary uric acid excretion.

The applicant is seeking approval of the uricosuric lesinurad 200 mg once daily (QD) in combination with a xanthine oxidase inhibitor for the chronic treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone. The safety and effectiveness of lesinurad were discussed at an FDA Arthritis Advisory Committee Meeting on October 23, 2015. The Committee voted 14–0 in favor of substantial evidence of benefit, 7–6 in favor of the safety profile being adequate to support approval, and 10–4 in favor of approval of lesinurad. Nearly all of the committee members who voted to approve lesinurad expressed a desire for additional postmarketing studies to more reliably evaluate benefit and/or risk (see excerpts from transcript in Appendix).

The goal of this review is to integrate the efficacy and safety findings in order to carry out a quantitative benefit-risk evaluation of lesinurad.

2 BENEFIT

The efficacy of lesinurad was evaluated in detail in the primary statistical review by Dr. Yu Wang, and I agree with the key conclusion of Dr. Wang's review: there is convincing statistical evidence that lesinurad lowers serum uric acid levels in patients with gout when used in combination with a xanthine oxidase inhibitor. For example, in the two phase 3, randomized, double-blind, placebo-controlled trials in patients receiving background allopurinol, treatment with lesinurad 200 mg resulted in statistically significant, absolute increases of 26% (95% confidence interval: 17%, 36%) and 32% (23%, 41%) over placebo in the probability of achieving a target serum uric acid level less than 6 mg/dL at Month 6.

Dr. Wang's review also notes that there was no statistical evidence of benefit for any of the key secondary endpoints. Secondary endpoints such as gout flare rate between Month 6 and Month 12, tophi resolution at Month 12, and improvement (by at least 0.25 units) in the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Month 12 provide important supportive information in trials of chronic gout treatments, as these endpoints might be considered direct measures of patient benefit. Therefore, it is notable that there was no evidence of benefit, nor any consistent trends toward benefit, for these endpoints, and in fact, there were slight but relatively consistent trends toward worse outcomes on lesinurad 200 mg than placebo for patient-reported outcomes such as HAQ-DI, patient pain score, SF-36 physical component summary (PCS), and patient global assessment of disease activity score (Table 1, Appendix). Additional details on the design and results of the key phase 3 studies can be found in Dr. Wang's review.

The primary efficacy endpoint in the phase 3 clinical trials was the proportion of patients achieving a target serum uric acid level, either <6 or <5 mg/dL, at Month 6. For chronic gout treatments, reduction in serum uric acid is a surrogate endpoint, i.e., it is a replacement endpoint for direct measures of how patients function, feel, or survive. The achievement of target urate levels might be considered a surrogate for direct measures of patient benefit such as long-term reduction in flare rate, resolution of symptoms from tophi, and improvement in pain, physical functioning, and quality of life. Both the FDA clinical review team and members of the FDA Arthritis Advisory Committee expressed high confidence that because hyperuricemia is the principal pathway through which gout affects how patients function and feel, reduction in serum uric acid level with an intervention will lead to long-term improvements in direct measures of patient benefit. In addition, despite some disappointment expressed with the lack of evidence or trends toward benefit for important secondary endpoints, there was general agreement that one-year studies are likely not long enough to capture improvements in direct measures of patient benefit that are expected to be mediated through persistent lowering of serum urate. However, even if one believes strongly in the validity of serum uric acid as a surrogate endpoint, reliable evaluation of the benefit-risk profile of lesinurad requires additional considerations regarding: (1) the expected magnitude of direct patient benefit achieved through treatment with lesinurad; and (2) the unintended off-target effects (safety) of lesinurad. I discuss the magnitude of benefit next and the off-target effects in the following section on risk.

Given the use of a biomarker as the primary endpoint in the phase 3 trials and the absence of long-term randomized clinical trial data for chronic gout treatments estimating the magnitude of direct patient benefit (e.g., number of flares prevented per year or extent of improvement in quality of life) that would be expected based on the magnitude of effect on serum uric acid level, there is considerable uncertainty in the magnitude of benefit expected with lesinurad. However, I can use results from the phase 3 trials of lesinurad to help estimate a rough upper bound on the magnitude of benefit. In particular, I consider the potential long-term effect of lesinurad on the frequency of gout flares requiring treatment, an important direct measure of patient benefit that is expected to improve due to reduction in serum urate. Three placebo-controlled phase 3 trials were carried out in the intended-use population consisting of patients with hyperuricemia despite treatment with an XOI. In the placebo arms of these three trials, the estimated rates of gout flares requiring treatment between Month 6 and Month 12 were 0.6, 0.8, and 1.3 events per 6 months, or approximately 1–2 flares per year. Suppose I assume that the flare rate beyond one year would plateau in patients receiving only background XOI treatment. With the best-case assumption that the additional serum urate reduction achieved with lesinurad would reduce the flare rate to zero, the addition of lesinurad to an XOI might reduce the flare rate beyond one year by approximately 1–2 flares per year on average. This should be considered an estimated upper bound for the magnitude of benefit since: (1) the first assumption is questionable because the frequency of gout flares in the phase 3 trials was slightly declining over the final study months (Table 2, Appendix) and may have continued to decline in the absence of lesinurad treatment; and (2) the second assumption that lesinurad would completely eliminate gout flares is likely implausible given that nearly half of the patients in the lesinurad arms failed to achieve target serum urate levels in the phase 3 studies.

3 RISK

The safety of lesinurad was reviewed in detail by the clinical reviewer Dr. Rosemarie Neuner and I refer the reader to Dr. Neuner's review for a comprehensive summary of the safety results. Here, I briefly highlight a few of the major safety findings, focusing on results for renal-related adverse events (AEs), major adverse cardiovascular events (MACE), and death, and also discuss the potential effect of missing data on the reliability of the safety analyses. I exclude the phase 3 monotherapy study and focus on

results from the three phase 3 XOI add-on studies, as FDA and the applicant agree that the risk profile of lesinurad as a monotherapy is likely worse because of greater uric acid available for excretion.

Renal safety was a pre-specified topic of special interest because of both the high-risk gout population and the mechanism of action of lesinurad. In the integrated phase 3 XOI add-on studies, there was a dose-dependent trend toward greater risk of renal-related on-treatment adverse events, with 23 (4.5%), 29 (5.7%), and 60 (11.8%) patients having events on placebo, lesinurad 200 mg, and lesinurad 400 mg, respectively. This was primarily due to a dose-dependent trend in serum creatinine increases. For example, 12 (2.3%), 29 (5.7%), and 73 (14.3%) patients had elevations at least 1.5 times baseline, and 0 (0%), 9 (1.8%), and 34 (6.7%) patients had elevations at least 2.0 times baseline on placebo, lesinurad 200 mg, and lesinurad 400 mg, respectively. The majority of these creatinine elevations resolved, although some did not: for example, 0, 2, and 2 patients still had serum creatinine levels at least 2.0 times baseline at least 84 days after the first detected elevation on the placebo, lesinurad 200 mg, and lesinurad 400 mg arms. There were few renal-related serious AEs and no clear trend, with only 2 (0.5%), 0 (0%), and 5 (1.3%) patients having events on placebo, lesinurad 200 mg, and lesinurad 400 mg, respectively.

The applicant suggests that the dose-dependent increases in serum creatinine and renal AEs are due to acute precipitation of uric acid in renal tubules, and that these elevations are temporary and can be identified and monitored. However, many Advisory Committee members expressed concerns with the potential renal toxicity. In particular, members expressed concerns with the uncertainty in the true magnitude of risk due to the small numbers of events, the unknown but potentially worse safety profile in patients with renal impairment, and the effectiveness of the proposed risk management plan, as the applicant is proposing less frequent monitoring of serum creatinine in clinical practice than was carried out in the phase 3 trials.

Cardiovascular (CV) safety was also a pre-specified topic of special interest because of the high level of CV risk in the gout population, and all deaths and potential CV AEs were adjudicated by an independent, blinded committee. In the integrated phase 3 XOI add-on studies, the number of MACE was very low, although there was a slight signal toward an increased number of events in patients receiving lesinurad. The number (incidence rate per 100 person-years) of patients with events were 3 (0.7), 4 (1.0), and 8 (1.9) on placebo, lesinurad 200 mg, and lesinurad 400 mg, respectively. This yielded an estimated incidence rate ratio (95% confidence interval) of 1.4 (0.2, 9.3) and 2.7 (0.7, 16.0) for lesinurad 200 and 400 mg, respectively, as compared to placebo. Discussions with the clinical review team did not identify any understood mechanisms through which lesinurad might increase CV risk, and the wide confidence intervals indicate that the numerical imbalances may have been due to chance alone. Nevertheless, the slight signal is concerning, and the upper bounds of those same confidence intervals indicate that even large (10+ fold) increases in CV risk with lesinurad cannot be ruled out based on the data collected to date.

In the integrated phase 3 XOI add-on studies, there were 0 (0 deaths per 100 person-years), 2 (0.5), and 4 (0.9) deaths among patients on placebo, lesinurad 200 mg, and lesinurad 400 mg, respectively. As with the MACE results, the slight signal for increased mortality on lesinurad is concerning, but the small number of events makes it difficult to determine whether the imbalance was due to chance or to a true off-target effect of lesinurad.

There was considerable missing data in the phase 3 studies, as approximately 15–25% of patients dropped out of the study early, with exact rates depending on the study, treatment arm, and time point of assessment. The lesinurad arms tended to have slightly higher overall dropout rates than the placebo arm. In particular, there was greater discontinuation due to adverse events on the lesinurad arms in the integrated phase 3 XOI add-on studies, with rates of 5% and 6% on the 200 and 400 mg arms, as

compared to 3% on placebo. Sensitivity analyses demonstrated that the efficacy of lesinurad with respect to serum uric acid reduction was convincing notwithstanding the missing data. However, the potential effect of missing data might be more problematic with respect to the evaluation of safety. The slightly greater overall dropout rates and greater dropout rates due to adverse events on the lesinurad arms suggests that those patients remaining on treatment on lesinurad may have represented a healthier subset of patients than the subset of patients remaining on treatment on the placebo arm. This potential lack of comparability between patients remaining on treatment on the two arms could induce bias in favor of lesinurad in key safety analyses.

Finally, I note that the applicant is seeking marketing of only the 200 mg dose, as there is general agreement between FDA and the applicant that the benefit-risk profile for lesinurad 400 mg is not favorable. That being said, for the serious and potentially irreversible adverse events discussed here, although there was some dose-dependent trends indicating worse toxicity with the higher 400 mg dose, numerical imbalances were generally present for the 200 mg dose as well. In addition, there is some overlap in the exposure distributions of the 200 and 400 mg doses, and it is possible that a greater subset of patients receiving the 200 mg dose in real clinical practice than in the phase 3 clinical trials will have internal or external factors (e.g., renal impairment or use of interacting concomitant medications) that increase exposure and potentially toxicity, as well. More details on the clinical pharmacologic profile of lesinurad are available in Dr. Jianmeng Chen's review. Furthermore, it is a strong assumption (and one that cannot be verified with the sparse safety data) that the 200 mg dose lies below the steep part of the dose-toxicity curves for these serious AEs. The bottom line is that if there are true increases in the risks of off-target irreversible morbidity and mortality on lesinurad 400 mg, there would likely also be true increases in risk (albeit potentially smaller in magnitude) on the 200 mg dose.

4 BENEFIT-RISK

In this section, I summarize and integrate the major conclusions regarding benefit and risk. The major findings regarding the effectiveness of lesinurad for treatment of hyperuricemia associated with gout were the following:

- There was convincing statistical evidence that lesinurad lowers serum uric acid levels in patients with gout when used in combination with a xanthine oxidase inhibitor. Despite the lack of any supportive evidence of benefit for secondary endpoints in the phase 3 clinical trials, both the FDA clinical review team and the Advisory Committee are confident based on their understanding of the disease process that reduction in serum urate will lead to direct patient benefit (e.g., reduction in flare rate and improvement in quality of life) over a longer period of time than the 6–12 month trials.
- Given the short-term nature of the phase 3 clinical trials and the lack of historical trial data to help predict effects on clinical outcomes based on effects on the surrogate endpoint serum uric acid, there is considerable uncertainty in the magnitude of long-term direct patient benefit provided by lesinurad.
- Using short-term phase 3 clinical trial data and extrapolating into the future with best-case scenario assumptions in favor of lesinurad, I estimated a rough upper bound for the magnitude of direct patient benefit: the addition of lesinurad to an XOI might reduce the flare rate by up to approximately 1–2 flares per year on average.

The major findings regarding the safety of lesinurad were the following:

- There were dose-dependent trends toward greater renal adverse events, primarily due to greater increases in serum creatinine, on lesinurad, and renal toxicity is plausible based on the drug's

mechanism of action. The applicant claims that the renal toxicity is acute and monitorable, but there are some concerns about the uncertainty around the true magnitude of risk, whether the toxicity is truly reversible, and about the sufficiency of the proposed monitoring plan in real clinical practice.

- There were slight signals toward greater numbers of MACE and deaths on lesinurad than placebo. No mechanistic explanations have been expressed. Due to the small numbers of events, I cannot rule out that the numerical imbalances were due to chance alone or that there are truly large (several-fold) increases in risk of these events with lesinurad.
- Considerable missing data in the phase 3 trials could induce bias in favor of lesinurad in key safety analyses.

Because of the considerable uncertainty in both the magnitude of benefit and the potential risks, a quantitative benefit-risk evaluation is challenging. If the renal AEs are truly acute and monitorable and there are no increases in the risks of chronic or end-stage renal disease, MACE, or mortality, then the expected benefits (e.g., a reduction on average in up to 1–2 flares per year) of lesinurad treatment likely outweigh the risks. However, it is difficult to rule out the possibility of moderate to large increases in the risk of irreversible morbidity and mortality with the available data, and even small increases in risk might be unacceptable from a benefit-risk perspective. For example, suppose that treatment with lesinurad increases the risk of MACE by 50%. In its Cardiovascular Safety Report, the applicant cited two estimates of baseline CV risk in patients with gout: an incidence rate of 1.4 MACE per 100 person-years in an open-label allopurinol study and a rate of 2.3 CV deaths per 100 person-years based on the National Health and Nutrition Examination Survey (NHANES). If I assume a baseline MACE rate of 2 events per 100 person-years, a 50% increase in risk would result in 1 extra major adverse cardiovascular event for every 100 patients treated with lesinurad for 1 year. It is questionable whether the symptomatic benefit of at-best preventing 100–200 flares in these 100 patients would be worth this risk. If there was an additional increase in the long-term risk of end-stage renal disease and/or if the benefit was less, e.g., only 25–50 flares prevented, it would be even more difficult to conclude that the benefits outweigh the risks. Furthermore and perhaps more importantly, such an informed benefit-risk evaluation by an individual patient and prescriber is not possible based on the current data due to the considerable uncertainty in the expected magnitudes of both benefit and risk.

5 CONCLUSIONS AND RECOMMENDATIONS

Based on the benefit-risk considerations discussed above, I have the following conclusions and recommendations:

- Moderate to large increases in the risks of renal and cardiovascular toxicities of lesinurad have not been ruled out, and even small increases in these risks might outweigh the expected symptomatic benefit of lesinurad. Furthermore, an informed benefit-risk evaluation and treatment decision by an individual patient and prescriber is not possible because of the considerable uncertainty in both the magnitude of benefit and magnitude of risk of lesinurad. Because "there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed" (21 C.F.R. 314.125), FDA should refuse to approve the NDA.

- If the NDA is approved, FDA should require a postmarketing clinical trial to more reliably "assess signals of serious risk related to the use of the drug" (U.S.C. 505(o)(3)). The observational study proposed by the applicant at the Advisory Committee meeting is not adequate, as such non-randomized studies are subject to confounding and therefore likely capable of reliably ruling out only large increases in risks. As discussed above, ruling out only large (e.g, two-to-three fold) increases in

risk likely will not give patients a sufficiently informed choice. Instead, FDA should require a randomized, double-blind, placebo-controlled clinical trial in patients receiving a xanthine oxidase inhibitor designed to rule out moderate increases in the risks of serious renal adverse events (e.g., incidence or progression of chronic kidney disease, or incidence of end-stage renal disease) in a real-world setting. Consideration should be given to additionally ruling out moderate increases in the risk of MACE with the same trial. To reliably assess the safety of lesinurad, and in particular, whether the risks may be outweighed by the benefits, better quantification of the magnitude of benefit is also important. Therefore, the postmarketing clinical trial should evaluate important direct measures of patient benefit (e.g., long-term flare rate and quality-of-life measures) as secondary endpoints. Similar recommendations for postmarketing studies to more reliably evaluate benefit and/or risk were made by many of the Advisory Committee members who voted in favor of approval of lesinurad (see excerpts from transcript in Appendix).

- Given the lack of historical trial data to help predict the magnitudes of effects of a urate-lowering therapy on direct measures of patient benefit based on the magnitude of effect on serum uric acid, drug development programs that rely on phase 3 clinical trials of only 6–12 months in duration will be unable to quantify effectiveness with reasonable precision. When unexpected safety signals appear, considerable uncertainty in the magnitude of benefit makes benefit-risk evaluations and regulatory decisions challenging. Therefore, phase 3 development programs should include at least one randomized clinical trial that is longer in duration, e.g., two to three years, with the goal of reliably evaluating the effect of the drug on direct measures of patient benefit expected to be mediating through persistent lowering of serum uric acid.

6 APPENDIX

Excerpts from Transcript for October 23, 2015 Arthritis Advisory Committee Meeting

Dr. Berney: “I voted yes. I would like to see three additional trials. One would be a split dosing, say 1 at 7 and at 2, to look at the efficacy and safety of 100 milligrams twice a day, but the second dose would be earlier in the afternoon. I would like to see whether it truly over several years decreases flares. And three, I'd like a long-term side effect profile or adverse event profile to see if it's really safe or not.”

Dr. Oliver: “I voted yes. I'd like to see studies looking at longer extension times than 24 months that include a placebo, as well as looking at adverse events, specifically cardiovascular and renal.”

Ms. Chauhan: “I voted a conflicted yes. I think more studies need to be done around safety...”

Dr. Becker: “I voted yes. I switched my vote a few times, and I ended up yes. I think I'm happy with that. I agree with a lot of what has already been said for me... And I'd really be interested in the long-term safety data as it comes out and as these long-term extension trials are ongoing…”

Dr. Reimold: “I voted yes. I think I can agree with a lot of the sentiments that we need a good phase 4 study to look at comorbidities, to look at real-world adverse events…”

Dr. Jonas: “I voted yes… I think that real-world data is going to be really important here because we really don't know what's going to happen in large population of patients with multiple comorbidities. So I

would urge the FDA to think about lots of post-approval, real-world studies in this population. I also would like to see control data out to 24 months."

Dr. Caplan: "I voted yes. And as many of my colleagues have mentioned, I think there needs to be a specific study looking at patients with lower renal function to see more clearly the benefit versus harm in this medication..."

Dr. Neogi: "I voted yes... I think a post-approval study that I'd like to see is specifically in the subset with renal insufficiency."

Dr. Miller: I voted yes. I think the drug does meet an unmet need. I'm not sure I'd recommend any more randomized studies…"

Dr. Delost: "I voted yes. I'd like to see the continuation of the studies on the resolution of tophi and flares. That was my big concern to start with. So I'd like to have that retrospective study in that, as well as looking at the levels for creatinine clearance, you can put in there as well, reevaluated."

Table 1. Estimated Effects of Lesinurad on Selected Secondary Endpoints in the Three Phase 3 Studies in Patients with Gout Receiving a Background Xanthine Oxidase Inhibitor

Endpoint	Study 301		Study 302		Study 304	
	200 mg vs placebo	400 mg vs placebo	200 mg vs placebo	400 mg vs placebo	200 mg vs placebo	400 mg vs placebo
Gout Flare Rate Ratio from Month 7-12 (<1 favors lesinurad)	0.99 (0.61, 1.61)	0.88 (0.54, 1.43)	0.88 (0.57, 1.37)	0.93 (0.60, 1.45)	1.2 (0.7, 2.1)	0.5 (0.3, 1.0)
Tophi Resolution Difference by Month 12 (>0 favors lesinurad)	-0.29 (-0.51, -0.08)	-0.08 (-0.37, 0.20)	-0.02 (-0.24, 0.20)	-0.06 (-0.29, 0.17)	0.04 (-0.07, 0.16)	0.09 (-0.02, 0.21)
HAQ-DI Improvement Difference at Month 12 (>0 favors lesinurad)	-0.05 (-0.16, 0.06)	-0.06 (-0.17, 0.04)	-0.10 (-0.20, 0.01)	-0.01 (-0.12, 0.10)	-0.08 (-0.24, 0.07)	-0.19 (-0.34, -0.04)
Pain VAS Mean Difference at Month 12 (<0 favors lesinurad)	1.5 (-3.4, 6.5)	3.0 (-1.9, 8.0)	6.2 (1.4, 11.0)	5.3 (0.5, 10.1)	-3.7 (-10.1, 2.7)	-5.6 (-12.0, 0.8)
SF-36 PCS Mean Difference at Month 12 (>0 favors lesinurad)	-0.8 (-2.5, 1.0)	-1.3 (-3.0, 0.4)	-0.5 (-2.2, 1.2)	-0.2 (-1.8, 1.5)	-0.6 (-3.1, 1.9)	0.8 (-1.7, 3.4)
Patient Global Mean Difference at Month 12 (<0 favors lesinurad)	-1.6 (-6.0, 2.8)	2.2 (-2.1, 6.6)	5.8 (1.3, 10.2)	2.4 (-2.1, 6.9)	0.2 (-6.2, 6.6)	-6.9 (-13.3, -0.6)

Source of results: applicant's study reports

Cell contents are estimated difference in means (95% confidence interval) for pain VAS, SF-36 PCS, and patient global scores, difference in proportions (95% confidence interval) for tophi resolution and HAQ-DI improvement, and incidence rate ratio (95% confidence interval) for gout flare requiring treatment

Table 2. Proportion of Subjects Requiring Treatment for a Gout Flare in the Placebo Arm by Month over the Final Six Months of the Three Phase 3 Studies in Patients with Gout Receiving a Background Xanthine Oxidase Inhibitor

	Study 301 (N=201)	Study 302 (N=206)	Study 304 (N=109)
Month 7	19/172 (11%)	30/177 (17%)	23/95 (24%)
Month 8	10/164 (6%)	21/173 (12%)	15/94 (16%)
Month 9	16/161 (10%)	22/170 (13%)	11/91 (12%)
Month 10	13/157 (8%)	16/165 (10%)	9/89 (10%)
Month 11	13/156 (8%)	13/161 (8%)	9/88 (10%)
Month 12	9/152 (6%)	11/158 (7%)	8/87 (9%)

Source of results: applicant's study reports

Note: Some of the decline in the frequency of gout flares over time may be attributable to missing data, i.e.., the possibility that the group of subjects remaining in the study tended to represent a healthier and healthier subset of the randomized population as the study progressed

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/s/

GREGORY P LEVIN
11/25/2015

RUTHANNA C DAVI
12/01/2015

THOMAS J PERMUTT
12/15/2015
I concur.

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

CARCINOGENICITY STUDY

NDA:	207988
Drug Name:	Zurampic (lesinurad)
Indication:	Treatment of hyperuricemia.
Sponsor:	Ardea Biosciences San Diego, California
Date:	Data Submitted: 3 March 2015 Assigned to Reviewer: 8 January 2015
Review Priority:	Standard
Biometrics Division:	Division 6
Statistical Reviewer:	Steve Thomson
Concurring Reviewer:	Team Leader: Karl Lin, Ph. D.
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Toxicologist:	Reviewer: Matthew Whittaker, Ph.D. Team Leader: Marcie Wood, Ph.D.
Project Manager:	Michelle Jordan Garner, , MS, OTR/L CDR, U.S. Public Health Service
Keywords:	Carcinogenicity, Cox regression, Kaplan-Meier product limit, survival analysis, Trend test

Contents

1. EXECUTIVE SUMMARY

According to the report provided by Sponsor for the rat study: "The purpose of this study was to assess the carcinogenic potential of RDEA594 when administered orally to rats for up to 104 weeks. However, due to reduced survival, dosing was shortened to 100 weeks and selected groups were removed from the study between Weeks 90 and 97." (page 16 of report) The rat study was conducted by (b) (4).

For the mice study: "This study evaluated the carcinogenic potential and determined the toxicokinetics of the test article, RDEA594, when administered daily via oral gavage to CByB6F1-Tg(HRAS)2Jic mice for at least 26 weeks." This study was conducted by (b) (4)

1.1. Conclusions and Recommendations

The rat study summarizes presents results with daily oral gavage dosing. The Sponsor's report states that: "Based on mortality, dosing was terminated and animals were necropsied earlier than 104 weeks. All decisions to terminate dosing or remove a treatment group from the study were done following consultation and agreement by the FDA. There was no test article related increase in mortality as compared to control animals. For males at all dose levels, dosing was stopped and terminal necropsy was initiated in Week 97. For males at 0, 25, 75 and 200 mg/kg/day, the number (percentage) of males surviving to terminal necropsy was 20 (33%), 18 (30%), 20 (33%) and 27 (45%), respectively. For females at 0, 25, 75, and 200 mg/kg/day, dosing was stopped in Weeks 100, 97, 91 and 90, respectively. Terminal necropsy was conducted on 20 (33%), 15 (25%), 15 (25%) and 15 (25%) survivors in Weeks 100, 100, 91 and 97, respectively." (page 10 of rat report)!

Gross aspects of the study design for the rat study is summarized in Table 1 be1ow:

Table 1. Design of Rat Study (dose volume 10 mL/kg)

Treatment Group	Animals / Gender (TK)	Nominal Dose (mg/kg)	Concen-tration (mg/kg)	Week Dosing Stopped		Week of Scheduled Kill [2]	
				Males	Females	Males	Females
1. Vehicle[1]	60 (6)	0	0	97-99	100	97-99	100-101[3]
2. Low	60 (12)	25	2.5	97 [1]	97	97-99 [4]	100 [5]
3. Medium	60 (12)	75	7.5	97 [1]	91	97-99 [6]	91 [7]
4. High	60 (12)	200	20	97-99	90	97-99 [8]	97 [9]

[1] Dosing was terminated when the number of surviving animals in the group decreased to 20.
[2] All male groups were terminated when the number of surviving control males decreased to 20.
[3] Control females were terminated when the number of surviving animals in the group decreased to 20.
[4] Dosing was terminated when the number of surviving animals in the group decreased to 20.
[5] Group was terminated when the number of surviving animals decreased to 15.
[6] Dosing was terminated and animals were sacrificed when the number of surviving animals decreased to 15.
[7] Dosing was terminated when the number of surviving animals in the group decreased to 20.
[8] Group was terminated when the number of surviving animals decreased to 15.
(all comments from page 17 of report)

The Sponsor's report indicates that in the mouse study: "Male and female 001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic and 001178-W (wild type), CByB6F1-Tg(HRAS)2Jic mice were assigned to groups, and doses were administered as indicated in the following table. Hemizygous animals were assigned to carcinogenicity subgroups; wild-type animals were assigned to toxicokinetic subgroups." (page 10 of report) General aspects of the study design for the mice study are also summarized in Table 2 be1ow:

Table 2. Design of Mice Study (Volume 10 mL/kg)

Treatment Group[1]	# Main study animals (# toxicology study animals)/gender	Nominal Dose (mg/kg/day)		Concentration [2] (mg/mL)	
		Male	Female	Male	Female
1. Water[3]	25 (3)	0	0	0	0
2. Low	25 (18)	15	30	1.5	3
3. Medium	25 (18)	45	60	4.5	9
4. High	25 (18)	125	200	12.5	25
5. Positive[4] Control	20	75	75	7.5	7.5

1 Doses selected were based on the Maximum Tolerated Dose (MTD) in each gender due to renal and/or hepatic toxicity observed in a 28-day study ((b) (4) Study No. 8226465);
2 Concentrations (Groups 2 through 4 only) were based on the free acid content. A lot specific correction factor of 1.20 was used.
3 Group 1 received vehicle control article (reverse osmosis water) only.
4 Group 5 was dosed with one intraperitoneal dose of N-methyl-N-nitrosourea on Day 1 of the dosing phase.

Kaplan-Meier survival curves for the rat study are presented in Appendix 1. Summary incidence of death tables are presented on pages 20 and 21 of this report. From Figure A.1.1 in

the appendix, in male rats the Kaplan-Meier estimated survival curves are largely intertwined, consistent with no tests of differences in survival being close to statistical significance. From Figure A.1.2 survival in female, the vehicle and low dose groups track each other closely with the higher survival than the high and medium dose groups. These differences were statistically significant (Logrank p= 0.0204, Wicoxon p= 0.0225). The high and medium dose groups track each other somewhat closely, but with some tendency for higher survival in the high dose group. No other tests or comparisons quite reached the usual 0.05 level of statistical significance. The results of statistical tests of differences in survival are given below: !

Table 3. Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats

Hypotheses	Males		Females	
	Logrank	Wilcoxon	Logrank	Wilcoxon
Homogeneity over all four groups	0.4664	0.5764	0.0204	0.0225
No Trend over all four groups	0.1874	0.2968	0.0903	0.0655
No difference between high dose and vehicle	0.3168	0.4734	0.0941	0.0851

Tables 4 and 5, below, display the days of death among the Tg.rasH2 animals. These times are to be read as incidence over the approximate time line of the study. Multiple deaths, say for k deaths, at that numeric week are indicated by "k*week". Although this reviewer considers the plots/tables below to be more informative, traditional Kaplan-Meier survival plots are presented as plots in Appendix 1, along with the results of tests of dose related trend in survival and differences between the vehicle and various dose groups.

Table 4. Survival Times in Male Tg.rasH2 Mice

Dose Group	Dosage	Survival Time in Days
1.Vehicle	0	25*27
2. Low	15	24, 24*27
3. Medium	45	25*27
4. High	125	11 24*27
5. Positive Control	75	11,12, 15,16,17, 19,20,21,22, 3*24,2*25, 6*27

Table 5. Survival Times in Female Tg.rasH2 Mice

Dose Group	Dosage	Survival Time in Days
1.Vehicle	0	26,24*27
2. Low	30	25*27
3. Medium	90	15 24*27
4. High	250	7,8, 12, 19 21*27
5. Positive Control	75	12,13, 15, 2*18, 4*20,21, 2*23,2*24, 6*27

In female mice there is some evidence of decreasing survival over dose. Although arguably of less use than Tables 4 and 5 above, appendix 1 includes both exact logrank tests comparing survival across groups and asymptotic tests of trend in survival over dose comparing survival across groups. Except for comparisons involving the positive control, tests on survival in male mice were uniformaly not statistically significant, while the corresponding tests in female mice were generally at or close to statistical significance (please see Table A.1.4 in that appendix).

Note that a large number of tumors are typically identified in the analysis of neoplasms, implying a large number of statistical tests. Following the frequentist paradigm, when interpreting significance levels (i.e., p-values), one can use the Haseman-Lin-Rahman (HLR) rules to adjust for the multiplicity of tests. Two approaches have been investigated, one for testing dose related trend and pairwise comparison between the high dose and control seperately and the other these hypotheses jointly (please see Section 1.3.1.5, below, for details). Usual statistical practice would be to test these hypotheses separately, but some scientists want to control Type I error only when simultaneously testing both the trend and pairwise hypotheses. That is, in the two year study, when testing for trend over dose and, separately, the difference between the highest dose group with a control group, to control the overall Type I error rate for the joint tests in a two species submission to roughly 10%, one compares the unadjusted significance level of the trend test to 0.005 for common tumors and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. For the testing these hypothese jointly for common tumors one compares the unadjusted significance level of the trend test to 0.005 and the pairwise test to 0.05, and for rare tumors 0.025 for tests of trend and 0.10 the pairwise comparison. Using these adjustments for other tests, like testing the comparisons between the Low and Medium dose groups versus vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate. For the alternative short term study simulations suggest a 0.05 level for both the test of trend and pairwise comparisons.

Table 6 shows the tumors in rats that had at least one non-multiplicity adjusted test that was statistically significant at or close, to a 0.10 level (or contributed to a significant test). For each tumor-organ combination the tumor incidence over the four dose groups is listed first, followed by the significance levels of the overall test of trend over all four dose groups, and finally the comparison of the high, medium and low dose groups with vehicle.

Table 6. Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats

Gender Organ/Tumor	Overall Results Tumor Incidence Veh	Low	Med	High	Significance Levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
Male Rats								
SKIN								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	37.8	42.1				
MYXOSARCOMA	0	0	0	2	.0721	.2657	.	.
THYROID								
# Evaluated	59	60	60	60				
Adj. # at Risk	39.7	38.0	39.0	41.8				
C-CELL ADENOMA	0	2	2	4	.0482	.0640	.2403	.2337
Female Rats								
PANCREAS								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.2	33.9				
ISLET CELL ADENOMA	0	0	0	2	.0527	.2009	.	.
PITUITARY								
# Evaluated	60	60	60	60				
Adj. # at Risk	54.0	56.2	49.8	54.7				
PARS DISTALIS ADENOMA	43	41	41	49	.0158	.0872	.3933	.8452
Adj. # at Risk	41.0	41.3	31.2	33.8				
PARS DISTALIS: CARCINOMA	0	3	4	1	.4539	.4521	.0324	.1249
Adj. # at Risk	54.0	57.1	51.7	54.7				
Pars Dist. Adenoma/Carcinoma	43	44	45	50	.0092	.0463	.1761	.7056

Using the tumor incidence in the vehicle to determine whether a tumor should be classified as rare or common, only pars distalis adenoma and pooled adenoma and carcinoma would be classified as common tumors, the rest rare. However, after adjusting for multiplicity using the Haseman-Lin-Rahman rules, in both genders in rats when testing hypotheses of trend or pairwise differences, strictly speaking no tests were statistically significant. Complete tables of tumor incidence are given in Tables A.2.2 and A.2.3, in Appendix 2, below.

With the exception of the comparisons between the vehicle and the positive control, in mice no tests achieved even the nominal 0.10 level, let alone any multiplicity adjusted level of statistical significance. Since it was felt that the tests between the vehicle and positive control were only of use to assess the appropriateness of the mouse model, they are not addressed further. Complete tables of tumor incidence are given in Tables A.2.4 and A.2.5, in Appendix 2, below.

1.2. Brief Overview of the Studies

Two studies were submitted, the first from [redacted](b) (4):

Study No. 09-2168, Sponsor Study No. SR09-070 RDEA594: An Oral Gavage 24-Month Carcinogenicity Study in Sprague-Dawley Rats.

and the second, conducted by (b) (4)

(b) (4) **Study No. 8226466: RDEA594: 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study in CByB6F1-Tg(HRAS)2Jic Mice.**

These studies were designed to assess the carcinogenic potential of Zurampic. In the rat study, the actual dose groups were labeled in this report as the Low, Medium, and High dose groups, respectively, plus the Vehicle control group. In the mouse study, the dose groups were labeled Vehicle, Low, Medium, High, and a Positive Control.

Due to high mortality, dosing in the rat study stopped early and were usually terminated sone thereafter (dosing stopped after 90 weeks in high dose females, and weeks 97-99 in high dose males with termination in weeks 97-99). The Sponsor reports that the termination of dosing thereafter was staggered based on the number of survivors for each group. This early termination may complicate interpretation of results. However, the Sponsor concludes that "In conclusion, RDEA594 administered orally to rats at doses of 25, 75 or 200 mg/kg/day for up to 97 weeks did not affect survival and did not induce an increase in neoplasms in either males or females." (page 11 of rat report)

The Sponsor summarizes results in the Tg.rasH2 mouse report as follows: "In conclusion, daily administration of RDEA594 by oral gavage to 001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic mice for 26 weeks at a dose level of 15, 45, or 125 mg/kg/day to males or 30, 90, or 250 mg/kg/day to females resulted in no effect on survival and no microscopic evidence of increased oncogenicity." (page 11 of mice report)

1.3. Statistical Issues and Findings

1.3.1. Statistical Issues

In this section, several issues, typical of statistical analyses of these studies, are considered. These issues include comments on the details of the survival analyses, tests on tumorigenicity, multiplicity of tests on neoplasms, and the validity of the designs.

1.3.1.1 Design

In any experiment, when assessing the effects of different levels of dosing, it is important that, except for the actual dose, dose groups should be treated as similarly as possible. In female rats mice the very early sacrifice in the medium dose group and the early cessation of dosing in the high dose group may violate this principle. Note, however, that the poly-k test used does automatically adjust for such reductions in the risk set. Whether that adjustment is adequate or not is not clear

1.3.1.2. Survival Analysis:

In rats, the survival analyses presented here are based on both the log rank test and the Wilcoxon test comparing survival curves. The Wilcoxon statistic provided by SAS® (technically the Gehan-Wilcoxon statistic) can be cast as a log rank test weighted by the number of subjects at risk, and thus is more sensitive to earlier differences (when more subjects are at risk). The logrank test is most powerful when the survival curves track each other, and thus the hazards, i.e., the conditional probability of the event in the next infinitesimal interval, would be roughly proportional. Note the logrank test seems to be the test usually recommended by statisticians, and is one of the tests used by the Sponsor (in rats in addition to Tarone's test). Both the logrank and the Wilcoxon tests are used in the FDA analysis of mortality.

For Tg.rasH2 mice, simple tables that are essentially histograms are used as the primary display to show differences in survival. It is this reviewer's contention that they display the needed information to demonstrate differences. The relatively small number of animals and the relatively low event rate suggest that the asymptotic results jstifying the usual tests of survival differences, particularly the pairwise comparisons, may have problems. For that reason only the tests of trend in survival, using all animals and displayed in Appendix 1, depend upon the usual asymptotic results. The pairwise tests used for mice are exact versions of the logrank test.

Appendix 1 reviews the specific FDA animal survival analyses in more detail. The results of the Sponsor's analysis are summarized in Sections 3.2.1.1 and 3.2.2.1.

1.3.1.3. Multiplicity of Tests on Survival:

Using both the logrank and Wilcoxon tests, for each gender in rats and, ignoring the positive control, mice there are six tests of survival differences in each gender in each species. Assuming tests were performed at the usual 0.05 level, and the tests were stochastically independent, but there were actually absolutely no differences in survival across groups (so one would hope no tests would be statistically significant), the probability of at least one statistically significant result in each gender in each species was about 0.2649 in rats and 0.708 in both genders in both species. These bounds assume the tests are stochastically independent, which they clearly are not, but these values can give some idea of the possible price paid for the multiplicity of hypothesis tests in the statistical frequentist paradigm.

1.3.1.4. Tests on Neoplasms:

Sponsors are requested to provide data in either SEND (Standard for the Exchange of Nonclinical Data) format, part of the CDISC consortium, or in the older FDA Biometrics format. Data from both studies fit the latter format. The FDA Biometrics format data sets requested for the analysis of rodent carcinogenicity studies are supposed to include a record for each animal organ combination that was not evaluated. If a number of the animals are not examined, but the proportions of animals showing the tumor under study in each treatment group is roughly the same as in the subset of animals actually reported the calculated p-values will generally be too large, i.e., results will be less statistically significant than they should be, possibly much less. If we can assume the process that determines whether or not a tumor is analyzed in each specific

tumor is random, it is perhaps appropriate to consider such endpoints to be both analyzed and have the tumor.

Ignoring these possible problems, the Sponsor's analyses of tumorigenicity in rats are Peto tests, with incidental and fatal plus mortality independent tumors. Note that Peto methods require accurate determination of whether a tumor is fatal or incidental. In mice, except for the positive control, survival was consistent across study dose groups. The the Cochran-Armitage tests for carcinogenicity used by the Sponsor's CRO in the mice study should be appropriate, as were the pairwise comparisons were made using Fisher exact tests.

The FDA analysis in both species is based on a modification of the Cochran-Armitage test of trend (please see Bailer & Portier, 1988, Bieler & Williams, 1993), adjusted for differential mortality. Inspecting a large number of studies, Bailer and Portier noted that survival time seemed to fit a Weibull distribution, generally with a shape parameter of between 1 and 5, with 3 a typical value. With t_{max} denoting the maximal time to terminal sacrifice and t_{obs} the time to detection of the tumor in the animal, they proposed weighting the animal by $(t_{obs}/t_{max})^k$, so that an animal that survives for say 52 weeks in 104 week study without the tumor being analyzed is counted as $(1/2)^k$ of an animal in the risk set for that tumor. For k = 3, that means that particular animal would count as 1/8 of an animal. Further, the k = 3 specification seems to represent tumor incidence where some animals are perhaps more sensitive and respond earlier to the insult than the remining animals. Under this structure time to incidence would tend to follow a cubic expression. Thus an animal with the specific tumor being studied or who survives to terminal sacrifice without the tumor will be given a weight of 1 when counting the number of animals at risk. However, animals that die early without the tumor are down weighted when counting the number of animals in the risk set for that specific tumor. With differential mortality, as in male mice, this can mean a substantial reduction in the size of that risk set. Note this seems to be an appropriate adjustment for dose groups that are terminated early. The report of the Society of Toxicological Pathology "town hall" meeting in June 2001 recommeded the use of this poly-k modification of the so-called Cochran-Armitage tests of trend over the corresponding Peto tests used by the Sponsor.

The computed significance levels are based on small sample exact permutation tests of tumor incidence. In the tumor incidence tables the effective size of the risk set for each tumor is listed in the row labeled "Adjusted # at risk ", and seems to be a more appropriate denominator when comparing incidence rates than the simple unadjusted number evaluated.

1.3.1.5. Multiplicity of Tests on Neoplasms:

Testing dose related treatment differences for each species by gender by organ by tumor combination involves a large number of comparisons. Current FDA practice is based on the Haseman-Lin-Rahman multiplicity adjustments.

The Haseman-Lin-Rahman rules are based on the original multiplicity adjustment of Haseman (1983) and extended by Lin and Rahman on the basis of various simulations. Based on

his extensive experience with such analyses, for pairwise tests in a two species study comparing control to the High dose group, Haseman (1983) claimed that for a roughly 0.10 (10%) overall false positive error rate, rare tumors should be tested at a 0.05 (5%) level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. Lin & Rahman (1998) proposed a further p-value adjustment for tests of trend. That is, for a roughly 0.10 (10%) overall false positive error rate in tests of trend, rare tumors should be tested at a 0.025 (2.5%) level and common tumors at a 0.005 (0.5%) level. The general specifications are presented in the Table 4 below. This approach is intended to balance both Type I error and Type II error (i.e., the error of concluding there is no evidence of a relation to tumorgenicity when there actually is such a relation).

The proposed Haseman-Lin-Rahman bounds are taken from *Guidance for Industry Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals*, (HHS, 2013). The bounds on the right in table 7, below, are grouped so that the last four columns correspond to testing both trend and the pairwise comparison between the high dose and control jointly. The previous four columns (columns 2-5), correspond to testing both overall trend and pairwise tests between the high dose and control seperately. Within each group there is a column giving the corresponding bounds for a two year, one species study, and another column for the alternate 6-month study. In this analysis we follow the usual practice of testing parameters separately, so the bounds in the leftmost columns are used. The observed tumor incidence in the vehicle group is used to decide if a tumor is classified rare or common.

Table 7. Recommended Multiplicity Adjusted Bounds on Significance Levels

	Testing trend or pairwise difference				Joint testing of trend and pairwise			
	Two Year		Alternative		Two Year		Alternative	
	Trend	Pairwise	Trend	Pairwise	Trend	Pairwise	Trend	Pairwise
Common Tumor	0.005	0.01	0.05	0.05	0.005	0.05	0.05	0.05
Rare Tumor	0.025	0.05	0.05	0.05	0.025	0.10	0.05	0.05

In words, as noted in the FDA Guidance (2013) "For tests for positive trend alone, it is recommended that common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively, in the two-year study; and at 0.05 and 0.05 significance levels, respectively in the alternative study.

"For [the] control-high pairwise comparison alone, it is recommended that common and rare tumors are tested at 0.01 and 0.05 significance levels, respectively, in the two-year study; and at 0.05 and 0.05 significance levels, respectively, in the alternative study.

"For tests for positive trend and control-high pairwise comparison jointly, it is recommended that common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively in trend test, and at 0.05 and 0.10 significance levels, respectively, in control-high pairwise comparison

in the two-year study; and at 0.05 and 0.05 significance levels, respectively, in both trend test and control-high pairwise comparison in the alternative study." (page 32 of 2013 Guidance)

The significance levels of the pairwise tests between the vehicle control with the Low and Medium dose groups are also provided in the tumor analysis tables below. Following the HLR rules, adding these comparisons can be expected to increase the overall type I error rate to some level above the usual rough 10% level, possibly considerably larger. Again, because of the possibility of genetic drift and for convenience, incidence in the vehicle group is used to determine if the tumor is classified as rare or common.

1.3.1.6. Validity of the Designs:

When determining the validity of designs there are two key points:
1) adequate drug exposure
2) tumor challenge to the tested animals.

1) is related to whether or not sufficient animals survived long enough to be at risk of forming late-developing tumors and 2) is related to the Maximum Tolerated Dose (MTD), designed to achieve the greatest likelihood of tumorigenicity.

Lin and Ali (2006), quoting work by Haseman, have suggested that in standard laboratory rodent species, a survival rate of about 25 animals, out of 50 or more animals (i.e. 50%), between weeks 80-90 of a two-year study may be considered a sufficient number of survivors as well as one measure of adequate exposure. From tables 14 and 15 in Section 3.2.1.2 below, as a percentage of the High dose group animals that survived to week 91, this criterion is considerably exceded in both genders (Male rats high dose: 31.7% and Female rats: 56.7%). This may be evidence that the MTD was somewhat exceded in male mice, but such a determination requires the expertise of the toxicologist.

Chu, Ceuto, and Ward (1981), citing earlier work by Sontag et al. (1976) recommend that the MTD "is taken as 'the highest dose that causes no more than a 10% weight decrement as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span' " From Tables 9 and 10 below, it seems that the weight criterion is slightly exceed in both genders in rats. trongly exceded in female rats and to a somewhat lesser strength in male rats. Although its applicability to Tg.rash2 studies is not clear, from Tables 11 and 12 above, it seems that the weight criterion is strongly exceded in both mouse genders in the high-medium and high dose groups.

The mean weight values used to derive differences and ratios in the following tables were taken directly from the Sponsor's reports (Rat Table 5, pages 425-434, and Mice Table 4, pages 50-68). The change from baseline in the table below is the simple difference between the means at the specified dates, and thus animals that die early are only counted at the study initiation, not at the end of the study.

Table 8. Mean Weights and Changes (in g) in Male Rats

Dose Group	Dose mg/kg/day	Week		Change from Baseline	% change relative to vehicle
		1	82		
1. Vehicle	0	159.8	947.8	788.0	
2. Low	25	157.8	982.7	824.9	104.7%
3. Medium	75	158.4	976.4	818.0	103.8%
4. High	200	155.4	831.4	676.0	85.8%

Table 9. Mean Weights and Changes (in g) in Female Rats

Dose Group	Dose mg/kg/day	Week		Change from Baseline	% change relative to vehicle
		0	89		
1. Vehicle	0	151.0	616.2	465.2	
2. Low	25	152.2	647.2	491.0	105.5%
3. Medium	75	148.3	610.2	461.9	99.3%
4. High	200	146.4	553.0	406.6	87,4%

Chu, Ceuto, and Ward (1981), citing earlier work by Sontag et al. (1976) recommend that the MTD "is taken as 'the highest dose that causes no more than a 10% weight decrement as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span' " From Tables 9 and 10 above, it seems that the weight criterion is slightly exceed in both genders in rats.

Due to the short time frame in transgenic mouse studies there will be little change in body weight during the duration of the study, so ratios in change are not very meaningful. Thus the Chu, Ceuto, and Ward criteria are likely of little relevance in transgenic mouse studies. Nonetheless the following Tables 11 and 12 are presented for completeness, although this reviewer doubts they are of much use.

Table 10. Mean Weights and Changes (in g) in Male Mice

Study Group	Dose mg/kg	Week		Change from baseline	% change relative to vehicle
		1	6		
1. Vehicle	0	22.8	23.2	0.4	
2. Low	15	22.3	23.2	0.9	225%
3. Medium.	45	22.4	23.7	1.3	325%
4. High	125	22.6	23.3	0.7	175%
5. Positive Control	75	22.2	24.8	2.6	650%

Table 11. Mean Weights and Changes (in g) in Female Mice

Study Group	Dose mg/kg	Week		Change from baseline	% change relative to vehicle
		1	6		
1. Vehicle	0	18.7	19.5	0.8	
2. Low	15	18.7	19.7	1.0	125%
3. Medium.	45	18.9	20.3	1.4	175%
4. High	125	18.5	19.7	1.2	150%
5. Positive Control	75	18.2	20.0	1.8	225%

More generally, in the rat study, the Sponsor summarizes weight results as "Test article-related body weight effects were noted at 200 mg/kg/day. In males, there were statistically significant decreases throughout the study in mean body weight (-5 to -13%) and body weight gain (-6 to -15%), as compared to controls. Body weight decreases were evident even with an increase in food consumption in this group . . . . In females, there were statistically significant increases in body weight gain at several intervals between Weeks 1 and 18 (+6 to +16%), followed by gradual decreases in mean body weight and body weight gain between Weeks 76 and 95. In Week 95, there were statistically significant decrease in mean body weight (-17%) and body weight gain (-21%) in females. The initial body weight gain in the females was consistent with an increase in food consumption in this group.

"The statistically significant increase in mean body weight gain in Week 1 in females given 75 mg/kg/day was attributed to normal variability." (pages 52-53 of report)

The Sponsor also reports that there were "Statistically significant increases in food consumption were present in males at 75 and 200 mg/kg/day and in females at all doses." (page 53 of report)

Again from 2) above, excess mortality not associated with any tumor or sacrifice in the higher dose groups might suggest that the MTD was exceeded. This suggests that a potentially useful way to assess whether or not the MTD was achieved is to measure early mortality not associated with any identified tumor. If this mortality is related to dose, it suggests that animals tend to die before having time to develop tumors. From the table below it seems that in rats there is no particular evidence of heterogeneity across dose groups.

Table 12. Natural Death with No Identified Tumor in Rats (Male/Female)

	1.Vehicle	2. Low	3.Medium	4.High
Males Event	2	1	6	4
No event	58	59	54	56
Females Event	14	18	13	11
No event	46	42	47	49

The apparent lack of heterogeneity in natural death without tumor is confirmed the results of Fisher exact tests of homogeneity (Males p =0.2180 and Females p = 0.5267). However, the general applicability of this criterion in Tg.rasH2 mice studies is not as clear, but in the Tg.rasH2 mice study there were no early deaths without tumor. Whether or not these observations are appropriate requires the expertice of the toxicologist.

1.3.2. Statistical Findings

Please see Section 1.1 above.

2. INTRODUCTION

2.1. Overview

The Sponsor's reports summarize results from one two-year study, in Sprague-Dawley rats, and the other a 26-week study, in hemizygous Tg.rasH2 mice, both with daily gavage, to assess the carcinogenic potential of Zurampic in the Sponsor's reports.

2.2. Data Sources

SAS data sets for both species, largely following the requested FDA format, both labeled tumor.sas7bdat, plus were translated from SAS transport files both labeled tumor.xpt. It should be noted that in the rat study the SAS variable DTHSACTM (i.e. death or sacrifice time) was renamed to DTHSACTW. In the mouse study a variable SUBGRP was used to discriminate between the Tg.rasH2 mouse carcinogenic study (SUBGRP=1) and the toxicological study in wild type mice (SUBGRP=2). Only the former sub group was analyzed in this report.

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

NA

3.2. Evaluation of Safety

More detailed results on the study are presented below.

(b) (4) **Study No. 09-2168, Sponsor Study No. SR09-070 RDEA594: An Oral Gavage 24-Month Carcinogenicity Study in Sprague-Dawley Rats.**

and the second, conducted by (b) (4),

(b) (4) **Study No. 8226466: RDEA594: 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study in CByB6F1-Tg(HRAS)2Jic Mice.**

3.2.1. (b) (4) Study No. 09-2168, Sponsor Study No. SR09-070 RDEA594: An Oral Gavage 24-Month Carcinogenicity Study in Sprague-Dawley Rats.

CRO: (b) (4)
STUDY DURATION: Weeks 90-101
DOSING STARTING DATE: 4 February 2010
STUDY COMPLETED: 28 July 2014 (Date Final Report Signed)
RAT STRAIN: Sprague-Dawley CD® Rats
ROUTE: Daily Oral gavage

Animals were dosed once daily by oral gavage. The Sponsor's report states that: "Based on mortality, dosing was terminated and animals were necropsied earlier than 104 weeks. All decisions to terminate dosing or remove a treatment group from the study were done following consultation and agreement by the FDA. There was no test article related increase in mortality as compared to control animals. For males at all dose levels, dosing was stopped and terminal necropsy was initiated in Week 97. For males at 0, 25, 75 and 200 mg/kg/day, the number (percentage) of males surviving to terminal necropsy was 20 (33%), 18 (30%), 20 (33%) and 27 (45%), respectively. For females at 0, 25, 75, and 200 mg/kg/day, dosing was stopped in Weeks 100, 97, 91 and 90, respectively. Terminal necropsy was conducted on 20 (33%), 15 (25%), 15 (25%) and 15 (25%) survivors in Weeks 100, 100, 91 and 97, respectively." (page 10 of rat report)

Gross aspects of the study designs for the main study animals are summarized in Table 13 be1ow (a repeat of Table 1 above):

Table 13. Design of Rat Study (dose volume 10 mL/kg)

Treatment Group	Animals / Gender	Nominal Dose (mg/kg)	Concen-tration (mg/kg)	Week Dosing Stopped		Week of Scheduled Kill [2]	
				Males	Females	Males	Females
1. Vehicle[1]	60 (6)	0	0	97-99	100	97-99	100-101[3]
2. Low	60 (16)	25	2.5	97 [1]	97	97 [4]	100 [5]
3. Medium	60 (16)	75	7.5	97 [1]	91	94 [6]	91 [7]
4. High	60 (16)	200	20	97-99	90	92 [8]	97 [9]

[1] Dosing was terminated when the number of surviving animals in the group decreased to 20.
[2] All male groups were terminated when the number of surviving control males decreased to 20.
[3] Control females were terminated when the number of surviving animals in the group decreased to 20.
[4] Dosing was terminated when the number of surviving animals in the group decreased to 20.
[5] Group was terminated when the number of surviving animals decreased to 15.
[6] Dosing was terminated and animals were sacrificed when the number of surviving animals decreased to 15.
[7] Dosing was terminated when the number of surviving animals in the group decreased to 20.
[8] Group was terminated when the number of surviving animals decreased to 15.
(all comments from page 17 of report)

According to the Sponsor's report the "dose levels were selected by the Sponsor based on results from a 13-week interim sacrifice as part of a 6-month study with RDEA594, … in Sprague-Dawley rats. In the 6-month study at a dose of 600 mg/kg/day there was significant toxicity beginning at Study Day 5 consisting of a severe reduction in food consumption and weight loss. This was followed by moribundity leading to death and unscheduled euthanasia. The entire 600-mg/kg/day group was terminated on Study Day 23. At a dose of 300 mg/kg/day, there were no treatment-related deaths during the 6 months of dosing. During the first two weeks of dosing at 300 mg/kg/day there was a transient decrease in food consumption and corresponding decrease in body weight gain. Over the length of the study, food consumption normalized and body weights compensated for the initial decrease. There were no treatment-related observations at this dose by the end of 6 months. Based on the information from the 13-week interim study the FDA recommended a high dose of 200 mg/kg/day for the 2-year study based on maximum tolerated dose (MTD) criteria. Low and mid doses of 25 and 75 mg/kg/day were selected to provide information on the dose relationship of findings." (page 19-20 of rat report) The oral route of administration was selected for this study as this route has been defined by the Sponsor as the intended route of clinical administration.

The suggested mechanism of action is "RDEA594 is an inhibitor of the uric acid transporter 1 (URAT-1) in the proximal tubule of the kidney. RDEA594 blocks the reabsorption of uric acid in the kidney leading to a reduction in serum uric acid levels." (page 20 of rat report)

Animals were housed individually with food and water available ad libitum. The Sponsor states that detailed clinical examinations were made at least weekly.

3.2.1.1 Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigencity in rats.

Survival analysis:

The CRO's report summarizes survival results as follows: "Based on mortality, (unscheduled, including accidental deaths), dosing was terminated and males and females in all dose groups were necropsied prior to the scheduled intervals. However, mortality was not considered to be test article related." (page 51 of report)! !

!

Tumorigenicity analysis:

The Statistical CRO describes a typical Peto style analysis of carcinogenicity. The results are summarized as follows:

" Males

"There were no statistically significant differences between the treated groups and the control group."

"Females
"Pituitary (pars distalis) …
"For benign adenoma and malignant carcinoma combined, the trend test was not statistically significant when all groups were included in the analysis (p=0.011). The pairwise comparison of the control group with the 75 mg/kg treated group was statistically significant (p=0.006)." (page 8 of statistical report, 3423 of rat report)

3.2.1.2 FDA Reviewer's Results

This section will present the current Agency findings on survival and tumorigenicity in male and female rats.

Survival analysis:

Kaplan-Meier plots comparing treatment groups in both studies are given in Appendix 1, along with more details of the analyis. The following tables (Table 14 for male rats, Table 15 for female rats) summarize the mortality results for the dose groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent survived at the end of the interval.

Table 14. Summary of Male Rats Mortality (dose/kg/day)

Period	1.Vehicle	2.Low	3.Medium	4.High
0-52	4/60 93.3%	2/60 96.7%	6/60 90.0%	6/60 90.0%
53-70	7/56 81.7%	9/58 81.7%	11/54 71.7%	10/54 73.3%
71-91	19/49 50.0%	20/49 48.3%	27/43 26.7%	25/44 31.7%
92-100	10/30 33.3%	14/29 25.0%	1/16 25.0%	4/19 25.0%
terminal	20	15	15	15

[1] number deaths / number at risk
[2] per cent survival to end of period.

Table 15. Summary of Female Rats Mortality (dose/kg/day)

Period	1.Vehicle	2.Low	3.Medium	4.High
0-52	4/60 93.3%	6/60 90.0%	5/60 91.7%	5/60 91.7%
53-78	7/56 81.7%	8/54 76.7%	11/55 73.3%	7/55 80.0%
79-91	19/49 50.0%	19/46 45.0%	16/44 46.7%	14/48 56.7%
92-104	10/30 33.3%	9/27 30.0%	8/28 33.3%	7/34 45.0%
terminal	20	18	20	27

[1] number deaths / number at risk
[2] per cent survival to end of period.

!

Kaplan-Meier survival curves for the rat study are presented in Appendix 1. The results of statistical tests of differences in survival are given below (a repeat of Table 3):

Table 16. Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats

Hypotheses	Males		Females	
	Logrank	Wilcoxon	Logrank	Wilcoxon
Homogeneity over all four groups	0.4664	0.5764	0.0204	0.0225
No Trend over all four groups	0.1874	0.2968	0.0903	0.0655
No difference between high dose and vehicle	0.3168	0.4734	0.0941	0.0851

From Figure A.1.1 in the appendix, in male rats the Kaplan-Meier estimated survival curves are largely intertwined, consistent with no tests of differences in survival being close to statistical significance. From Figure A.1.2 survival in female, the vehicle and low dose groups track each other closely with the higher survival than the high and medium dose groups. These differences were statistically significant (Logrank p= 0.0204, Wicoxon p= 0.0225). The high and medium dose groups track each other somewhat closely, but with some tendency for higher survival in the high dose group. No other tests or comparisons quite reached the usual 0.05 level of statistical significance.

Tumorigenicity analysis:

Table 17 below, a repeat of Table 6 above and Table A.2.1 below, shows the tumors in rats that had at least one non-multiplicity adjusted test that was statistically significant at a 0.10 or lesser level . For each tumor-organ combination the tumor incidence over the four dose groups is listed first, followed by the significance levels of the overall test of trend over all four dose groups, and finally the comparison of the high, medium and low dose groups with vehicle. .

Table 17. Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats

Gender Organ/Tumor	Overall Results Tumor Incidence Veh	Low	Med	High	Significance Levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
Male Rats								
SKIN								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	37.8	42.1				
MYXOSARCOMA	0	0	0	2	.0721	.2657	.	.
THYROID								
# Evaluated	59	60	60	60				
Adj. # at Risk	39.7	38.0	39.0	41.8				
C-CELL ADENOMA	0	2	2	4	.0482	.0640	.2403	.2337
Female Rats								
PANCREAS								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.2	33.9				
ISLET CELL ADENOMA	0	0	0	2	.0527	.2009	.	.
PITUITARY								
# Evaluated	60	60	60	60				
Adj. # at Risk	54.0	56.2	49.8	54.7				
PARS DISTALIS ADENOMA	43	41	41	49	.0158	.0872	.3933	.8452
Adj. # at Risk	41.0	41.3	31.2	33.8				
PARS DISTALIS: CARCINOMA	0	3	4	1	.4539	.4521	.0324	.1249
Adj. # at Risk	54.0	57.1	51.7	54.7				
Pars Dist. Adenoma/Carcinoma	43	44	45	50	.0092	.0463	.1761	.7056

Using the tumor incidence in the vehicle to determine whether a tumor should be classified as rare or common, only pars distalis adenoma and pooled adenoma and carcinoma would be classified as common tumors, the rest rare. However, after adjusting for multiplicity using the Haseman-Lin-Rahman rules, in both genders in rats when testing hypotheses of trend or pairwise differences, strictly speaking no tests were statistically significant. Complete tables of tumor incidence are given in Tables A.2.2 and A.2.3, below.

Complete results of statistical poly-k tests of tumor trend and differences between dose groups in male rats and female rats are given in Tables A.2.3 and A.2.4 in appendix 2.

3.2.2. (b) (4) Study No. 8226466: RDEA594: 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study in CByB6F1-Tg(HRAS)2Jic Mice.

CRO: (b) (4)
STUDY DURATION: Weeks 90-101
DOSING STARTING DATE: 4 February 2010
STUDY COMPLETED: 28 July 2014 (Date Final Report Signed)
RAT STRAIN: Sprague-Dawley CD® Rats
ROUTE: Daily Oral gavage

The Sponsor's report indicates that in the mouse study: "Male and female 001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic and 001178-W (wild type), CByB6F1-Tg(HRAS)2Jic mice were assigned to groups, and doses were administered as indicated in the following table. Hemizygous animals were assigned to carcinogenicity subgroups; wild-type animals were assigned to toxicokinetic subgroups." (page 10 of report) General aspects of the study design for the mice study are also summarized in Table 18 be1ow (a repeat of Table 2 above):

Table 18. Design of Mice Study (Volume 10 mL/kg)

Treatment Group[1]	# Main study animals (# toxicology study animals)/gender	Nominal Dose (mg/kg/day)		Concentration[2] (mg/mL)	
		Male	Female	Male	Female
1. Water[3]	25 (3)	0	0	0	0
2. Low	25 (18)	15	30	1.5	3
3. Medium	25 (18)	45	60	4.5	9
4. High	25 (18)	125	200	12.5	25
5. Positive[4] Control	20	75	75	7.5	7.5

1 Doses selected were based on the Maximum Tolerated Dose (MTD) in each gender due to renal and/or hepatic toxicity observed in a 28-day study ((b) (4) Study No. 8226465);
2 Concentrations (Groups 2 through 4 only) were based on the free acid content. A lot specific correction factor of 1.20 was used.
3 Group 1 received vehicle control article (reverse osmosis water) only.
4 Group 5 was dosed with one intraperitoneal dose of N-methyl-N-nitrosourea on Day 1 of the dosing phase.

Animals were approximately six to seven weeks old at first dosing. After randomization animals were housed individually. The Sponsor states that animals were checked twice daily, with detailed physical examinations at least weekly. .

3.2.2.1 Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigencity in mice.

Survival analysis:

The CRO report summarizes results in survival as follows: "For males, the positive control group (Group 5) had a significant increase in mortality ($p = 0.0000$ by the Cox-Tarone and Gehan-Breslow tests). None of the groups given test article had any significance in mortality compared with the vehicle control group (Group 1).

"For females, the positive control group (Group 5) had a significant increase in mortality ($p = 0.0000$ by the Cox-Tarone and Gehan-Breslow tests). Females given the test article had a borderline positive trend in mortality ($p = 0.0275$ by the Cox-Tarone test and $p = 0.0257$ by the Gehan-Breslow test). None of the aforementioned groups had a

significant increase in mortality over the vehicle control group." (page 1364 of report, page 4 of statistical report)

Tumorigenicity analysis:

The Sponsor's analysis of carcinogenicity is based on Cochran-Armitage tests of trend. Considering that, except for the positive control, there are only small differences in mortality across dose groups so the standards Cochran-Armitage test of trend and the Fisher exact test for pairwise differences should be appropriate. The CRO report summarizes results as follows: "Males had no statistically significant positive trend or increase in neoplastic lesions in any of the groups given the test article. The male positive control group (Group 5) had increases in skin/subcutis squamous cell papilloma, nonglandular stomach squamous cell papilloma, and nonglandular stomach squamous cell papilloma and/or carcinoma and a statistically significant increase in body, whole/cavity lymphosarcoma (p = 0.0000).

"Females had no statistically significant positive trend or increase in neoplastic lesions in any of the groups given the test article. The female positive control group (Group 5) had increases in several cases with incomplete observations and a statistically significant increase in body, whole/cavity lymphosarcoma (p = 0.0000)." (page 1364 of report, page 4 of statistical report).e

Note the FDA analysis is base on the poly-k tests, which adjust the Cochran-Armitage test for any differential mortality.

3.2.1.2 FDA Reviewer's Results

This section will present the current Agency findings on survival and tumorigenicity in male and female mice.

Survival analysis:

The following tables (Table 19 for male mice, Table 20 for female mice, repeats of tables 4 and 5 above) summarize the mortality results for the dose groups. These times are to be read as incidence over the approximate time line of the study. Multiple deaths, say for k deaths, at that numeric week are indicated by "k*week". Although this reviewer considers the plots/tables below to be more informative, traditional Kaplan-Meier survival plots are presented as plots in Appendix 1, along with the results of tests of dose related trend in survival and differences between the vehicle and various dose groups.

Table 19. Survival Times in Male Tg.rasH2 Mice

Dose Group	Dosage	Survival Time in Days
1.Vehicle	0	25*27
2. Low	15	24, 24*27
3. Medium	45	25*27
4. High	125	11 24*27
5. Positive Control	75	11,12, 15,16,17, 19,20,21,22, 3*24,2*25, 6*27

Table 20. Survival Times in Female Tg.rasH2 Mice

Dose Group	Dosage	Survival Time in Days
1.Vehicle	0	26,24*27
2. Low	30	25*27
3. Medium	90	15 24*27
4. High	250	7,8, 12, 19 21*27
5. Positive Control	75	12,13, 15, 2*18, 4*20,21, 2*23,2*24, 6*27

Kaplan-Meier plots comparing treatment groups in both studies are given in Appendix 1, along with more details of the analysis.

Tumorigenicity analysis:

Table 21 below, a repeat of Table 7 above and Table A.2.2 below, shows the organ-tumor combinations associated with at least one non-multiplicity adjusted test that was statistically significant at a 0.10 level. To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman (HLR) rules discussed in Section 1.3.1.6 are often applied. In this particular case we have a two-year study in rats and an alternative short term study in mice. An adjustment that seems to work is that in the rat study for a roughly 10% overall error rate tests of trend would be considered significant it the tests for positive trend alone would be tested at 0.005 and 0.025 significance levels, for common and rare tumors respectively. Control-high pairwise would be tested 0.01 and 0.05 significance levels, respectively. In the alternative mouse study all levels comparisons would be tested at a 0.05 level. If we require both the tests of trend and the pairwise comparison to be significant, the only change would be that the pairwise test in the two year study be tested at a 0.10 level for rare tumors. Using these adjustments for other tests, like testing the comparisons between the low and medium dose groups versus vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate.

Table 21, below, shows those rows with at least one tumor with at least one non-multiplicity adjusted test that was statistically significant or close, to a 0.10 level.

Table 21. Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats

Gender Organ/Tumor	Overall Results Tumor Incidence Veh	Low	Med	High	Significance Levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
Male Rats								
SKIN								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	37.8	42.1				
MYXOSARCOMA	0	0	0	2	.0721	.2657	.	.
THYROID								
# Evaluated	59	60	60	60				
Adj. # at Risk	39.7	38.0	39.0	41.8				
C-CELL ADENOMA	0	2	2	4	.0482	.0640	.2403	.2337
Female Rats								
PANCREAS								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.2	33.9				
ISLET CELL ADENOMA	0	0	0	2	.0527	.2009	.	.
PITUITARY								
# Evaluated	60	60	60	60				
Adj. # at Risk	54.0	56.2	49.8	54.7				
PARS DISTALIS ADENOMA	43	41	41	49	.0158	.0872	.3933	.8452
Adj. # at Risk	41.0	41.3	31.2	33.8				
PARS DISTALIS: CARCINOMA	0	3	4	1	.4539	.4521	.0324	.1249
Adj. # at Risk	54.0	57.1	51.7	54.7				
Pars Dist. Adenoma/Carcinoma	43	44	45	50	.0092	.0463	.1761	.7056

Using the tumor incidence in the vehicle to determine whether a tumor should be cllassified as rare or common, only pars distalis adenoma and pooled adenoma and carcinoma would be classified as common tumors, the rest rare. However, after adjusting for multiplicity using the Haseman-Lin-Rahman rules, in both genders in rats when testing hypotheses of trend or pairwise differences, strictly speaking no tests were statistically significant. Complete tables of tumor incidence are given in Tables A.2.2 and A.2.3, below.

Complete results of statistical poly-k tests of tumor trend and differences between dose groups in male and female mice are given in Table A.2.5 and Table A.2.6 in Appendix 2.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

NA

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

Please see Section 1.3 above.

5.2. Conclusions and Recommendations

Please see section 1.1 above.

APPENDICES:

Appendix 1. Survival Analyses

Simple summary life tables in mortality in rats are presented in the report (Tables 14 and 15, above). Kaplan-Meier estimated survival curves across study groups for each gender in rats are displayed below in Figures A.1.1 and A.1.2. The plots include 95% confidence intervals around each survival curve (colored area around each curve). These plots are also supported by tests of homogeneity in survival over the treatment groups. The statistical significance levels (i.e., p-values) are provided in Table A.1.1., below. One might note that the log rank tests place greater weight on later events, while the Wilcoxon test tends to weight them more equally, and thus, it actually tends to place more weight on differences in earlier events than does the log rank test.

Table A.1.1 Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats

Hypotheses	Males		Females	
	Logrank	Wilcoxon	Logrank	Wilcoxon
Homogeneity over all four groups	0.4664	0.5764	0.0204	0.0225
No Trend over all four groups	0.1874	0.2968	0.0903	0.0655
No difference between high dose and vehicle	0.3168	0.4734	0.0941	0.0851

Kaplan-Meier survival curves for these studies are presented below. From Figure A.1.1, the Kaplan-Meier estimated survival curves in male rats are all largely intertwined, although near the end of the study up to terminal sacrifice the high dose group seems to have slightly higher survival than the other dose groups. However none of the comparisons in male rats would be categorized as statistically significant (i.e. all six $p \geq 0.1874$). In Figure A.1.2, in female rats, the comparisons in are more complicated. The vehicle and low dose groups are mostly intertwined while the medium and high dose largely track each other. These differences are sufficient to result in statistically significant test of homogeneity (Logrank p=0.0204, Wilcoxon p=0.0225). But the survival differences have only equivocal evidence of a simple linear order in dose (both $p \geq 0.0655$), while the pairwise tests between high dose and vehicle is also somewhat equivocal (both $p \geq 0.0851$).

Figure A.1.1 Kaplan-Meier Survival Curves for Male Rats

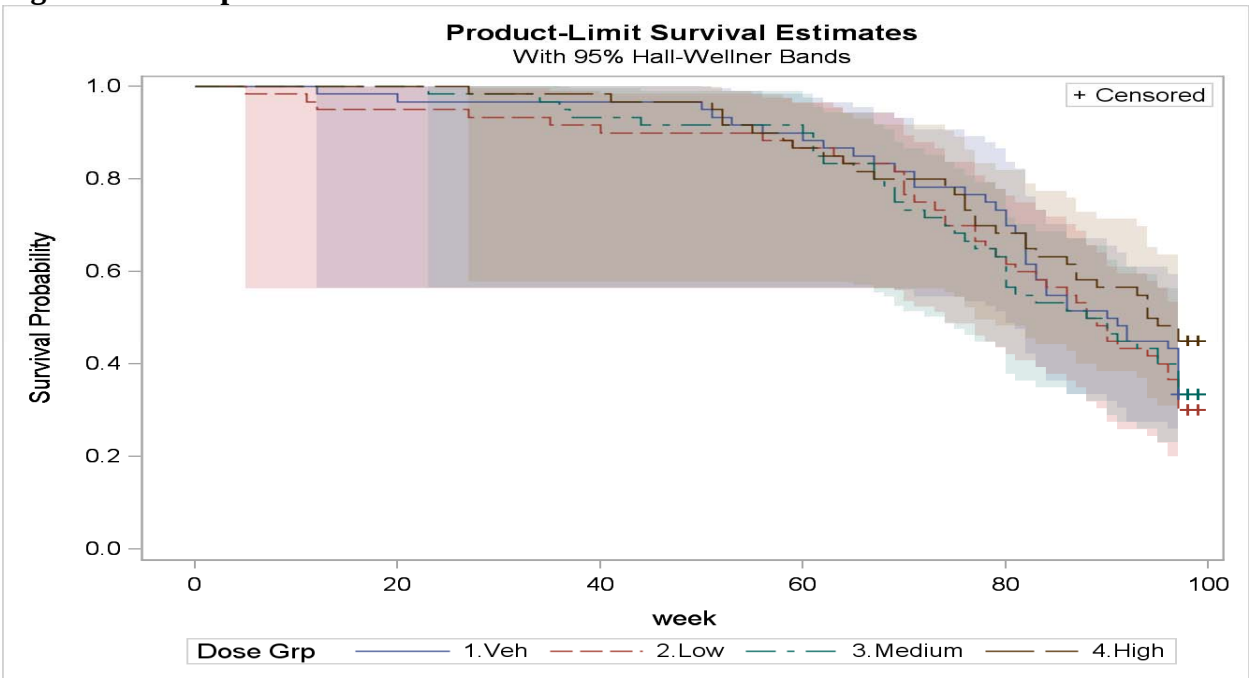
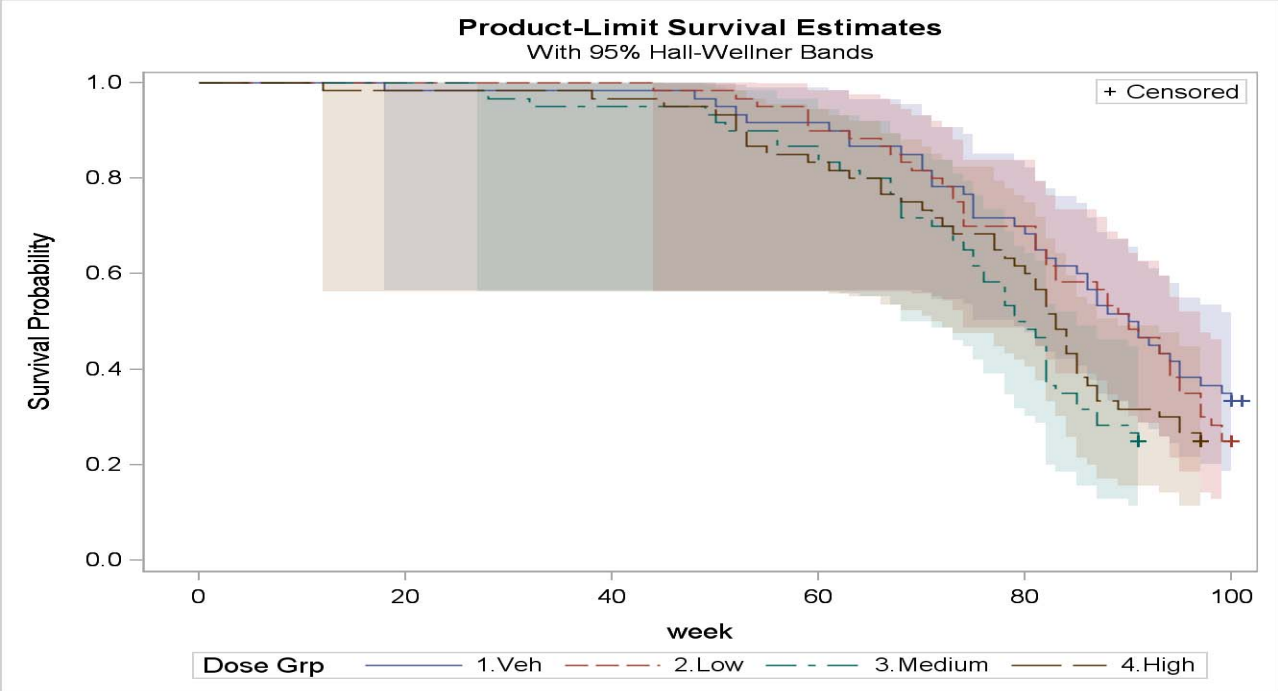


Figure A.1.2 Kaplan-Meier Survival Curves for Female Rats



Tables A.1.2 and A.1.3, below, display the weeks of death among the Tg.rasH2 animals. If there are multiple deaths in any week, the number of replicates precedes the week is places

before an asterisk (i.e. *). Note that although this reviewer considers these table displays to be the most informative presentation of results, traditional Kaplan-Meier survival plots are presented as Figures A.1.3 and A.1.4 below, while results of statistical tests in survival are presented in Table A.1.4.

Table A.1.2. Survival Times in Male Tg.rasH2 Mice

Dose Group	Dosage	Survival Time in Days
1.Vehicle	0	25*27
2. Low	15	24, 24*27
3. Medium	45	25*27
4. High	125	11 24*27
5. Positive Control	75	11,12, 15,16,17, 19,20,21,22, 3*24,2*25, 6*27

Table A.1.3. Survival Times in Female Tg.rasH2 Mice

Dose Group	Dosage	Survival Time in Days
1.Vehicle	0	26,24*27
2. Low	30	25*27
3. Medium	90	15 24*27
4. High	250	7,8, 12, 19 21*27
5. Positive Control	75	12,13, 15, 2*18, 4*20,21, 2*23,2*24, 6*27

Thus, in female mice, there is some evidence of increasing mortality over increasing dose. In male mice this relationship does not seem to hold. These observations are consistent with the results of survival tests in Table A.1.4 below. This table shows the results from tests of trend in survival over dose, and exact logrank tests comparing survival across groups. Because of the relatively small group sizes in the Tg.rasH2 study, the usual asymptotic tests for survival are only used for trend tests below (please see Section 1.3.1.3 abbove). Pairwise dose group comparisons are based on permutation versions of logrank exact tests from the corresponding StatXact SAS procedure. That is why Wilcoxon versions of the tests of differences among dose group means are not provided in Table A.1.2 below. Note that in male mice the only strong evidence of dose group differences in survival involves comparisons with the positive control (which are arguably of limited interest). Female mice show the same differences involving the positive control, but in addition the tests between survival in the high dose versus control, and the test of trend over the vehicle through high dose are statistically significant ($p = 0.0549$, 0.0166, respectively).

Table A.1.4 Statistical Significances of Tests of Homogeneity and Trend in Survival in Mice

Hypotheses	Males		Females	
	Logrank	Wilcoxon	Logrank	Wilcoxon
Homogeneity over all groups 1-4.	1.00		0.0663	
Pairwise Vehicle vs High (i.e., groups 1 vs 4)	0.50		0.0549	
Trend over groups 1 to 4	0.4774	0.4730	0.0166	0.0167
Homogeneity over all groups 1-5	0.0		0.0	
Pairwise Vehicle vs Positive Control (i.e., groups 1 vs 5)	0.0		0.0	

The Kaplan-Meier plots for the mice are displayed below:

Figure A.1.3 Kaplan-Meier Survival Curves for Male Mice

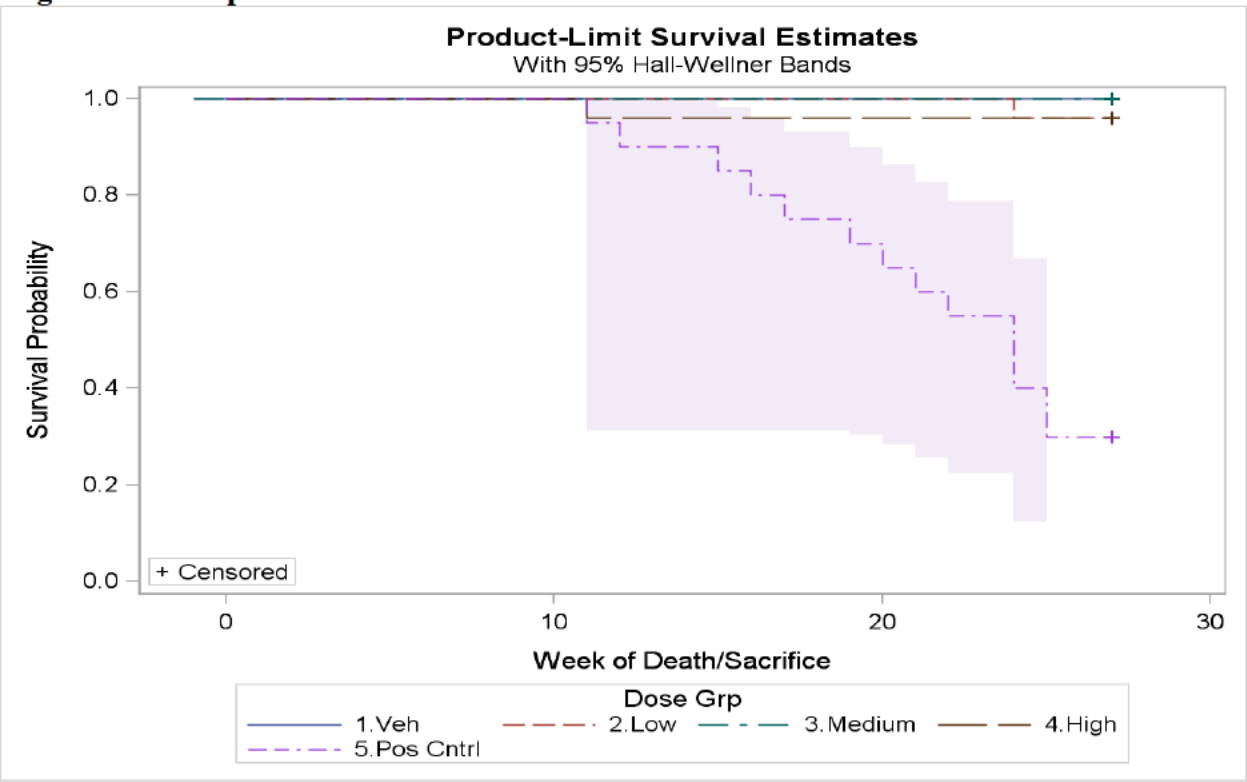
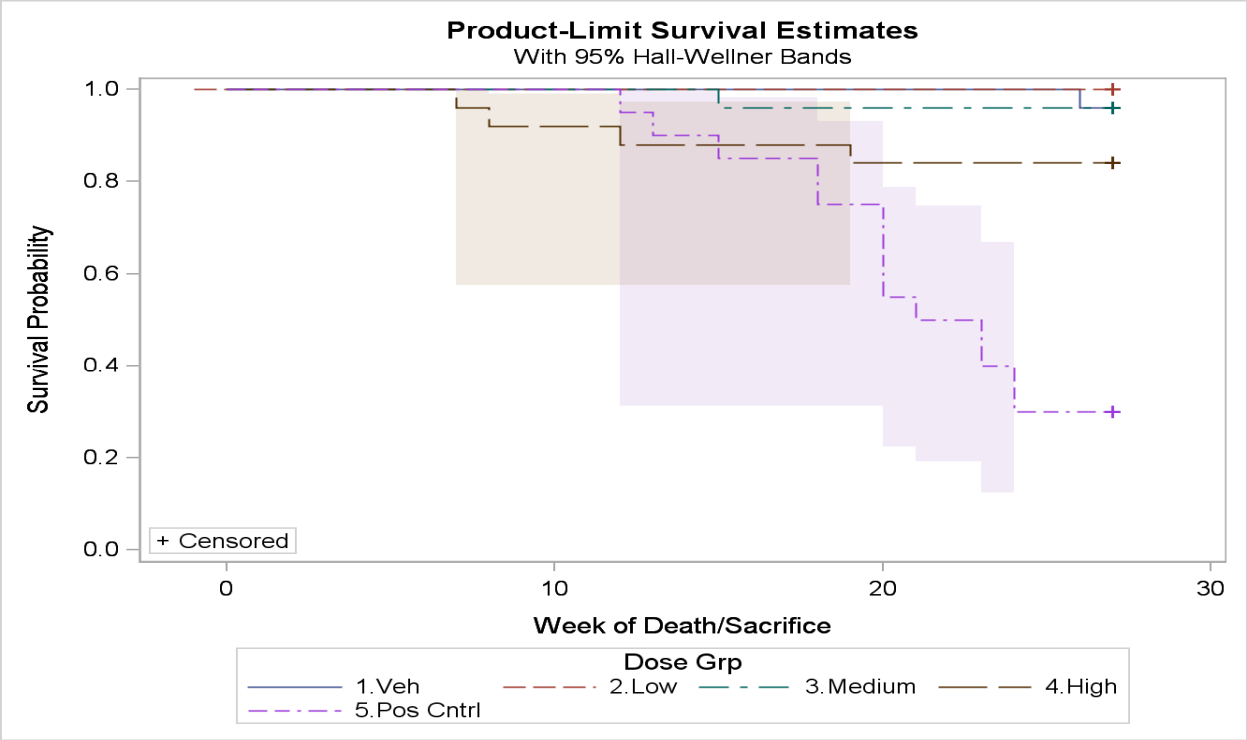


Figure A.1.4 Kaplan-Meier Survival Curves for Female Mice



Again, although this reviewer questions the value of the Kaplan-Meier plots in mice, it is clear that they are chonsistent with the results of statistical tests of survival discussed above. That is, the primary differences in survival are beween group 5, the positive control, and the remaning dose groups.

Appendix 2. FDA Poly-k Tumorigenicity Analysis

The poly-k test, here with k = 3, modifies the original Cochran-Armitage test to adjust for differences in mortality (please see Bailer & Portier, 1988, Bieler & Williams, 1993). The tests used here are small sample exact permutation tests of tumor incidence. When there were no tumors of the specific type being analyzed in either column of the 2x2 table corresponding to a pairwise comparison an argument could be made that the p-value for this test should be 1.0. However, largely for readability, in the tables below these p-values are considered as missing (i.e., corresponding to a null test), denoted by a period ".". Note that the StatXact program used for these analyses adjusts for the variance, which would be 0. Then the significance levels of the test statistics are based on the result of a division by 0, i.e., undefined, and hence StatXact codes these p-values as missing.

For each gender by organ combination the number of animals microscopically analyzed is presented first. Note that indicating an organ was not examined requires a specification in the data (please see section 2.2 above). It is possible that this specification could be missing in some of this data. Then the number of animals at risk could be inflated, and the proportion of animals with tumor would be artificially decreased. Thus, as discussed in Section 1.3.1.5 above, for some of these organs it is possibly more appropriate to define the actual endpoint used in the statistical analysis be the condition of being microscopically analyzed and show the tumor. This does have problems unless treatment groups are not treated equally except for actual treatment.

The entry for each tumor is preceded by the adjusted number of animals at risk for that endpoint. It seems clear that an animal that dies early without having displaying that endpoint reduces the size of the risk set for that getting that particular endpoint. The poly-k test down weights such animals, and as also discussed in Section 1.3.1.5, above, the sum of these poly-k weights seems to be a better estimate of the number of animals at risk of getting that tumor than the simple number of animals analyzed. This sum is given in the row labeled "Adjusted # at risk". In rats the tumor incidence is presented in the the next row, with the significance levels of the tests of trend, and the results of pairwise tests between the high, medium, and low dose groups versus vehicle. In mice the row indicating the tumor incidence also includes the incidence in the positive control, and continues with the results of the test of trend and pairwise tests between the high and medium dose groups. In mice there is a further row with the p-values of the pairwise tests between the low and positive control versus vehicle. For these analyses, incidence in the vehicle, water only, group is used to assess background tumor incidence, and thus whether a tumor is considered to be rare (background incidence < 1%) or common. Note that for this analysis a tumor is only classified as rare if the vehicle control group shows none of that particular tumor.

To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman (HLR) rules discussed in Section 1.3.1.6 are often applied. In this particular case we have a two-year study in rats and an alternative short term study in mice. An adjustment that seems to work is that in the rat study for a roughly 10% overall error rate tests of trend would be considered significant it the

tests for positive trend alone would be tested at 0.005 and 0.025 significance levels, for common and rare tumors respectively. Control-high pairwise would be tested 0.01 and 0.05 significance levels, respectively. In the alternative mouse study all levels comparisons would be tested at a 0.05 level. If we require both the tests of trend and the pairwise comparison to be significant, the only change would be that the pairwise test in the two year study be tested at a 0.10 level for rare tumors. Using these adjustments for other tests, like testing the comparisons between the low and medium dose groups versus vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate.

Table A.2.1, below, shows those rows with at least one tumor with at least one non-multiplicity adjusted test that was statistically significant or close, to a 0.10 level.

Table A.2.1. Potentially Statistically Significant Results for Organ-Tumor Combinations in Rats

Gender / Organ/Tumor	Overall Results Tumor Incidence Veh	Low	Med	High	Significance Levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
Male Rats								
SKIN								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	37.8	42.1				
MYXOSARCOMA	0	0	0	2	.0721	.2657	.	.
THYROID								
# Evaluated	59	60	60	60				
Adj. # at Risk	39.7	38.0	39.0	41.8				
C-CELL ADENOMA	0	2	2	4	.0482	.0640	.2403	.2337
Female Rats								
PANCREAS								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.2	33.9				
ISLET CELL ADENOMA	0	0	0	2	.0527	.2009	.	.
PITUITARY								
# Evaluated	60	60	60	60				
Adj. # at Risk	54.0	56.2	49.8	54.7				
PARS DISTALIS ADENOMA	43	41	41	49	.0158	.0872	.3933	.8452
Adj. # at Risk	41.0	41.3	31.2	33.8				
PARS DISTALIS: CARCINOMA	0	3	4	1	.4539	.4521	.0324	.1249
Adj. # at Risk	54.0	57.1	51.7	54.7				
Pars Dist. Adenoma/Carcinoma	43	44	45	50	.0092	.0463	.1761	.7056

Using the tumor incidence in the vehicle to determine whether a tumor should be cllassified as rare or common, only pars distalis adenoma and pooled adenoma and carcinoma would be classified as common tumors, the rest rare. However, after adjusting for multiplicity using the Haseman-Lin-Rahman rules, in both genders in rats when testing hypotheses of trend or pairwise differences, strictly speaking no tests were statistically significant. Complete tables of tumor incidence are given in Tables A.2.2 and A.2.3, below.

In mice, with the exception of the comparisons between the vehicle and the positive control, in mice, no tests achieved even the nominal 0.10 level, let alone any multiplicity adjusted level of statistical significance. Since it was felt that the tests between the vehicle and positive control seemed to be primarily used to assess the appropriateness of the mouse model, they are not addressed further. Complete tables of tumor incidence are given in Tables A.2.4 and A.2.5, below.

Table A.2.2. Incidence and Results for Organ-Tumor Combinations in Male Rats

	Overall Results							
	Tumor Incidcence				Significance Levels			
Organ/Tumor	Veh	Low	Med	High	ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
ADRENAL GLANDS								
# Evaluated	60	60	60	60				
Adj. # at Risk	40.2	37.8	37.8	41.4				
COMPLEX PHEOCHROMOCYTOMA	1	0	0	0	1	1	1	1
Adj. # at Risk	40.3	37.8	37.9	41.4				
CORTEX: ADENOMA	2	0	2	0	.8369	1	.6623	1
Adj. # at Risk	40.5	38.3	38.1	41.5				
MEDULLA BENIGN PHEOCHROMOCYTOMA	4	4	1	2	.8655	.9050	.9688	.6147
Adj. # at Risk	40.2	37.9	38.2	41.4				
MEDULLA: MALIGNANT PHEOCHROMO.	1	1	1	0	.8344	1	.7403	.7334
Adj. # at Risk	41.4	38.3	38.5	41.5				
Pheocromocytoma Any	6	4	2	2	.9403	.9715	.9636	.8117
BODY (ENTIRE)								
# Evaluated	0	1	0	0				
Adj. # at Risk	0.0	1.0	0.0	0.0				
SARCOMA, NOS	0	1	0	0	1	.	.	.
BRAIN								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.8	38.2	37.8	41.4				
ASTROCYTOMA	1	1	0	0	.9379	1	1	.7468
Adj. # at Risk	39.7	37.8	38.4	41.4				
OLIGODENDROGLIOMA	0	0	1	0	.5097	.	.4935	.
EAR(S)								
# Evaluated	0	0	0	2				
Adj. # at Risk	0.0	0.0	0.0	1.1				
AMELANOTIC MELANOMA	0	0	0	1	1	.	.	.
EXTREMITY								
# Evaluated	46	39	40	37				
Adj. # at Risk	32.0	29.0	29.7	29.9				
SQUAMOUS PAPILLOMA	0	0	0	1	.2458	.4754	.	.
EYES								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.9	37.8	41.4				
MELANOMA	0	1	0	0	.7468	.	.	.4868
JEJUNUM								
# Evaluated	59	54	52	52				
Adj. # at Risk	39.3	35.6	35.3	38.5				
ADENOCARCINOMA	2	0	0	0	1	1	1	1

Table A.2.2.(cont.) Incidence and Results for Organ-Tumor Combinations in Male Rats

	Overall Results							
	Tumor Incidcence				Significance Levels			
Organ/Tumor	Veh	Low	Med	High	ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
KIDNEYS								
# Evaluated	60	60	60	60				
Adj. # at Risk	40.2	37.8	37.8	41.4				
LIPOSARCOMA	1	0	0	0	1	1	1	1
Adj. # at Risk	39.7	37.8	37.8	41.4				
TUBULAR ADENOMA	0	0	1	0	.5065	.	.4868	.
LYMPH/RETIC SYS								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	37.8	41.9				
GRANULOCYTIC LEUKEMIA	0	0	0	1	.2662	.5125	.	.
Adj. # at Risk	41.0	38.3	37.8	41.4				
HISTIOCYTIC SARCOMA	2	1	0	0	.9841	1	1	.8701
Adj. # at Risk	39.7	38.0	37.8	41.4				
LARGE GRANULAR LYMPHOCYTE (LGL)	0	1	0	0	.7468	.	.	.4868
MAMMARY AREAS								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	38.4	41.4				
ADENOCARCINOMA	0	0	1	0	.5097	.	.4935	.
MESENTERIC LN								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	37.8	41.4				
HEMANGIOSARCOMA	0	0	1	0	.5065	.	.4868	.
Adj. # at Risk	39.8	37.8	37.8	41.4				
SARCOMA, NOS	1	0	0	0	1	1	1	1
MESENTERY/PERITO								
# Evaluated	1	2	0	0				
Adj. # at Risk	0.8	1.5	0.0	0.0				
SARCOMA, NOS	0	1	0	0	1	.	.	.
PANCREAS								
# Evaluated	60	60	60	60				
Adj. # at Risk	40.3	38.8	38.1	41.8				
ISLET CELL ADENOMA	2	5	4	2	.7399	.7016	.3131	.1948
Adj. # at Risk	40.2	37.9	38.0	41.5				
ISLET CELL CARCINOMA	1	1	3	1	.5334	.7593	.2785	.7334
Adj. # at Risk	40.7	38.9	38.3	42.0				
Islet Cell Adenoma/Carcinoma	3	6	7	3	.7309	.6854	.1350	.2152
PITUITARY								
# Evaluated	60	60	60	60				
Adj. # at Risk	47.8	44.6	47.7	49.5				
PARS DISTALIS ADENOMA	31	23	30	28	.6681	.8637	.6670	.9386
PREPUT/CLIT GL								
# Evaluated	0	0	0	1				
Adj. # at Risk	0.0	0.0	0.0	1.0				
ADENOMA	0	0	0	1	1	.	.	.
PROSTATE								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	37.8	41.4				
ADENOMA	0	0	0	1	.2662	.5125	.	.
RETROPERITONEAL								
# Evaluated	0	0	0	1				
Adj. # at Risk	0.0	0.0	0.0	1.0				
SARCOMA, NOS	0	0	0	1	1	.	.	.

Table A.2.2. (cont.) Incidence and Results for Organ-Tumor Combinations in Male Rats

	Overall Results							
	Tumor Incidcence				Significance Levels			
Organ/Tumor	Veh	Low	Med	High	ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
SKIN								
# Evaluated	60	60	60	60				
Adj. # at Risk	40.3	37.9	37.8	41.4				
FIBROMA	1	1	0	0	.9346	1	1	.7334
Adj. # at Risk	39.7	37.8	37.8	41.5				
FIBROSARCOMA	0	0	0	1	.2662	.5125	.	.
Adj. # at Risk	40.6	37.8	37.8	41.4				
HEMANGIOSARCOMA	1	0	0	0	1	1	1	1
Adj. # at Risk	40.6	37.9	39.3	42.2				
KERATOACANTHOMA	4	1	5	1	.8522	.9759	.4836	.9667
Adj. # at Risk	39.8	37.8	37.8	41.4				
MALIGNANT BASAL CELL TUMOR	1	0	0	1	.4629	.7655	1	1
Adj. # at Risk	39.7	37.8	37.8	42.1				
MYXOSARCOMA	0	0	0	2	.0721	.2657	.	.
Adj. # at Risk	39.7	37.8	38.6	41.4				
SARCOMA, NOS	0	0	1	0	.5097	.	.4935	.
Adj. # at Risk	39.7	38.8	37.8	41.4				
SCHWANNOMA	0	2	0	0	.8137	.	.	.2403
Adj. # at Risk	39.7	37.8	37.8	41.4				
SEBACEOUS CELL ADENOMA	0	0	0	1	.2662	.5125	.	.
Adj. # at Risk	39.7	37.9	37.8	41.4				
SQUAMOUS CELL PAPILLOMA	0	1	0	0	.7468	.	.	.4868
SPLEEN								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	38.3	41.4				
HEMANGIOMA	0	0	1	0	.5097	.	.4935	.
Adj. # at Risk	39.7	37.8	37.8	41.4				
HEMANGIOSARCOMA	0	0	1	0	.5065	.	.4868	.
Adj. # at Risk	39.7	37.8	37.8	41.4				
SARCOMA, NOS	0	1	0	0	.7468	.	.	.4868
Systemic								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	38.3	41.4				
Hemangioma/Hemangiosarcoma	0	0	1	0	.5097	.	.4935	.
Adj. # at Risk	39.7	37.8	38.3	41.4				
Hemangioma	0	0	1	0	.5097	.	.4935	.
TAIL								
# Evaluated	11	8	13	15				
Adj. # at Risk	7.5	6.3	10.9	10.5				
KERATOACANTHOMA	0	1	0	0	.7879	.	.	.4615
Adj. # at Risk	7.6	6.2	10.9	10.5				
SCHWANNOMA	1	0	0	0	1	1	1	1
TESTES								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	38.1	41.4				
BENIGN INTERSTITIAL CELL TUMOR	0	0	2	1	.2184	.5125	.2403	.
Adj. # at Risk	40.4	37.8	37.8	41.4				
SEMINOMA	1	0	0	0	1	1	1	1

Table A.2.2. (cont.) Incidence and Results for Organ-Tumor Combinations in Male Rats

Organ/Tumor	Overall Results Tumor Incidcence Veh	Low	Med	High	Significance Levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
THYROID								
# Evaluated	59	60	60	60				
Adj. # at Risk	39.7	38.0	39.0	41.8				
C-CELL ADENOMA	0	2	2	4	.0482	.0640	.2403	.2337
Adj. # at Risk	39.8	37.9	37.8	41.4				
C-CELL CARCINOMA	1	1	0	0	.9371	1	1	.7400
Adj. # at Risk	39.8	38.1	39.0	41.8				
C-Cell Adenoma/Carcinoma	1	3	2	4	.1571	.1955	.4901	.2977
Adj. # at Risk	40.3	38.9	38.4	42.2				
FOLLICULAR CELL ADENOMA	3	2	3	4	.2974	.5277	.6376	.8043
VASCULAR TISSUE								
# Evaluated	60	60	60	60				
Adj. # at Risk	39.7	37.8	38.3	41.4				
HEMANGIOMA	0	0	1	0	.5097	.	.4935	.
Adj. # at Risk	40.6	37.8	37.9	41.4				
HEMANGIOSARCOMA	1	0	2	0	.7020	1	.4704	1
ZYMBAL'S GLAND								
# Evaluated	1	0	0	1				
Adj. # at Risk	0.9	0.0	0.0	1.0				
ADENOMA	0	0	0	1	1	.	.	.
Adj. # at Risk	1.0	0.0	0.0	0.1				
CARCINOMA	1	0	0	0	1	.	.	.

Table A.2.3. Tumor Incidence and Test Results for Organ-Tumor Combinations in Female Rats

Organ/Tumor	Overall Results Tumor Incidence Veh	Low	Med	High	Significance levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
ADRENAL GLANDS								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.2	33.7				
COMPLEX PHEOCHROMOCYTOMA	1	0	0	0	1	1	1	1
Adj. # at Risk	41.0	40.4	29.5	33.7				
CORTEX: ADENOMA	1	0	1	0	.6843	1	.6675	1
Adj. # at Risk	41.0	40.4	29.2	33.8				
CORTEX: CARCINOMA	0	0	0	1	.2324	.4521	.	.
Adj. # at Risk	41.0	40.4	29.5	33.8				
Cortex Adenoma/Carcinoma	1	0	1	1	.3274	.7032	.6675	1
Adj. # at Risk	41.4	40.4	29.8	34.0				
MEDULLA BENIGN PHEOCHROMOCYTOMA	1	1	1	2	.2037	.4181	.6605	.7469
Adj. # at Risk	41.0	40.4	29.2	34.1				
MEDULLA: MALIGNANT PHEOCHROM.	1	0	0	1	.4203	.7112	1	1
Adj. # at Risk	41.4	40.4	29.8	34.4				
Pheocromocytoma Any	3	1	1	3	.2641	.5690	.8896	.9391
EAR(S)								
# Evaluated	0	0	2	0				
Adj. # at Risk	0.0	0.0	1.8	0.0				
AMELANOTIC MELANOMA	0	0	1	0	1	.	.	.
Adj. # at Risk	0.0	0.0	1.8	0.0				
LIPOMA	0	0	1	0	1	.	.	.

Table A.2.3. (cont.) Tumor Incidence and Test Results for Organ-Tumor Combinations in Female Rats

Organ/Tumor	Overall Results Tumor Incidence Veh	Low	Med	High	Significance levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
LYMPH/RETIC SYS								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.6	41.2	29.8	33.7				
HISTIOCYTIC SARCOMA	2	2	2	0	.8799	1	.5524	.6922
Adj. # at Risk	41.0	40.4	29.2	33.7				
LARGE GRANULAR LYMPHOCYTE (LGL)	1	0	0	0	1	1	1	1
Adj. # at Risk	41.0	40.4	29.2	33.8				
MALIGNANT LYMPHOMA	0	0	0	1	.2324	.4521	.	.
MAMMARY AREAS								
# Evaluated	60	60	60	60				
Adj. # at Risk	46.3	46.3	35.6	42.6				
ADENOCARCINOMA	20	20	15	19	.4351	.5193	.6105	.5832
Adj. # at Risk	41.0	40.7	30.3	35.5				
ADENOMA	4	1	3	5	.1207	.4137	.6496	.9726
Adj. # at Risk	46.5	47.5	40.5	41.6				
FIBROADENOMA	31	29	26	26	.5865	.7310	.6785	.7851
MESENTERIC LN								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.2	34.3				
HEMANGIOMA	0	0	0	1	.2378	.4595	.	.
Adj. # at Risk	41.0	40.4	29.2	33.8				
HEMANGIOSARCOMA	0	0	0	1	.2324	.4521	.	.
MUSCLE (OTHER)								
# Evaluated	0	1	0	1				
Adj. # at Risk	0.0	1.0	0.0	1.0				
SARCOMA, NOS	0	0	0	1	1	.	.	.
OVARIES								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.2	33.7				
MESOTHELIOMA	0	1	0	0	.7183	.	.	.5000
PANCREAS								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.2	33.9				
ISLET CELL ADENOMA	0	0	0	2	.0527	.2009	.	.
Adj. # at Risk	41.5	40.5	29.5	33.7				
ISLET CELL CARCINOMA	2	2	1	0	.9133	1	.8053	.6828
Adj. # at Risk	41.5	40.5	29.5	33.9				
Islet Cell Adenoma/Carcinoma	2	2	1	2	.4185	.6063	.8053	.6828
PITUITARY								
# Evaluated	60	60	60	60				
Adj. # at Risk	54.0	56.2	49.8	54.7				
PARS DISTALIS ADENOMA	43	41	41	49	.0158	.0872	.3933	.8452
Adj. # at Risk	41.0	41.3	31.2	33.8				
PARS DISTALIS: CARCINOMA	0	3	4	1	.4539	.4521	.0324	.1249
Adj. # at Risk	54.0	57.1	51.7	54.7				
Pars Distalis Adenoma/Carcinoma	43	44	45	50	.0092	.0463	.1761	.7056

Table A.2.3. (cont.) Tumor Incidence and Test Results for Organ-Tumor Combinations in Female Rats

Overall Results

Organ/Tumor	Tumor Incidence Veh	Low	Med	High	Significance levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
SKIN								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.5	40.4	30.2	33.8				
FIBROSARCOMA	1	0	3	1	.3354	.6964	.1995	1
Adj. # at Risk	41.0	40.5	29.2	33.7				
KERATOACANTHOMA	1	1	0	0	.9221	1	1	.7532
Adj. # at Risk	41.0	40.4	29.2	33.7				
MALIGNANT BASAL CELL TUMOR	1	0	0	0	1	1	1	1
Adj. # at Risk	41.0	40.8	29.2	33.7				
SARCOMA, NOS	0	1	0	0	.7183	.	.	.5000
Adj. # at Risk	41.7	40.7	29.2	33.7				
SCHWANNOMA	1	1	0	0	.9192	1	1	.7469
Adj. # at Risk	41.0	40.4	29.2	33.7				
SQUAMOUS CELL CARCINOMA	1	0	0	0	1	1	1	1
Adj. # at Risk	41.0	40.9	29.2	34.2				
SQUAMOUS CELL PAPILLOMA	0	1	0	1	.2863	.4595	.	.5000
Adj. # at Risk	41.0	40.9	29.2	34.2				
Squamous Cell Papilloma/Carc.	1	1	0	1	.5121	.7112	1	.7532
STOMACH								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.2	34.4				
FORESTOMACH: SQUAMOUS CELL PAP.	0	0	0	1	.2378	.4595	.	.
Systemic								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.4	40.4	29.2	34.3				
Hemagioma/Hemangiosarcoma	1	0	0	1	.4177	.7045	1	1
Adj. # at Risk	41.4	40.4	29.2	34.3				
Hemangioma	1	0	0	1	.4177	.7045	1	1
TAIL								
# Evaluated	7	10	1	7				
Adj. # at Risk	6.8	9.2	0.4	4.5				
SQUAMOUS CELL ADENOMA	1	0	0	0	1	1	.	1
Adj. # at Risk	6.6	9.3	0.4	4.5				
SQUAMOUS CELL PAPILLOMA	0	1	0	0	.6842	.	.	.6000
THYROID								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.5	41.6	30.2	34.6				
C-CELL ADENOMA	4	3	2	3	.5092	.6998	.8116	.7840
Adj. # at Risk	41.6	40.4	29.5	34.1				
C-CELL CARCINOMA	1	0	1	1	.3311	.7045	.6605	1
Adj. # at Risk	42.1	41.6	30.6	35.0				
C-Cell Adenoma/Carcinoma	5	3	3	4	.4055	.6421	.7319	.8599
Adj. # at Risk	41.0	41.1	30.6	33.7				
FOLLICULAR CELL ADENOMA	1	1	2	0	.7344	1	.3920	.7593
Adj. # at Risk	41.0	40.4	29.2	34.2				
FOLLICULAR CELL CARCINOMA	0	0	0	1	.2378	.4595	.	.
Adj. # at Risk	41.0	41.1	30.6	34.2				
Foll.Cell Adenoma/Carcinoma	1	1	2	1	.4316	.7112	.3920	.7593

Table A.2.3. (cont.) Tumor Incidence and Test Results for Organ-Tumor Combinations in Female Rats

Organ/Tumor	Overall Results Tumor Incidence Veh	Low	Med	High	Significance levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh
UTERUS W/ CERVIX								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.2	40.4	29.7	33.7				
BENIGN GRANULAR CELL TUMOR	1	0	1	0	.6809	1	.6605	1
Adj. # at Risk	41.7	41.2	29.5	33.8				
ENDOMETRIAL STROMAL POLYP	2	2	1	1	.6782	.8356	.8053	.6922
Adj. # at Risk	41.4	40.4	29.2	33.7				
HEMANGIOMA	1	0	0	0	1	1	1	1
Adj. # at Risk	41.0	40.4	29.2	34.1				
POLYP, CERVICAL	0	1	0	1	.2863	.4595	.	.5000
Adj. # at Risk	41.6	40.5	29.2	33.7				
SCHWANNOMA	2	2	0	0	.9684	1	1	.6828
VAGINA								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.0	40.4	29.5	33.7				
BENIGN GRANULAR CELL TUMOR	1	0	1	0	.6843	1	.6675	1
VASCULAR TISSUE								
# Evaluated	60	60	60	60				
Adj. # at Risk	41.4	40.4	29.2	34.3				
HEMANGIOMA	1	0	0	1	.4177	.7045	1	1
Adj. # at Risk	41.0	40.4	29.2	33.8				
HEMANGIOSARCOMA	0	0	0	1	.2324	.4521	.	.
ZYMBAL'S GLAND								
# Evaluated	1	0	1	0				
Adj. # at Risk	0.7	0.0	1.0	0.0				
CARCINOMA	0	0	1	0	1	.	.	.
Adj. # at Risk	1.0	0.0	0.7	0.0				
SARCOMA, NOS	1	0	0	0	1	.	.	.

The following two tables give similar results in mice. Again, for each identified neoplasm within organ, the adjusted number at risk is presented first. The next row provides the tumor incidence over all five dose groups, followed by the significance levels of test of trend over the actual dose groups 1-4, and then followed by the results of the comparisons between the high dose and the high-medium dose, respectively, with the vehicle. The next row, with slightly indented p-values lined up with those of the preceding row, presents the significance levels of the comparisons between the low and positive control, respectively, with vehicle.

Table A.2.4. Tumor Incidence and Test Results for Organ-Tumor Combinations in Male Tg.rash2 Mice

Overall Results

Organ/Tumor	Tumor Incidence Veh	Low	Med	High	+Ctrl	Significance Levels ptrend	phigh vsVeh	plow vsVeh	pmed p+cntrl vsVeh	vsVeh
Body, Whole/Cavity										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	25.0	24.7	25.0	24.1	12.2					
M-Hemangiosarcoma	1	1	0	2	0	.2279	.7449	.4844	1	1
Adj. # at Risk	25.0	24.7	25.0	24.1	17.1					
M-Lymphosarcoma	0	0	0	0	11	.	.	.	.	<0.0001
Liver										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	25.0	24.7	25.0	24.1	12.2					
B-Adenoma, hepatocellular	0	0	1	0	0	.5000	.	.	.5000	.
Lung										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	25.0	24.7	25.0	24.1	12.8					
Adenoma/Carc.bronch.alveolar	4	0	2	2	1	.5768	1	.8961	.9053	.8781
Adj. # at Risk	25.0	24.7	25.0	24.1	12.8					
B-Adenoma, bronchiolo-alveolar	4	0	2	2	1	.5768	1	.8961	.9053	.8781
Adj. # at Risk	25.0	24.7	25.0	24.1	12.2					
M-Carcinoma, bronchiolo-alv.	0	0	0	1	0	.2449	.	.4898	.	.
Skin/Subcutis										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	25.0	24.7	25.0	24.1	14.4					
B-Papilloma, squamous cell	0	0	0	0	7	.	.	.	.	.0002
Stomach, Nonglandular										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	25.0	24.7	25.0	24.1	14.7					
B-Papilloma, squamous cell	1	0	0	1	9	.4317	1	.7449	1	.0001
Adj. # at Risk	25.0	24.7	25.0	24.1	14.4					
M-Carcinoma, squamous cell	0	0	0	0	3	.	.	.	.	.0398
Thymus										
# Evaluated	24	25	23	25	19					
Adj. # at Risk	24.0	24.7	23.0	24.1	11.7					
B-Thymoma	0	0	0	0	1	.	.	.	.	.3143
Thyroid										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	25.0	24.7	25.0	24.1	12.5					
M-Carcinoma, squamous cell	0	0	0	0	1	.	.	.	.	.3243

Table A.2.5. Tumor Incidence and Test Results for Organ-Tumor Combinations in Female Tg.rash2 Mice

Organ/Tumor	Overall Results Tumor Incidence Veh	Low	Med	High	+Ctrl	Significance Levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh	p+cntrl vsVeh
Body, Whole/Cavity										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	24.9	25.0	24.2	21.5	11.7					
B-Hemangioma	0	0	1	0	0	.4787	.	.5000	.	.
Adj. # at Risk	24.9	25.0	25.0	21.5	13.2					
Hemangioma/Hemangiosarcoma	1	2	2	2	3	.2976	.5156	.5156	.4489	.1148
Adj. # at Risk	24.9	25.0	25.0	21.5	13.2					
M-Hemangiosarcoma	1	2	1	2	3	.2938	.5156	.7653	.4489	.1148
Adj. # at Risk	24.9	25.0	24.2	21.5	17.9					
M-Lymphosarcoma	0	0	0	0	14	.	.	.	.	<0.0001
Harderian Gland										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	24.9	25.0	24.2	21.5	11.7					
B-Adenoma	1	1	0	0	0	.9369	.7653	1	1	1
Lung										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	24.9	25.0	24.2	21.5	11.7					
B-Adenoma, bronchiolo-alveolar	2	2	0	0	0	.9799	.7110	1	1	1
Adj. # at Risk	24.9	25.0	24.2	21.5	11.7					
M-Carcinoma, bronchiolo-alv.	0	1	0	0	0	.7447	.5102	.	.	.
Skin/Subcutis										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	24.9	25.0	24.2	21.5	14.8					
B-Papilloma, squamous cell	0	2	0	0	9	.7996	.2551	.	.	<0.0001
Adj. # at Risk	24.9	25.0	24.2	21.5	12.0					
M-Carcinoma, Zymbal's gland	0	0	0	0	2	.	.	.	.	.0924
Stomach, Nonglandular										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	24.9	25.0	24.2	21.5	15.0					
B-Papilloma, squamous cell	0	0	0	0	13	.	.	.	.	<0.0001
Adj. # at Risk	24.9	25.0	24.2	21.5	12.5					
M-Carcinoma, squamous cell	0	0	0	0	1	.	.	.	.	.3333
Thymus										
# Evaluated	25	24	24	24	20					
Adj. # at Risk	24.9	24.0	24.0	20.5	11.7					
B-Thymoma	1	0	0	0	0	1	1	1	1	1

Table A.2.5. (cont.) Tumor Incidence and Test Results for Organ-Tumor Combinations in Male Tg.rash2 Mice

Organ/Tumor	Overall Results Tumor Incidence Veh	Low	Med	High	+Ctrl	Significance Levels ptrend	phigh vsVeh	pmed vsVeh	plow vsVeh	p+cntrl vsVeh
Uterus										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	24.9	25.0	24.2	21.5	12.6					
B-Polyp, endometrial stromal	0	0	0	0	6	.	.	.	.	.0005
Vagina										
# Evaluated	25	25	25	25	20					
Adj. # at Risk	24.9	25.0	24.2	21.5	12.0					
B-Papilloma, squamous cell	0	0	0	0	2	.	.	.	.	.0924
Adj. # at Risk	24.9	25.0	24.2	21.5	11.7					
M-Carcinoma, squamous cell	0	0	0	0	1	.	.	.	.	.3143

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEVEN F THOMSON
11/17/2015
Statistical Carcinogenicity Review
(Late, was informed panorama would be archive)

KARL K LIN
11/17/2015
Concur with review

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

CLINICAL STUDIES

NDA/BLA #:	NDA 207-988
Drug Name:	Zurampic (Lesinurad) 200 mg QD
Indication(s):	Use in combination with xanthine oxidase inhibitor for the chronic treatment of hyperuricemia associated with gout
Applicant:	Ardea Biosciences, Inc.
Date(s):	Stamp date: December 29, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Yu (Jade) Wang
Concurring Reviewers:	Ruthanna C. Davi, Division of Biometrics II Deputy Director
	Tom Permutt, Division of Biometrics II Director
Medical Division:	Division of Pulmonary, Allergy and Rheumatology Products.
Clinical Team:	Rosemarie Neuner, Medical Reviewer
	Sarah Yim, Medical Team Leader
Project Manager:	Michelle Jordan Garner

Keywords:

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1 EXECUTIVE SUMMARY

Ardea Biosciences, Inc. has proposed Lesinurad (RDEA594) 200 mg once daily (qd), an add-on therapy to a xanthine oxidase inhibitor (XOI) for the chronic treatment of hyperuricemia associated with gout.

Effectiveness and safety of two different dosages of Lesinurad (LESU) were examined with this submission: LESU200mg + XOI and LESU400mg + XOI. The review focused on three phase 3 studies to investigate the efficacy of Lesinurad in terms of serum uric acid (sUA) level, gout flare rate and tophi resolution.

The contribution of LESU over placebo in the presence of background allopurinol (ALLO) for all major endpoints was directly examined. In support of the efficacy of LESU in the presence of ALLO use, after 6 months of treatment, patients assigned to receive LESU 200 and LESU 400 showed statistically greater improvement in pre-defined sUA responder rate than patients assigned to receive placebo. However, statistical significance was not reached in the clinical endpoints, tophi resolution and gout flare rate. In the presence of ALLO use, neither dose of LESU was found to be statistically significant better than placebo in terms of these endpoints.

For the efficacy of LESU over placebo in the presence of background febuxostat (FBX) use, after 6 months of treatment, patients assigned to receive LESU 200 did not show statistically greater improvement in pre-defined sUA responder rate than patients assigned to receive placebo.

Subgroup analyses were conducted to investigate the level of consistency or heterogeneity of the treatment effect across subgroups of interest, including demographic factors age, sex, race, region, and baseline disease characteristics including background allopurinol dose, baseline renal impairment, and baseline sUA group. Possibly due to the small number of females included in the study of a male pre-dominant disease and lack of multiplicity control, among the series of subgroup analysis conducted, there are two statistically significant findings, one of sex, one of baseline sUA level. While the one with sex may due to chance, the one found with sUA level in study investigating the add-on effect to Febuxostat is reasonable. However, as the primary efficacy was not established in this study, interpretation is complicated.

This submission supports effectiveness of LESU200mg in the presence of ALLO for once daily treatment of hyperuricemia associated with gout (b) (4) in terms of the primary efficacy endpoint, sUA responder rate at month 6. However, no statistically significant benefit for lesinurad over placebo in terms of any of the secondary clinical efficacy endpoints was found.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

The Applicant, Ardea Biosciences, Inc. seeks to market lesinurad (RDEA594) 200 mg once daily (qd) in combination with a xanthine oxidase inhibitor (XOI) for the chronic treatment of hyperuricemia associated with gout.

Hyperuricemia is a metabolic disorder with an abnormally high level of uric acid in the blood. In the pH conditions of body fluid, uric acid exists largely as urate, the ion form. In humans, the upper end of the normal range is 6 mg/dL for women and 6.8 mg/dL for men. Causes of hyperuricemia can be classified into three functional types: increased production of uric acid, decreased excretion of uric acid, and mixed type (Wikipedia).

Gout results from hyperuricemia. It is a type of inflammatory arthritis induced by the deposition of monosodium urate crystals in synovial fluid and other tissues (Neogi, 2011). In most gout patients, inadequate uric acid excretion leads to hyperuicemia (Vazquez-Mellado, 2007) and subsequent deposition of urate crystals. These crystals can form in and around joints causing recurrent attacks of inflammatory arthritis. Eventually chronic, progressive arthropathy and tophus formation can occur (Schlesinger, 2011). Accordingly, the course of classic gout passes through three distinct stages: asymptomatic hyperuricemia, acute intermittent gout, and chronic tophaceous gout or advanced gout (Klippel, 2007).

Figure 1(Burns & Wortmann, 2011) illustrates the pathogenic steps of gouts together with gout treatments and prophylaxis drugs targeting these steps. These drugs have either inhibitory or stimulatory effects on the targeted steps. They were classified by the steps: xanthine oxidase inhibitors, uricosurics, uricases and inflammation inhibitors.

Among the classes, the use of XOI is recommended by treatment guidelines as the first line treatment of gout. Allopurinol (ALLO) and Febuxostat (FBX) are oral XOIs approved by the FDA. Table 1 describes the main efficacy and safety summary of these two XOI. The current XOI drugs at the prescribed doses have an efficacy range from 42% to 67% in terms of response rate.

Further information and description of the typical disease characteristics of gout and hyperuricemia and possible treatment options may be found in the FDA clinical review of this application.

According to the sponsor, the proposed drug, lesinurad is a selective uric acid reabsorption inhibitor that inhibits uric acid transporter 1 (URAT1). The sponsor contends that lesinurad increases uric acid excretion and thereby lower sUA. The sponsor indicates that Lesinurad is being developed to be used with an XOI, allopurinol or febuxostat, in patients with gout who have uncontrolled disease. In the Applicant's regulatory submission, lesinurad is not

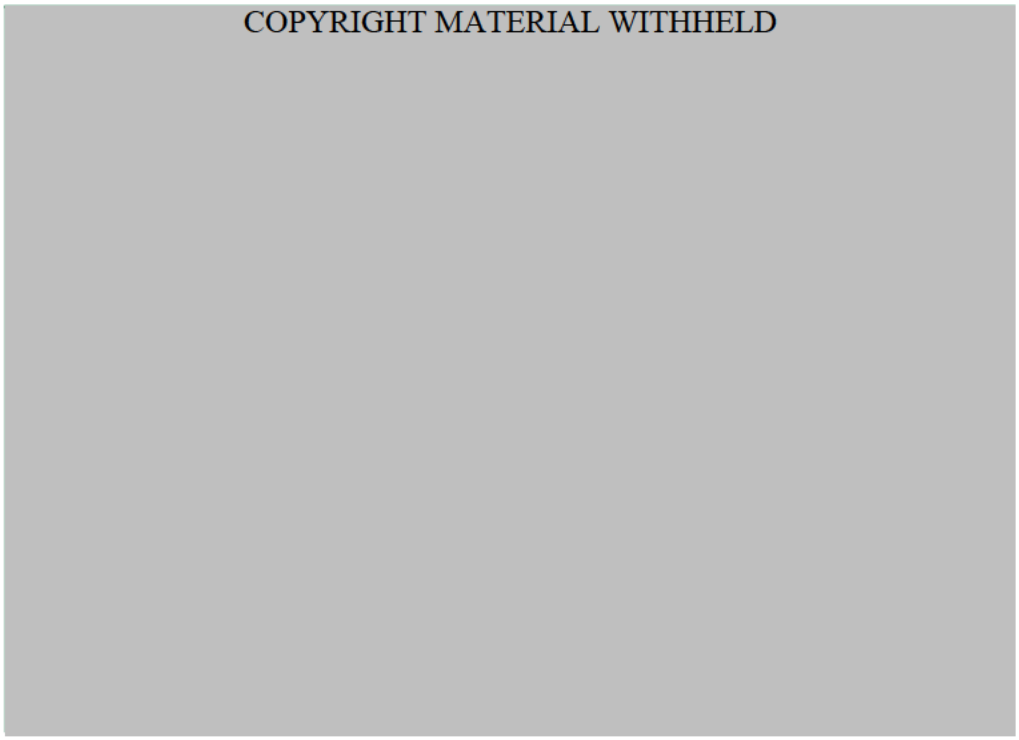
recommended for the treatment of asymptomatic hyperuricemia and it is indicated that it should not be used as monotherapy.

Table 1: Summary of Efficacy of the XOI Approved by the FDA

Drug Name	Dose/Dosing Frequency	Response Rate	Patient with Kidney Disease	Safety Concern
Allopurinol	<300 mg QD			Life-threatening allergic reaction
	300 mg QD	42%		
	>300 mg QD	NA	No	
Febuxostat	40mg QD	45%	Yes	Cardiovascular adverse events
	80mg QD	67%		

Source: Reviewer

Figure 1: Targets for Intervention in the Treatment and Prophylaxis of Gout



Source: Figure 1 in Burns & Wortmann, 2011.

2.1.2 History of Drug Development

During both IND 102128 development and the Pre-NDA meeting, statistical advice regarding the design and analysis of the phase 3 trials has been given to the Applicant. Advice and comments from the Division were delivered through one EOP II meeting, two rounds of Protocol/SAP reviews and one Pre-NDA meeting. Table 2 ummarizes these interactions.

Table 2: List of Meeting Minutes, Protocol/SAP Reviews and Correspondence to the Applicant

Document	Meeting Date/ Document Date	Topic	Reference Number
EOP II Meeting Minutes	July 21, 2011/ August, 29, 2011	End-of-Phase-2 meeting to discuss plans for the phase 3 program and registration activities to support a new drug application	IND 102128
Information Request and Comments	March 30, 2012	Review comments on protocols and SAP of four phase 3 studies: 301, 302, 303, and 304.	IND 102128
Statistical Review	July 17, 2012 July 31, 2012 August 10, 2012	Review of Response to comments for Studies 301, 302, 303 and 304	IND 102128
Statistical Review	September 19, 2012	Review of SAP for Study 303	IND 102128
Statistical Review	October 13, 2013	Review of SAP for Study 301, 302 and 304	IND 102128

There are several topics that have been discussed extensively during the development of the program:

1. Type I error control has been discussed extensively over the IND process. Multiple comments were given to the Applicant to clarify the plan for control of type I error in the complex situation of multiple doses and multiple endpoints under study.

2. Missing data handling comments have been given to the Applicant regarding multiple situations including None Responder Imputation for responder analysis and general concern with collection of post-study-treatment-discontinuation efficacy outcomes.

2.1.3 Specific Studies Reviewed

The Applicant has submitted the results of three randomized, placebo controlled, double-blind, multicenter, pivotal core studies of 12 month duration. Studies 301 and 302 are two replicate studies that evaluated the efficacy and safety of LESU 200mg and 400 mg qd versus placebo with ALLO as background medication in subjects who warranted additional therapy despite ALLO use. Study 304 evaluated the efficacy and safety of LESU 200mg and 400 mg qd versus placebo with FBX 80 mg as background medication in subjects who have tophaceous gout and elevated sUA. Design elements and study population are described in detail in Table 3.

Table 3: List of Key Phase 3 Studies in the Clinical Development Program

	Treatment Period	# of Randomized Subjects per Arm	Study Population
301 (CLEAR 1)	12 month	PBO/LESU200 /LESU400 =203/202/202 with ALLO as background therapy	Inadequate responders to ALLO: -Had a history of at least 2 gout flares in the prior year -Already on a stable medically appropriate dose of ALLO for at least 8 weeks at screening -Had sUA levels repeatedly greater than the recommended treatment goal
302 (CLEAR 2)	12 month	PBO/LESU200 /LESU400 =206/204/201 with ALLO as background therapy	
304 (CRYSTAL)	12 month	PBO/LESU200 /LESU400=109/106/109 with FBX as background therapy	Subjects with: -Tophaceous gout -Elevated sUA

Source: Reviewer
Abbreviations: ALLO, Allopurinol; FBX, Febuxostat.

2.1.4 Statistical Issues

2.2 Data Sources

The ADaM and SDTM data sets for the key phase 3 studies were submitted electronically and utilized in the review of this application.

All submitted data sets were found to be adequately documented and organized.

3 STATISTICAL EVALUATION

Lesinurad is intended in this submission as an add-on therapy to a background XO drug, allopurinol (replicate studies 301 and 302) or febuxostat (study 304), respectively. So, study design, analysis method, and results of studies 301 and 302 are reviewed together; those of study 304 are reviewed separately.

3.1 Data and Analysis Quality

The Applicant's clinical study reports documented two significant data quality issues:

1. GCP non-compliance in two investigational sites affecting three phase 3 studies.

Data related to subjects who received randomized drugs at GCP non-compliance sites were not included in the clinical study reports. Table 4 summarizes the numbers of subjects and sites being affected.

Table 4: Summary Table of GCP Non-Compliance

	301	303	304
Number of sites	2	2	2
Number of screened subjects	25	1	22
Number of randomized subjects	4	0	2

2. Mis-stratification during the randomization process

There were differences in the values reported for the tophi status during screening and day -7 renal function (i.e., the stratification factors) between information collected as part of the electronic data capture (EDC) and the interactive voice response system (IVRS). There were seven subjects for whom tophus at screening was recorded as absent by the EDC system but present by the IVRS system. In addition, there were six subjects for whom tophus at screening was recorded as present by the EDC system but absent by the IVRS system. For study 301 and 302, there is one subject that was mis-categorized with respect to day -7 renal function groups in each study. The EDC values were ultimately deemed correct. The outcome of these discrepancies is that in these cases, subjects were randomized to treatment as part of an incorrect randomization stratum.

In the Applicant's data analyses, such cases were handled differently for different analyses: for all efficacy inferential analyses, the IVRS randomized stratification factor values were used; for subgroup analyses, and a dedicated sensitivity analysis addressing this issue, the actual EDC stratification factor values were used. This is an appropriate approach in that the stratification factor for the efficacy analysis should represent that actually used for randomization (i.e. the IVRS value) even though the EDC values where ultimately deemed correct. In the case of the subgroup analyses, treatment assignment was random despite the fact that some were randomized as part of an incorrect stratum so that there is no need to adhere to the incorrect IVRS stratification variable and it is most appropriate to subgroup based upon the accurate EDC values.

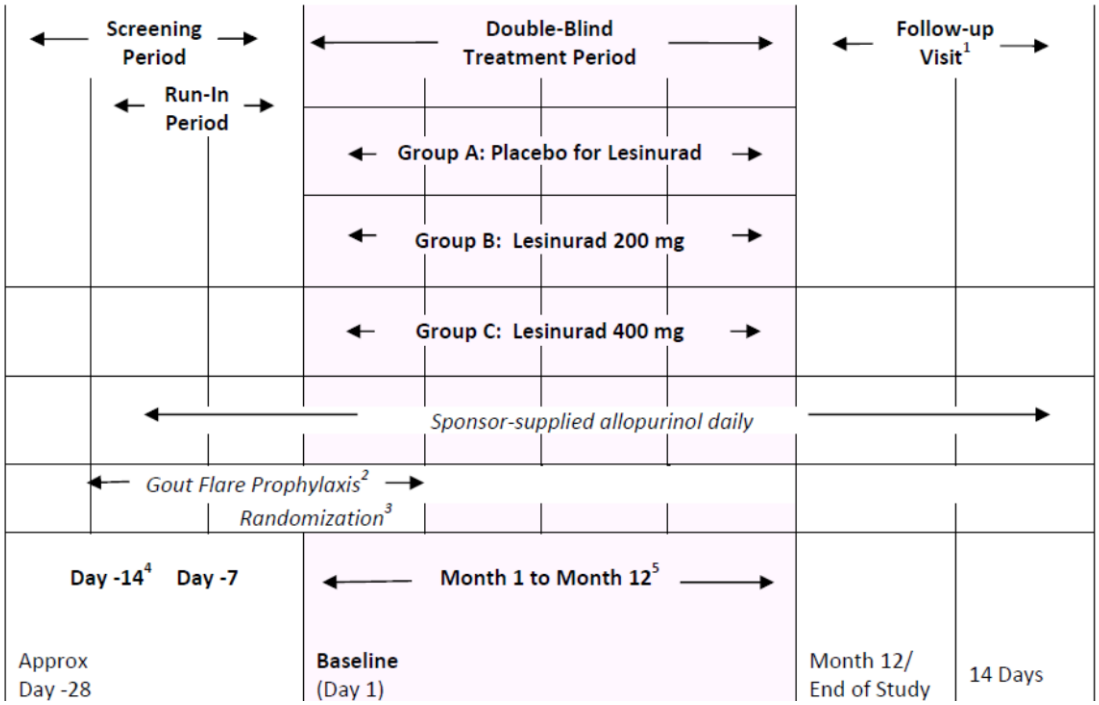
The impact of these discrepancies on the efficacy analyses is likely negligible in that only a small proportion of subject were affected and although these subjects were enrolled as part of an incorrect stratum, the assignment of treatment to that subject was nonetheless random.

3.2 Evaluation of Efficacy

3.2.1 Study Design

The designs of the three pivotal Phase 3 lesinurad add-on studies were very similar in terms of most of the design elements except for target patient population and background XOI drug. So the description here focuses on studies 301 and 302, differences between study 304 and the two will be pointed out. Figure 2 is the design scheme for studies 301 and 302.

Figure 2: Design Scheme for Studies 301 and 302



Source: Figure 1 in Applicant's Study 301 and 302 SAP.

Study 301 and 302 were replicate phase 3, randomized, double-blind, multicenter, placebo-controlled studies to compare the efficacy and safety of lesinurad in combination with allopurinol versus allopurinol alone in gout patients who have had an inadequate hypouricemic response to allopurinol. The target patient population was defined as patients with gout who had sUA≥6.5 mg/dL, reported at least 2 gout flares in the prior year and had been on a stable, medically appropriate dose of allopurinol (at least 200 mg/day for moderate renal impairment, at least 300 mg/day for others) for at least 8 weeks.

Subjects who qualified for the studies were randomized in a double-blind manner in a 1:1:1 ratio to the three treatment arms for up to 12 months:

- LESU 200: LESU 200mg + ALLO
- LESU 400: LESU 400mg + ALLO
- PBO: PBO + ALLO

From now on, when referred to in this review, the short forms of the arms LESU 200, LESU 400 and PBO will be used instead of the full name.

Randomization was stratified in these two studies by two baseline disease characteristics:
- Renal function at Day -7 (eCrCl>=60 mL/min versus <60 mL/min)
- Tophus status during Screening (presence of >=1 tophus versus absence of tophi)

Sponsor-supplied allopurinol and gout flare prophylaxis drug were initiated on Day -14. All subjects were prescribed gout flare prophylaxis with colchicine 0.5 or 0.6 QD as available. Subjects continued gout flare prophylaxis through Month 5 unless they became intolerant of the prophylaxis.

Double blinded study treatment started on Day 1 and subjects were seen monthly with an extra visit on Week 2. Efficacy was assessed through measurement of sUA, tophus resolution using digital caliper measurements; flare rates using a subject eDiary, and quality of life using various questionnaires.

Study 304 was conducted similarly, with ALLO replaced by a FBX 80mg as background therapy. The same renal function stratification factor was used in randomization. As the study targeted tophaceous patients, sUA level at day -7 was used as the second stratification factor. The enrollment criteria in study 304 are different from studies 301 and 304 too. Both disease condition and sUA control before and during the screening period of tophaceous patients are generally different from the less severe patient population in studies 301 and 302.

3.2.2 Study endpoints

There are two types of endpoints in measuring treatment effect on gout: clinically meaningful endpoints that directly measure incidence and severity of clinical gout such as frequency of acute gout flare and size and number of palpable tophi; and surrogate markers that reflect clinical benefit on gout such as sUA level.

Benefit of persistent sUA lowering in the reduction of the above mentioned clinical endpoints were established by multiple published studies and recommended by multiple international guidelines (FDA AC June 2004, EULAR 2014, BSR 2007, and ACR 2012). SUA level is often viewed as a valid surrogate endpoint in measuring clinical benefit in gout. Limited by the duration of clinical trials, in gout trials, the sUA level is usually used as the primary efficacy endpoint as it takes longer time to observe significant clinical benefit.

Due to the differences in population disease severity, the allopurinol add-on studies and the febuxostat add-on study are similar but different in both primary and secondary endpoints selection. Table 5 ummarizes the key endpoints used in the 3 studies.

Table 5: Primary and secondary endpoints of the three Phase 3 studies

	Studies 301 and 302	Study 304
Primary Endpoint	The proportion of subjects by Month 6 achieving the recommended target sUA level of <6.0 mg/dL	The proportion of subjects by Month 6 achieving the recommended target sUA level of <5.0 mg/dL
Key Secondary Endpoints	The proportion of subjects with >=1 target tophus at Baseline who experienced complete resolution (CR) of >=1 target tophus by Month 12	
	Mean rate of gout flares requiring treatment from the end of Month 6 to the end of Month 12	The proportion of subjects who experienced complete or partial resolution (CR/PR) of >=1 target tophus by Month 12
		The proportion of subjects with at least 0.25 improvement in the Health Assessment Questionnaire – Disability Index (HAQ-DI)

Source: Reviewer.

3.2.3 Statistical Methodologies

3.2.3.1 Analysis Method for Key Endpoints

The primary endpoint is the proportion of subjects with a sUA < 6.0 (or 5.0 in study 304) mg/dL at Month 6 (sUA response). The difference in sUA response rates between each LESU group and placebo was tested using the CMH test statistic for the ITT population, stratifying by Day -7 renal function and tophus status during Screening (randomized values). For study 304, Day -7 renal function and sUA level at Day -7 were used as stratifying factors. The 2 treatment comparisons with placebo were tested at the alpha = 0.025 level after Bonferroni correction within each study.

Absolute and percent change from Baseline sUA levels at each scheduled visit were analyzed using ANCOVA models with the Baseline sUA value as a covariate and treatment group, Day -7 renal function, and tophus status during Screening as factors in the model; associated 95% CIs and p-values were reported. In study 304, tophus status is replaced with sUA level at Day -7.

Rates of gout flares requiring treatment data were analyzed using a negative binomial model. The response variable in the model was the number of gout flares requiring treatment experienced by a subject from the end of Month 6 to the end of Month 12. The model included treatment group, Day -7 renal function, and tophus status during Screening as factors. To be able to estimate gout flare rate every six months, time on-study was calculated as a proportion relative to the six-month interval (168 days). The logarithm of the transformed version of time on-study was used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

Complete resolution of tophi or CR/PR was analyzed with CMH test similarly with primary endpoint. So was the proportion of subjects with at least 0.25 improvements in the Health Assessment Questionnaire – Disability Index (HAQ-DI).

3.2.3.2 Missing Data Handling

Two types of missing data imputation were used for the primary analyses of sUA data. For the responder analysis, subjects with missing values at month 6 for any reason were considered non-responders (NRI). This is considered a fair representation of the efficacy of the study treatment in that patients who chose to prematurely discontinue study treatment have in fact indicated that they are not willing to continue taking the study medication in exchange for what level of efficacy is being received (i.e., that the study treatment is ineffective for that patient). In addition, sensitivity of the treatment effect to the use of non-responder imputation is explored using tipping point analyses. For the absolute change from baseline analysis, an LOCF imputation was used but sensitivity to that assumption is explored using cumulative responder plots.

3.2.3.3 Sensitivity Analyses

The Applicant performed a series of sensitivity analyses (Table 6) with the intention to assessing the robustness of the findings based on primary analyses of data. These analyses provide a means to assess the impact of the following assumptions: data collection error – actual stratification factor values; missing data handling – LOCF or observed cases; definitions of outcome – reached target at each of month 4, 5, 6 or at any time or personal median; methods of analysis – logistic regression; protocol deviation – Per Protocol analysis.

Table 6: Results Summary of Sensitivity Analyses Performed by the Applicant

Sensitivity Methods	Table Number in Sponsor CSR	Study 301	Study 302	Study 304
Use Actual Stratification Factor Values	T14.2.1.2	X	X	X
LOCF of sUA level	T14.2.1.3	X	X	X
Observed Cases	T14.2.1.3	X	X	X
Reached Target at each of Months 4, 5, and 6	T14.2.1.4	X	X	pvalue=0.003 (LESU 200 vs. PBO)
Per Protocol Analysis	T14.2.1.5	X	X	X
Logistic Regression	T14.2.1.6	X	X	X
Reached target at any time on-study	T14.2.1.19	X	X	pvalue=0.02 (LESU 200 vs. PBO)
Subject personal median sUA reached target	T14.2.1.20	X	X	Pvalue<0.01 (LESU 200 vs. PBO)

Source: Applicant's CSR 301, 302 and 304
X indicates sensitivity analysis of the treatment effect p-value was consistent with the primary analysis.

Generally, the above methods provide results regarding the treatment effect that are qualitatively consistent with the results of the primary efficacy results for comparisons of LESU200 or LESU 400 vs. Placebo. After the Bonferroni correction, qualitatively different results of treatment comparison between LESU200 and placebo were found with tests based on three criteria as indicated in Table 6. Results of these three sensitivity analyses had p-values associated with the treatment effect of LESU200 versus placebo that were smaller than the Bonferroni corrected alpha level of 0.025 while results of the primary analysis comparing LESU200 versus placebo

were not statistically significant. Qualitative conclusions regarding the treatment effect for LESU400 vs. placebo in all sensitivity analyses are consistent with primary analysis indicating a benefit of LESU400 over placebo in all cases.

In general, we agree with the sponsor that sensitivity analyses addressing the data collection error, definition of outcome, method of analysis, and analysis set indicate that the effect of lesinurad on sUA observed in the primary efficacy analyses is not an artifact of these choices. However, part of the focus of this review is on testing the robustness to missing data handling since we believe the sensitivity analyses provided for this purpose do not appropriately address the relevant questions surrounding missing data. From past gout treatment development programs (ULORIC and KRYSTEXXA), there were high dropout rates (18% - 33%). As shown in the next section, across the 3 studies in this application, the dropout rates at month 6 is 15% - 17% and 23% - 25% at month 12. See section 5.1 for sensitivity analyses addressing missing data conducted for this review.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

3.2.4.1 Patient Disposition

In this application, among the three pivotal studies, *Screened* was defined as signing an informed consent form. Among the 2401 subjects that were screened under study 301, 2377 subjects were reported as screened population, the remaining 26 were excluded from all analyses in the sponsor's CSR due to GCP noncompliance at 2 study sites (4 subjects from site 05060, 21 subjects from site 05333) or missing ICF (1 subject). Table 7 numbers are based on the 2377 screened subjects.

Six hundred and seven subjects were randomized (1:1:1) into study 301: 203 to receive placebo, 202 to receive LESU200, and 202 to receive LESU400. For study 302 (Table 8), 611 subjects were randomized to the three arms at 206, 204 and 201 respectively.

Across the studies 5% to 10% of subjects had protocol deviation. And across the treatment arms, there is a trend that placebo group has the lowest protocol deviation while LESU400 group have a higher deviation rate.

The responder endpoint were assessed at month 6, the gout flare rates were assessed between month 6 and month 12, the tophi CR/PR data were assessed at month 12. Accordingly, disposition data were summarized with respect to different time-point: completed study (with or without completing randomized study medication), completed 6 months of treatment with randomized study medication, completed 12 months of treatment with randomized study medication.

Table 7: Subject Disposition - Study 301

	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	Total
Screened				2377
Screen failure				1709
Consent withdrawn				61
Randomized	203	202	202	607
Withdraw prior to receiving randomized study medication	2	1	1	4
Intent-to-Treat (ITT)	**201**	**201**	**201**	**603**
Safety	201 (100%)	201 (100%)	201 (100%)	603 (100%)
Per Protocol	186 (93%)	183 (91%)	175 (87%)	544 (90%)
Completed study (with or without completing randomized study medication)	**152 (76%)**	**151 (75%)**	**150 (75%)**	**453 (75%)**
Adverse event	5 (2%)	7 (3%)	8 (4%)	20 (3%)
Consent withdrawn	10 (5%)	9 (4%)	12 (6%)	31 (5%)
Death	0	1 (<1%)	0	1 (<1%)
Gout flare	0	1 (<1%)	0	1 (<1%)
Lost to follow-up	9 (4%)	13 (6%)	16 (8%)	38 (6%)
Non-compliance/protocol violation	22 (11%)	17 (8%)	15 (7%)	54 (9%)
Sponsor terminated study	2 (<1%)	2 (<1%)	0	4 (<1%)
Completed 6 months of treatment with randomized study medication	**174 (87%)**	**163 (81%)**	**163 (81%)**	**500 (83%)**
Adverse event	4 (2%)	10 (5%)	10 (5%)	24 (4%)
Consent withdrawn	4 (2%)	6 (3%)	9 (4%)	19 (3%)
Lost to follow-up	4 (2%)	9 (4%)	9 (4%)	22 (4%)
Non-compliance/protocol violation	14 (7%)	13 (6%)	10 (5%)	37 (6%)
Requires treatment with protocol prohibited or contraindicated medication	1 (<1%)	0	0	1 (<1%)
Completed 12 months of treatment with randomized study medication	**149 (74%)**	**140 (70%)**	**141 (70%)**	**430 (71%)**
Adverse event	7 (3%)	15 (7%)	14 (7%)	36 (6%)
Consent withdrawn	8 (4%)	9 (4%)	12 (6%)	29 (5%)
Death	0	1 (<1%)	0	1 (<1%)
Lost to follow-up	9 (4%)	13 (6%)	16 (8%)	38 (6%)
Non-compliance/protocol violation	27 (13%)	22 (11%)	18 (9%)	67 (11%)
Requires treatment with protocol prohibited or contraindicated medication	1 (<1%)	1 (<1%)	0	2 (<1%)

Table 8: Subject Disposition - Study 302

	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	Total
Screened				2199
Screen failure				1538
Consent withdrawn				50
Randomized	206	204	201	611
Withdraw prior to receiving randomized study medication			1	1
Intent-to-Treat (ITT)	**206**	**204**	**200**	**610**
Safety	206 (100%)	204 (100%)	200 (100%)	610 (100%)
Per Protocol	194 (94%)	182 (89%)	181 (91%)	557 (91%)
Completed study (with or without completing randomized study medication)	**158 (77%)**	**163 (80%)**	**150 (75%)**	**471 (77%)**
Adverse event	9 (4%)	4 (2%)	12 (6%)	25 (4%)
Consent withdrawn	11 (5%)	16 (8%)	13 (7%)	40 (7%)
Death	0	0	1 (<1%)	1 (<1%)
Gout flare	2 (<1%)	3 (1%)	0	5 (<1%)
Lost to follow-up	11 (5%)	5 (2%)	7 (4%)	23 (4%)
Non-compliance/protocol violation	12 (6%)	8 (4%)	15 (8%)	35 (6%)
Sponsor terminated study	3 (1%)	5 (2%)	2 (1%)	10 (2%)
Completed 6 months of treatment with randomized study medication	**175 (85%)**	**175 (86%)**	**171 (86%)**	**521 (85%)**
Adverse event	6 (3%)	6 (3%)	9 (5%)	21 (3%)
Consent withdrawn	8 (4%)	10 (5%)	9 (5%)	27 (4%)
Gout flare	0	2 (<1%)	1 (<1%)	3 (<1%)
Lost to follow-up	6 (3%)	5 (2%)	4 (2%)	15 (2%)
Non-compliance/protocol violation	10 (5%)	6 (3%)	5 (3%)	21 (3%)
Requires treatment with protocol prohibited or contraindicated medication	1 (<1%)	0	1 (<1%)	2 (<1%)
Completed 12 months of treatment with randomized study medication	**154 (75%)**	**162 (79%)**	**145 (73%)**	**461 (76%)**
Adverse event	12 (6%)	6 (3%)	18 (9%)	36 (6%)
Consent withdrawn	11 (5%)	15 (7%)	12 (6%)	38 (6%)
Gout flare	2 (<1%)	3 (1%)	1 (<1%)	6 (<1%)
Lost to follow-up	11 (5%)	5 (2%)	7 (4%)	23 (4%)
Non-compliance/protocol violation	14 (7%)	9 (4%)	14 (7%)	37 (6%)
Requires treatment with protocol prohibited or contraindicated medication	2 (<1%)	4 (2%)	3 (2%)	9 (1%)

Table 9: Subject Disposition – Study 304

	PBO + FBX 80 mg	LESU 200 mg+ FBX 80 mg	LESU 400 mg+ FBX 80 mg	Total
Screened				1045
Screen failure				
Consent withdrawn				
Randomized				330
Withdraw prior to receiving randomized study medication				
Intent-to-Treat (ITT)	**109**	**106**	**109**	**324**
Safety	109 (100%)	106 (100%)	109 (100%)	324 (100%)
Per Protocol	106 (97%)	102 (96%)	99 (91%)	307 (95%)
Completed study (with or without completing randomized study medication)	87 (80%)	79 (75%)	84 (77%)	250 (77%)
Adverse event	4 (4%)	7 (7%)	6 (6%)	17 (5%)
Consent withdrawn	3 (3%)	3 (3%)	4 (4%)	10 (3%)
Death	0	1 (<1%)	1 (<1%)	2 (<1%)
Gout flare	1 (<1%)	0	3 (3%)	4 (1%)
Lost to follow-up	5 (5%)	5 (5%)	1 (<1%)	11 (3%)
Non-compliance/protocol violation	9 (8%)	11 (10%)	10 (9%)	30 (9%)
Completed 6 months of treatment with randomized study medication	94 (86%)	87 (82%)	88 (81%)	269 (83%)
Adverse event	5 (5%)	7 (7%)	11 (10%)	23 (7%)
Consent withdrawn	1 (<1%)	1 (<1%)	2 (2%)	4 (1%)
Death	0	1 (<1%)	0	1 (<1%)
Gout flare	0	1 (<1%)	3 (3%)	4 (1%)
Lost to follow-up	4 (4%)	3 (3%)	0	7 (2%)
Non-compliance/protocol violation	5 (5%)	6 (6%)	5 (5%)	16 (5%)
Completed 12 months of treatment with randomized study medication	83 (76%)	76 (72%)	76 (70%)	235 (73%)
Adverse event	9 (8%)	10 (9%)	15 (14%)	34 (10%)
Consent withdrawn	3 (3%)	2 (2%)	4 (4%)	9 (3%)
Death	0	1 (<1%)	0	1 (<1%)
Gout flare	1 (<1%)	1 (<1%)	4 (4%)	6 (2%)
Lost to follow-up	4 (4%)	5 (5%)	1 (<1%)	10 (3%)
Non-compliance/protocol violation	9 (8%)	11 (10%)	9 (8%)	29 (9%)

Demographics data for the ITT population are summarized in Table 10 to Table 12. As is expected due to the random treatment assignment, the treatment arms are fairly balanced with respect to each factors considered.

Table 10: Patient Demographics - Study 301

		PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	Total
Sex	N	201	201	201	603
	F	12 (6%)	9 (4%)	15 (7%)	36 (6%)
	M	189 (94%)	192 (96%)	186 (93%)	567 (94%)
Age (yrs)	N	201	201	201	603
	< 65 years	169 (84%)	181 (90%)	168 (84%)	518 (86%)
	>= 65 years	32 (16%)	20 (10%)	33 (16%)	85 (14%)
Race	N	201	201	201	603
	AMERICAN INDIAN OR ALASKA NATIVE	1 (<1%)	2 (<1%)	0	3 (<1%)
	ASIAN	10 (5%)	9 (4%)	7 (3%)	26 (4%)
	BLACK OR AFRICAN AMERICAN	29 (14%)	31 (15%)	30 (15%)	90 (15%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDE	5 (2%)	4 (2%)	5 (2%)	14 (2%)
	OTHER	3 (1%)	4 (2%)	3 (1%)	10 (2%)
	WHITE	153 (76%)	151 (75%)	156 (78%)	460 (76%)

Table 11: Patient Demographics - Study 302

		PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	Total
Sex	N	206	204	200	610
	F	10 (5%)	7 (3%)	6 (3%)	23 (4%)
	M	196 (95%)	197 (97%)	194 (97%)	587 (96%)
Age (yrs)	N	206	204	200	610
	< 65 years	185 (90%)	184 (90%)	175 (88%)	544 (89%)
	>= 65 years	21 (10%)	20 (10%)	25 (13%)	66 (11%)
Country	N	206	204	200	610
	Australia	4 (2%)	4 (2%)	9 (5%)	17 (3%)
	Belgium	2 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)
	Canada	12 (6%)	7 (3%)	6 (3%)	25 (4%)
	Switzerland	0	1 (<1%)	0	1 (<1%)
	Germany	8 (4%)	9 (4%)	8 (4%)	25 (4%)
	Spain	2 (<1%)	2 (<1%)	4 (2%)	8 (1%)
	New Zealand	7 (3%)	12 (6%)	7 (4%)	26 (4%)
	Poland	6 (3%)	5 (2%)	11 (6%)	22 (4%)
	Ukraine	25 (12%)	25 (12%)	24 (12%)	74 (12%)
	United States	107 (52%)	108 (53%)	94 (47%)	309 (51%)
	South Africa	33 (16%)	30 (15%)	36 (18%)	99 (16%)
Race	N	206	204	199	609
	Missing	0	0	1 (<1%)	1 (<1%)
	AMERICAN INDIAN OR ALASKA NATIVE	1 (<1%)	1 (<1%)	0	2 (<1%)
	ASIAN	14 (7%)	10 (5%)	9 (5%)	33 (5%)
	BLACK OR AFRICAN AMERICAN	22 (11%)	15 (7%)	21 (11%)	58 (10%)
	MAORI	1 (<1%)	4 (2%)	1 (<1%)	6 (<1%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDE	5 (2%)	3 (1%)	2 (1%)	10 (2%)
	OTHER	8 (4%)	4 (2%)	6 (3%)	18 (3%)
	WHITE	155 (75%)	167 (82%)	160 (80%)	482 (79%)

Table 12: Patient Demographics - Study 304

		PBO+ FBX 80 mg	LESU 200 mg+ FBX 80 mg	LESU 400 mg+ FBX 80 mg	Total
Sex	N	109	106	109	324
	F	2 (2%)	6 (6%)	7 (6%)	15 (5%)
	M	107 (98%)	100 (94%)	102 (94%)	309 (95%)
Age (yrs)	N	109	106	109	324
	< 65 years	89 (82%)	89 (84%)	90 (83%)	268 (83%)
	>= 65 years	20 (18%)	17 (16%)	19 (17%)	56 (17%)
Country	N	109	106	109	324
	Australia	4 (4%)	6 (6%)	6 (6%)	16 (5%)
	Canada	6 (6%)	9 (8%)	2 (2%)	17 (5%)
	Switzerland	1 (<1%)	0	1 (<1%)	2 (<1%)
	New Zealand	5 (5%)	2 (2%)	6 (6%)	13 (4%)
	Poland	14 (13%)	8 (8%)	10 (9%)	32 (10%)
	United States	79 (72%)	81 (76%)	84 (77%)	244 (75%)
Race	N	109	106	109	324
	AMERICAN INDIAN OR ALASKA NATIVE	0	1 (<1%)	0	1 (<1%)
	ASIAN	6 (6%)	8 (8%)	6 (6%)	20 (6%)
	BLACK OR AFRICAN AMERICAN	8 (7%)	14 (13%)	13 (12%)	35 (11%)
	MAORI	0	0	3 (3%)	3 (<1%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDE	0	1 (<1%)	2 (2%)	3 (<1%)
	OTHER	1 (<1%)	2 (2%)	0	3 (<1%)
	WHITE	94 (86%)	80 (75%)	85 (78%)	259 (80%)

3.2.5 Results and Conclusions

Primary and secondary endpoints and analysis methods were introduced in section 3.2.2. Across the three studies, there are 15% to 17% of the patients who discontinued from study treatment before end of month 6. The pre-specified non-responder imputation method was used for the missing data. The primary efficacy results for studies 301 and 302 are given in Table 13.

Table 13: Primary Efficacy Analysis (Study 301 and Study 302): Proportion of Subjects with an sUA Level < 6.0 mg/dL by Month 6 – Non-Responder Imputation[1] (ITT Population)

	RDEA594 - 301			RDEA594 - 302		
	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO
ITT Population	N = 201	N = 201	N = 201	N = 206	N = 204	N = 200
Proportion with sUA < 6.0 mg/dL by Month 6, [n (%)]	56 (27.86)	109 (54.23)	119 (59.20)	48 (23.30)	113 (55.39)	133 (66.50)
Difference in proportions vs. PBO + ALLO(95% CI)[2]		0.26 (0.17, 0.36)	0.31 (0.22, 0.41)		0.32 (0.23, 0.41)	0.43 (0.34, 0.52)
p-value for comparison to PBO[3,4]		< 0.001	< 0.001		< 0.001	< 0.001

1. Subjects missing the Month 6 sUA result are treated as non-responders
2. Binomial confidence interval for difference in proportions
3. Cochran-Mantel Haenszel test stratified by Day -7 renal function and tophus status during Screening (randomized values)
4. p-value should be compared to α=0.025 to determine statistical significance according to the pre-specified Bonferroni correction to control type I error

Under both study 301 and 302, in which all subject were receiving allopurinol, taking into account of control of type 1 error by comparing the p-value to a significance level of 0.025, each of the two dose arms of lesinurad are superior to placebo in terms of the proportion of subjects achieving sUA < 6.0 mg/dL.

The primary efficacy results for study 304 are given in Table 14. A significant treatment effect is observed for LESU400 versus PBO. However, the estimated proportional difference between LESU 200 and PBO is only 10%, and is not statistically significant with an associated 95% CI of (-0.03, 0.23), even before the Bonferroni correction.

Table 14: Primary Efficacy Analysis (Study 304): Proportion of Subjects with an sUA Level < 5.0 mg/dL by Month 6 – Non-Responder Imputation[1] (ITT Population)

	RDEA594 - 304		
	PBO + FBX 80 mg	LESU 200 mg + FBX 80 mg	LESU 400 mg + FBX 80 mg
ITT Population	N = 109	N = 106	N = 109
Proportion with sUA < 5.0 mg/dL by Month 6, [n (%)]	51 (46.79)	60 (56.60)	83 (76.15)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)[2]		0.10 (-0.03, 0.23)	0.29 (0.17, 0.42)
p-value for comparison to PBO[3,4]		0.13	< 0.001

1. Subjects missing the Month 6 sUA result are treated as non-responders
2. Binomial confidence interval for difference in proportions
3. Cochran-Mantel Haenszel test stratified by Day -7 renal function and sUA level at Day -7.
4. p-value should be compared to α=0.025 to determine statistical significance according to the pre-specified Bonferroni correction to control type I error

Tables 15 to Table 17 summarize the analysis results for the key secondary efficacy endpoints. No statistically significant benefit for either dose of LESU over PBO in the presence of ALLO as background therapy was demonstrated for any of the key secondary endpoints. In terms of gout flare rate, the LESU+ALLO arms have similar half year rate as ALLO alone. However, as results of study 301 and 302 are presented here in Table 15 shoulder by shoulder, averagely speaking, there is a higher rate of event on all treatment arms in study 302 compared with 301. The explanation for why this would occur remains uncertain; however, we note that the main difference between these two studies is that study 301 was conducted at US sites only while study 302 is a global study. As for the measure of tophi resolution, study 302 has more tophi resolution cases than 301. A frequency table of the distribution of the stratification factors was generated and is displayed in Table 16 to help explore possible imbalances between the two studies in terms of baseline disease characteristics. But, aside from the relatively different proportions of patients with tophi at baseline, there is not much difference between the two study populations.

Table 15: Key Secondary Efficacy Endpoints (Study 301 and 302): Mean Rate of Gout Flares Requiring Treatment[1] per Subject for the 6-Month Period from the End of Month 6 to the End of Month 12 (ITT Population)

	RDEA594 - 301			RDEA594 - 302		
	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO
ITT Population	N = 201	N = 201	N = 201	N = 206	N = 204	N = 200
Adjusted rate[2, 3] of gout flare requiring treatment per subject per 6 months (Standard Error)[2]	0.62 (0.11)	0.62 (0.11)	0.55 (0.10)	0.89 (0.14)	0.78 (0.13)	0.83 (0.14)
Incidence Rate Ratio[2] (95% CI) vs. PBO + ALLO		0.99 (0.61, 1.61)	0.88 (0.54, 1.43)		0.88 (0.57, 1.37)	0.93(0.60, 1.45)
p-value[2]		0.98	0.61		0.57	0.75

1. A gout flare requiring treatment is defined as one with a protocol-specified medication recorded with indication of "Treatment for Gout Flare" beginning within 3 days prior to the start or 3 days after the end of the gout flare.
2. Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl $\geq$ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values, and log follow-up time as the offset variable.
3. Estimates of adjusted rate for each treatment group obtained from inputting empirical proportion of each stratification factor level under each study.

Table 16: Proportion of ITT Subjects for Stratification Factors (Supporting Table for Table 15)

Stratification Factor	Category	RDEA594 - 301		RDEA594 - 302	
		Frequency Count	Percent of Total Frequency	Frequency Count	Percent of Total Frequency
CRF Renal Function on Day -7	eCrCl < 60 mL/min	108	17.9104	90	14.7541
	eCrCl >= 60 mL/min	495	82.0896	520	85.2459
Tophus Status at Screening (Rand)	Absent	516	85.5721	468	76.7213
	Present	87	14.4279	142	23.2787

Table 17: Key Secondary Endpoint (Study 301 and Study 302): Proportion of Subjects with at Least One Target Tophus at Baseline Who Experience Complete Resolution of at Least One Target Tophus by Month 12 – Non-Responder Imputation (ITT Population, Subjects with at Least One Target Tophus at Baseline)

	RDEA594 - 301			RDEA594 - 302		
	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO
Subjects with at least one target tophus at baseline - ITT Population	N = 17	N = 18	N = 19	N = 33	N = 35	N = 29
Proportion with a best response of CR by Month 12 [n (%)]	5 (29.4)	0	4 (21.1)	11 (33.3)	11 (31.4)	8 (27.6)
Difference in proportions vs. PBO + ALLO (95% CI)[1]		-0.29 (-0.51 - 0.08)	- 0.08 (-0.37, 0.20)		-0.02 (-0.24, 0.20)	-0.06 (-0.29, 0.17)
p-value[2]		0.02	0.60		0.85	0.63

1. Binomial confidence interval for difference in proportions
2. Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min), randomized values.

Table 18 to Table 20 summarize the analysis results for the key secondary efficacy endpoints for study 304. Since the study had failed to demonstrate a statistically significant effect of treatment on the primary efficacy endpoint already, statistically significant effects for the treatment should not be claimed for endpoints further down in the testing hierarchy. But just for descriptive purposes, we can see it failed to show any add-on efficacy of LESU+FBX over FBX alone in terms of CR/PR of tophi or improvement of the PRO instrument Health Assessment Questionnaire – Disability Index.

Table 18: Key Secondary Endpoint (Study 304): Proportion of Subjects Who Experience Complete Resolution of at Least One Target Tophus by Month 12 (ITT Population)

	RDEA594 - 304		
	PBO + FBX 80 mg	**LESU 200 mg + FBX 80 mg**	**LESU 400 mg + FBX 90 mg**
ITT Population	N = 109	N = 106	N = 109
Proportion with a best response of CR by Month 12 [n (%)]	23 (21.1)	27 (25.5)	33 (30.3)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)[1]		0.04 (-0.07 0.16)	0.09 (-0.02, 0.21)
p-value[2]		0.45	0.12

1. Binomial confidence interval for difference in proportions
2. Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min), and Day -7 sUA status (sUA ≥ 6.0 mg/dL versus < 6.0 mg/dL), randomized values.

Table 19: Key Secondary Endpoint (Study 304): Proportion of Subjects Who Experience Complete or Partial Resolution of at Least One Target Tophus by Month 12 (ITT Population)

	RDEA594 - 304		
	PBO + FBX 80 mg	**LESU 200 mg + FBX 80 mg**	**LESU 400 mg + FBX 90 mg**
ITT Population	N = 109	N = 106	N = 109
Proportion with a CR or PR by Month 12 [n (%)]	55 (50.51)	60 (56.6)	64 (58.7)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)[1]		0.06 (-0.09 0.21)	0.08 (-0.07, 0.23)
p-value[2]		0.45	0.12

1. Binomial confidence interval for difference in proportions
2. Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min), and Day -7 sUA status (sUA ≥ 6.0 mg/dL versus < 6.0 mg/dL), randomized values.

Table 20: Key Secondary Endpoint (Study 304): Proportion of Subjects Achieving Health Assessment Questionnaire – Disability Index Improvement of >= 0.25 at Month 12 – Observed Cases (ITT Population)

	RDEA594 - 304		
	PBO + FBX 80 mg	**LESU 200 mg + FBX 80 mg**	**LESU 400 mg + FBX 90 mg**
ITT Population	N = 109	N = 106	N = 109
Observed Cases	N_a= 80	N_a= 77	N_a= 78
Proportion with a HAQ-DI improvement of >= 0.25 at Month 12 [n (%)]	42 (52.5)	34 (44.2)	26 (33.3)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)[1]		-0.08 (-0.26 0.09)	-0.19 (-0.36, -0.02)
p-value[2]		0.30	0.02

1. Binomial confidence interval for difference in proportions
2. Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min), and Day -7 sUA status (sUA ≥ 6.0 mg/dL versus < 6.0 mg/dL), randomized values.

3.3 Evaluation of Safety

See review of safety evaluation in the medical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this review, subgroup analyses were conducted on two measures of month 6 sUA level:

1. The primary endpoint, proportion of subjects achieving sUA < 6.0 (or 5.0) mg/dL by month 6, a binary responder version of month 6 sUA level.
2. Change from baseline mean sUA level at month 6, the continuous version.

For each endpoint, subgroup analyses were performed for each of the following two sets of factors:

1. Demographic factors: age (<65, >=65), sex (male, female), race (non-white, white), and region (US, non-US)
2. Baseline disease characteristics: baseline renal function (eCrCl: <45, 45 to <60, >=60), baseline background ULT (Allopurinol) dose (< 300, =300, >300) in studies 301 and 302, and in study 304, baseline sUA level (<5, >=5).

Subgroup analyses were performed in each individual phase 3 study as long as the subgrouping factor variable data is available in that study. As none of the three studies was powered to detect subgroup treatment effect, studies 301 and 302 data were pooled to give more precise estimates as these two studies are similar in design.

For the binary sUA responder endpoint, interaction tests were performed using a logistic regression model with treatment, subgroup variable and treatment by subgroup variable interaction as fixed effects in the model. All the three treatment arms LESU200 + XO, LESU 400 + XO and Placebo + XO were included for the test of interaction. Estimates of by group treatment effect versus placebo were derived with the assumption of a binomial distribution of responder.

The continuous version of change from baseline sUA levels was used to explore the numerical improvement across the subgroup factor levels. It may also help to mitigate the lack of power associated with responder rate data and the small sample size. The interaction tests were performed using an ANCOVA model with treatment, baseline sUA level, subgroup variable and treatment by subgroup variable interaction as fixed effects in the model. All the three treatment arms LESU200 + XO, LESU 400 + XO and Placebo + XO were included for the test of interaction. By group treatment effect was estimated with an ANCOVA regression model including treatment, baseline sUA on that specific subgroup of data.

4.1 Sex, Race, Age, and Geographic Region

For the primary endpoint, the proportion of subjects with month 6 sUA level less than 6.0 mg/dL, Table 23 to Table 26 provide a complete summary of the differences between LESU 200 mg and placebo within each demographic characteristic and baseline disease characteristic. Cases where statistically significant treatment-by-subgroup interactions are observed are comment upon in detail here.

Gout is a male predominant disease. About 95% of the subjects in each of the studies were male. The small female sample sizes result in some statistical issues including: sampling zero in the case of female non-responder count (Table 22) in study 304; close to zero in the case of female responder count (Table 21) in study 301. In consequence, in Study 301, a statistically significant treatment by sex interaction (p=0.03) was observed possibly due to this highly variant count data within a small subgroup. In study 304, the zero frequency in female patients in placebo group did not allow maximum likelihood model fitting approaches and an exact test for the interaction effect was performed instead and was found not statistically significant (p=0.8). In the pooled analysis combining studies 301 and 304, the interaction test for sex was not statistically significant (p-value = 0.06). In all, for the factor sex, due primarily to the small number of females included in the studies, no claims can be made regarding whether the treatment effect varies in males and females.

Table 21: Study 301, Cross-Classification of Treatment Arm and sUA Responder by Sex

	Male		Female	
	sUA Responder sUA< 6.0 mg/dL	Non- Responder sUA≥ 6.0 mg/dL	sUA Responder sUA< 6.0 mg/dL	Non-Responder sUA≥ 6.0 mg/dL
PBO	51 (27%)	138 (73%)	5 (42%)	7 (58%)
LESU 200	108 (56%)	84 (44%)	1 (11%)	8 (89%)
LESU 400	108 (58%)	78 (42%)	11 (73%)	4 (27%)

Table 22: Study 304, Cross-Classification of Treatment Arm and sUA Responder by Sex

	Male		Female	
	sUA Responder sUA< 5.0 mg/dL	Non- Responder sUA≥ 5.0 mg/dL	sUA Responder sUA< 5.0 mg/dL	Non- Responder sUA≥ 5.0 mg/dL
PBO	51 (48%)	56 (52%)	0	2 (100%)
LESU 200	58 (58%)	42 (42%)	2 (33%)	4 (67%)
LESU 400	78 (76%)	24 (24%)	5 (71%)	2 (29%)

Table 23: Study 304, Cross-Classification of Treatment Arm and sUA Responder by Baseline Renal Function

	eCrCl <45		45 ≤ eCrCl < 60		eCrCl ≥ 60	
	sUA Responder sUA< 5.0 mg/dL	Non-Responder sUA≥ 5.0 mg/dL	sUA Responder sUA< 5.0 mg/dL	Non-Responder sUA≥ 5.0 mg/dL	sUA Responder sUA< 5.0 mg/dL	Non-Responder sUA≥ 5.0 mg/dL
PBO	0	4 (100%)	11 (52%)	10 (48%)	40 (48%)	44 (52%)
LESU 200	3 (37.5%)	5 (62.5%)	13 (65%)	7 (35%)	44 (56%)	34 (44%)
LESU 400	6 (75%)	2 (25%)	9 (64%)	5 (36%)	68 (78%)	19 (22%)

The Applicant categorized the age into two groups: <65 years and >=65 years; 83% to 89% of the subjects across the three phase 3 studies was younger than 65 years. There was no statistically significant treatment by age group interaction across the three individual studies and the pooled studies. Also, there was no numerical trend between the two age groups.

The white population comprised 76% to 80% of the subjects in each of the studies. There was no statistically significant treatment by race interaction across the studies.

Study 301 was conduct in the US only. In study 302, 51% of subjects were from the US and in study 304, this proportion is 75%. Similar with the race subgroup, there was no statistically significant treatment by region interaction across the two studies. No overall trend was detected either.

Table 24: Study 301, Differences of Proportion of Subjects with Month 6 sUA Levels < 6.0 mg/dL (NRI, ITT), and Difference of Least Square Means (LOCF, ITT) by Subgroup Factors

	Difference of Proportion (sUA < 6.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
Subgroup	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value
--------Age Group--------	.	.	.	.	0.812	.		.	.	0.902
< 65 years	0.275	0.192	0 358	350	.	-1.04	-1.43	-.660	341	.
>= 65 years	0.188	-.040	0.415	52	.	-.788	-1.53	-.052	50	.
----------Sex----------	.	.	.	.	0.034	.		.	.	0.158
F	-.306	-.596	-.015	21	.	0.245	-1.23	1.723	20	.
M	0.293	0.213	0 372	381	.	-1.07	-1.43	-.711	371	.
-------Race Group--------	.	.	.	.	0.520	.		.	.	0.314
Non-White	0.150	-.003	0 303	98	.	-.622	-1.46	0.211	95	.
White	0.302	0.213	0 391	304	.	-1.14	-1.51	-.762	296	.
--Baseline Allopurinol---	.	.	.	.	0.866	.		.	.	0.471
300	0.273	0.191	0 354	363	.	-1.04	-1.41	-.675	355	.
< 300	-.050	-.409	0 309	17	.	0.221	-1.11	1.556	16	.
> 300	0.282	-.059	0.623	22	.	-1.22	-3.09	0.656	20	.
-Baseline Renal Function-	.	.	.	.	0.422	.		.	.	0.315
<45	-.050	-.316	0 216	32	.	0.527	-.850	1.903	30	.
45 to <60	0.226	0.000	0.451	53	.	-.595	-1.39	0.204	52	.
>= 60	0.286	0.199	0 373	315	.	-1.16	-1.55	-.761	307	.

Figure 3: Study 301, Differences of Proportion, LESU 200 + ALLO vs. ALLO for Subjects with Month 6 sUA Levels < 6.0 mg/dL, by Subgroup Factors (None Responder Imputation, ITT)

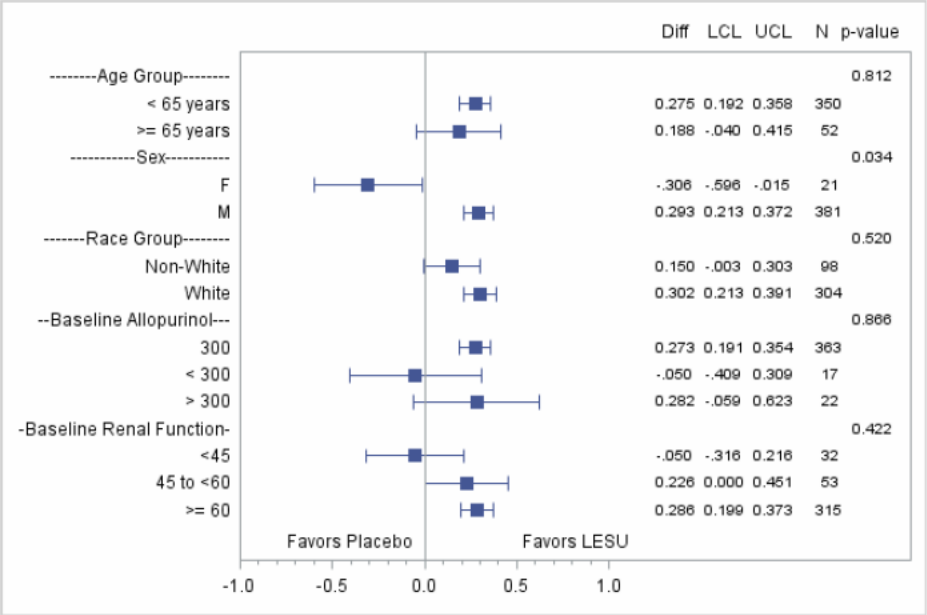


Table 25: Study 302, Differences of Proportion of Subjects with Month 6 sUA Levels < 6.0 mg/dL (NRI, ITT), and Difference of Least Square Means (LOCF, ITT) by Subgroup Factors

	Difference of Proportion (sUA < 6.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
Subgroup	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value
--------Age Group--------		.	.		0.813	.	.	.	.	0.606
< 65 years	0.311	0.232	0.390	369		-1.10	-1.45	-.743	358	.
>= 65 years	0.412	0.179	0.645	41		-1.05	-1.92	-.181	41	.
----------Sex----------		.	.		0.907	.	.	.	.	0.961
F	0.229	-.143	0.600	17		-1.08	-3.18	1.016	15	.
M	0.324	0.247	0.400	393		-1.08	-1.41	-.748	384	.
-------Race Group--------		.	.		0.279	.	.	.	.	0.394
Non-White	0.317	0.154	0.481	88		-1.07	-1.88	-.251	86	.
White	0.318	0.233	0.403	322		-1.06	-1.41	-.709	313	.
--------Region ---------		.	.		0.420	.	.	.	.	0.061
Non-USA	0.320	0.211	0.429	195		-.936	-1.47	-.400	191	.
USA	0.322	0.219	0.425	215		-1.22	-1.61	-.838	208	.
--Baseline Allopurinol---		.	.		0.519	.	.	.	.	0.727
300	0.321	0.239	0.403	344		-1.07	-1.41	-.720	334	.
< 300	0.505	0.263	0.747	29		-1.78	-2.92	-.637	29	.
> 300	0.167	-.099	0.433	37		-.861	-2.40	0.682	36	.
-Baseline Renal Function-		.	.		0.901	.	.	.	.	0.611
<45	0.400	0.030	0.770	16		-.799	-2.86	1.260	16	.

Subgroup	Difference of Proportion (sUA < 6.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value
45 to <60	0.309	0.092	0.525	53		-1.02	-1.71	-.324	53	.
>= 60	0.318	0.236	0.400	340		-1.11	-1.49	-.739	330	.

Figure 4: Study 302, Differences of Proportion, LESU 200 + ALLO vs. ALLO for Subjects with Month 6 sUA Levels < 6.0 mg/dL, by Subgroup Factors (None Responder Imputation, ITT)

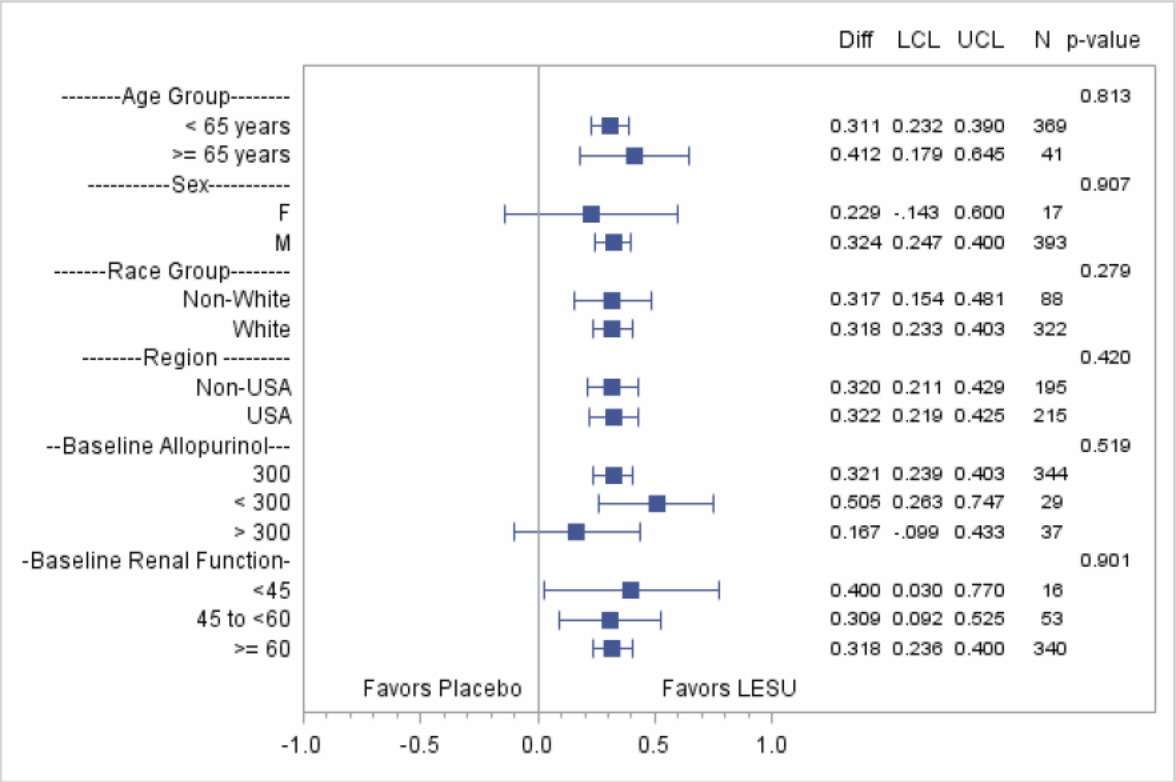


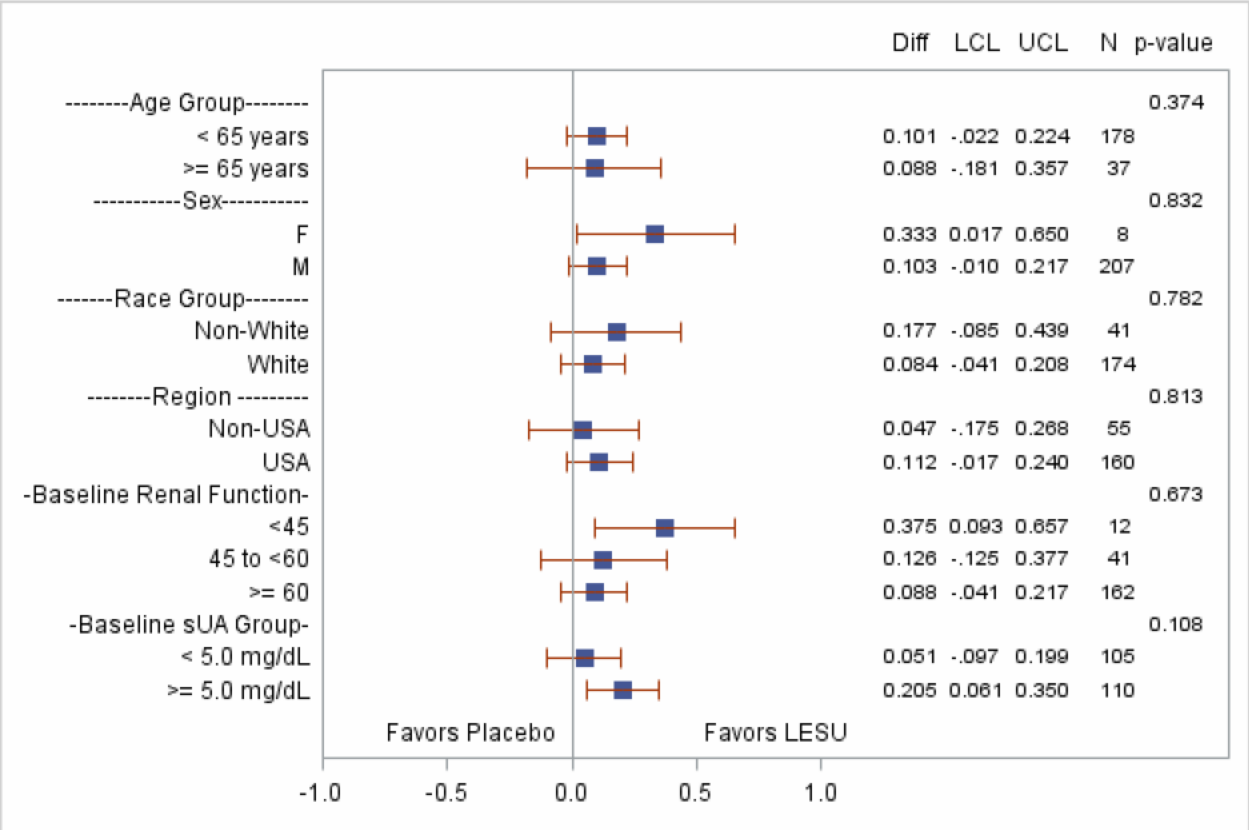
Table 26: Study 304, Differences of Proportion of Subjects with Month 6 sUA Levels < 5.0 mg/dL (NRI, ITT), and Difference of Least Square Means (LOCF, ITT) by Subgroup Factors

Subgroup	Difference of Proportion (sUA < 5.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
	LESU200 + FBX v. FBX	LL	UL	N	Interaction Test p-value	LESU200 + FBX v. FBX	LL	UL	N	Interaction Test p-value
--------Age Group--------	.			.	0.374	.	.	.	.	0.059
< 65 years	0.101	-.022	0 224	178		-.561	-1.09	-.030	173	.
>= 65 years	0.088	-.181	0 357	37		-2.00	-3.30	-.714	36	.
----------Sex----------	.			.	0.832*	.	.	.	.	0.880
F	0.333	0.017	0.650	8		-1.70	-5.47	2.064	8	.
M	0.103	-.010	0 217	207		-.841	-1.34	-.341	201	.
-------Race Group--------	.			.	0.782	.	.	.	.	0.455
Non-White	0.177	-.085	0.439	41		-1.32	-2.58	-.064	38	.

Subgroup	Difference of Proportion (sUA < 5.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
	LESU200 + FBX v. FBX	LL	UL	N	Interaction Test p-value	LESU200 + FBX v. FBX	LL	UL	N	Interaction Test p-value
White	0.084	-.041	0 208	174		-.738	-1.29	-.190	171	.
--------Region ---------	.			.	0.813	.	.	.	.	0.541
Non-USA	0.047	-.175	0 268	55		-.459	-1.48	0.564	54	.
USA	0.112	-.017	0 240	160		-.949	-1.51	-.386	155	.
-Baseline Renal Function-	.			.	0.673**	.	.	.	.	0.626
<45	0.375	0.093	0.657	12		-.015	-2.55	2.524	12	.
45 to <60	0.126	-.125	0.377	41		-.965	-2.12	0.191	41	.
>= 60	0.088	-.041	0.217	162		-.828	-1.39	-.262	156	.
-Baseline sUA Group-	.			.	0.108	.	.	.	.	0.048
< 5.0 mg/dL	0.051	-.097	0 199	105		-1.20	-1.86	-.530	102	.
>= 5.0 mg/dL	0.205	0.061	0 350	110		-.588	-1.31	0.131	107	.

*: Due to the existence of quasi-complete separation, an exact test was performed for Sex by Treatment interaction effect, the score statistic associated exact p-value is 0.81.
**: For the Baseline Renal Function by Treatment interaction effect, the score statistic associated exact p-value is 0.40.

Figure 5: Study 304, Differences of Proportion, LESU 200 + FBX vs. FBX for Subjects with Month 6 sUA Levels < 5.0 mg/dL, by Subgroup Factors (None Responder Imputation, ITT)



Note: Due to the existence of quasi-complete separation, an exact test was performed for Sex by Treatment interaction effect, the score statistic associated exact p-value is 0.81. For the Baseline Renal Function by Treatment interaction effect, the score statistic associated exact p-value is 0.40.

Figure 6: Study 304, Differences of Proportion, LESU 400 + FBX vs. FBX for Subjects with Month 6 sUA Levels < 5.0 mg/dL, by Subgroup Factors (None Responder Imputation, ITT)

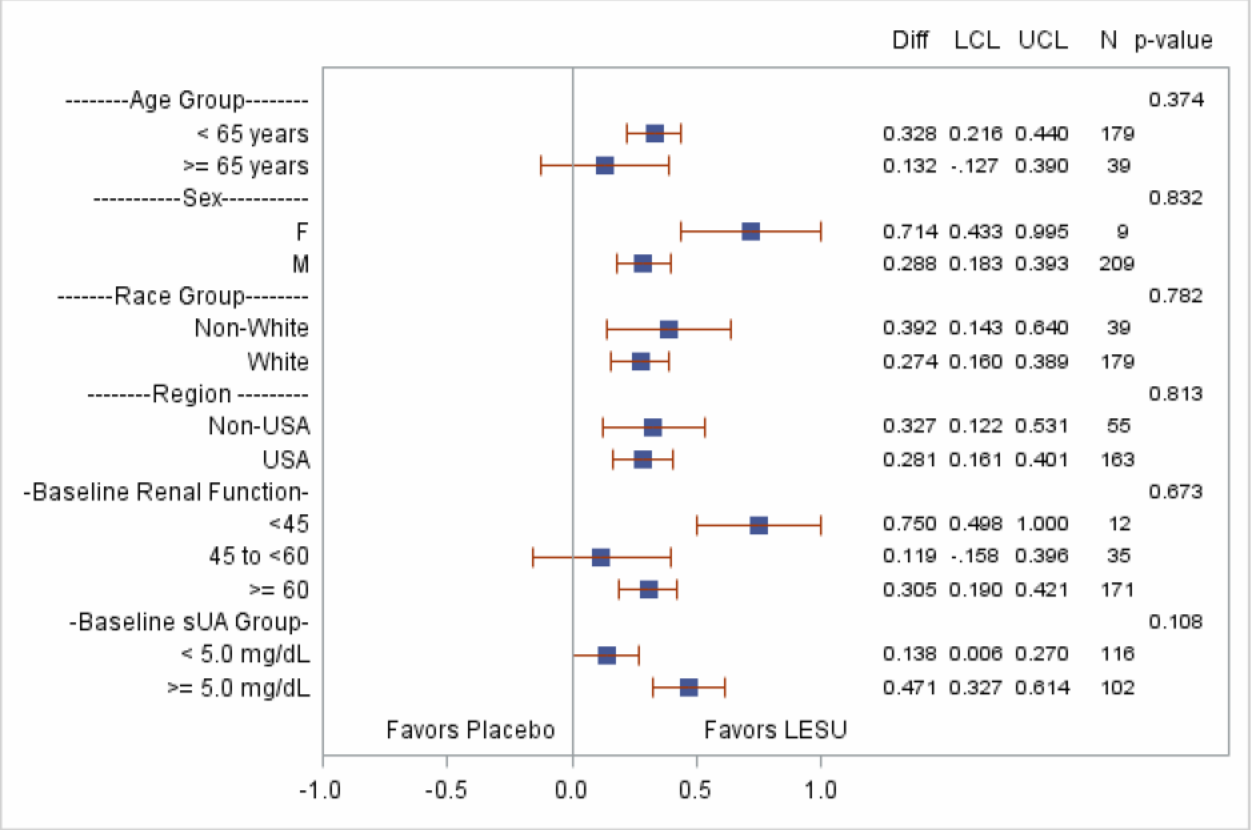
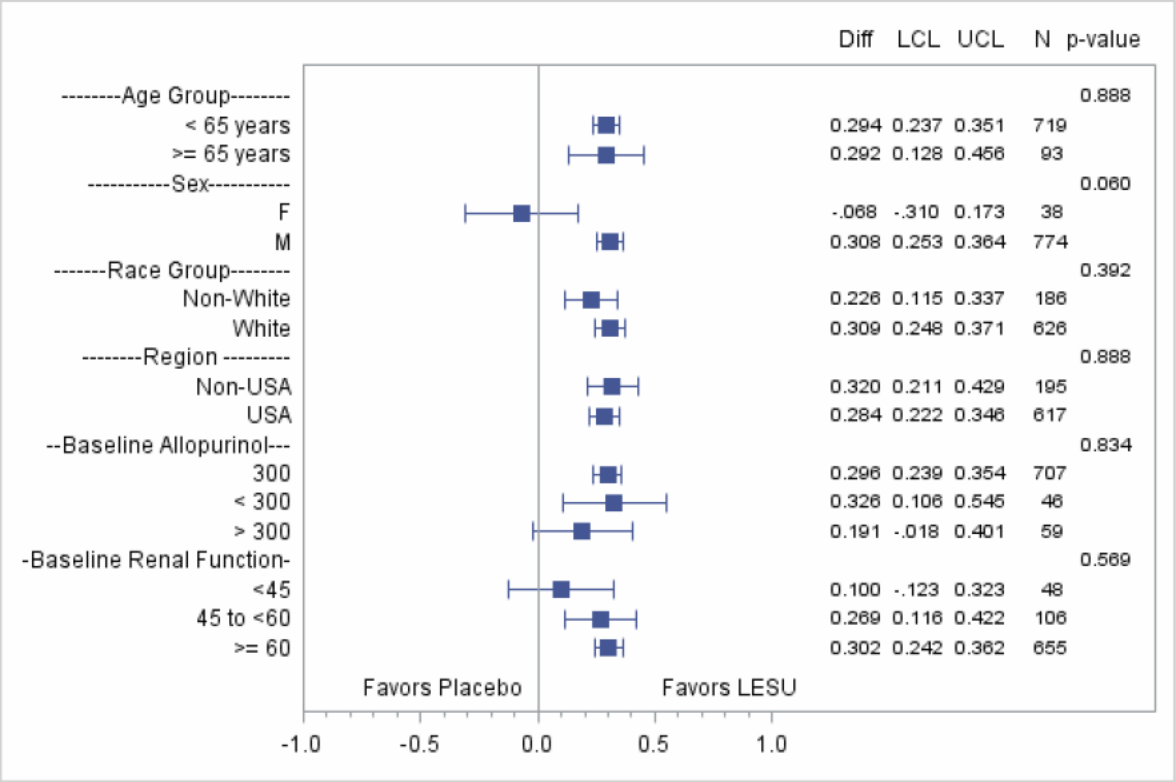


Table 27: Pooled Studies 301 and 302, Differences of Proportion of Subjects with Month 6 sUA Levels < 6.0 mg/dL (NRI, ITT), and Difference of Least Square Means (LOCF, ITT) by Subgroup Factors

	Difference of Proportion (sUA < 6.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
Subgroup	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value
--------Age Group--------		.	.		0.888	.	.	.	.	0.575
< 65 years	0.294	0.237	0.351	719	.	-1.08	-1.34	-.815	699	.
>= 65 years	0.292	0.128	0.456	93	.	-.979	-1.53	-.430	91	.
----------Sex----------		.	.		0.060	.	.	.	.	0.366
F	-.068	-.310	0.173	38	.	-.352	-1.55	0.843	35	.
M	0.308	0.253	0.364	774	.	-1.08	-1.33	-.840	755	.
-------Race Group--------		.	.		0.392	.	.	.	.	0.194
Non-White	0.226	0.115	0.337	186	.	-.867	-1.44	-.290	181	.
White	0.309	0.248	0.371	626	.	-1.10	-1.36	-.843	609	.
--------Region ---------		.	.		0.888	.	.	.	.	0.382

	Difference of Proportion (sUA < 6.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
Subgroup	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value	LESU200 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value
Non-USA	0.320	0.211	0.429	195	.	-.936	-1.47	-.400	191	.
USA	0.284	0.222	0.346	617	.	-1.08	-1.35	-.819	599	.
--Baseline Allopurinol---		.	.		0.834	.	.	.	.	0.823
300	0.296	0.239	0.354	707	.	-1.06	-1.32	-.812	689	.
< 300	0.326	0.106	0.545	46	.	-1.12	-1.98	-.255	45	.
> 300	0.191	-.018	0.401	59	.	-.843	-2.03	0.343	56	.
-Baseline Renal Function-		.	.		0.569	.	.	.	.	0.441
<45	0.100	-.123	0.323	48	.	-.288	-1.37	0.795	46	.
45 to <60	0.269	0.116	0.422	106	.	-.807	-1.32	-.294	105	.
>= 60	0.302	0.242	0.362	655	.	-1.13	-1.40	-.861	637	.

Figure 7: Pooled Studies 301 and 302, Differences of Proportion, LESU 200 + FBX vs. FBX for Subjects with Month 6 sUA Levels < 6.0 mg/dL, by Subgroup Factors (None Responder Imputation, ITT)



As supporting and sensitivity analyses to subgroup analyses on responders, subgroup analyses on change from baseline month 6 sUA levels were performed with the same subgroup factors.

The analyses were performed using an ANCOVA model with treatment, baseline sUA level, subgroup variable and treatment by subgroup variable interaction as fixed effects in the model.

Across the factors and studies, there is no statistically significant interaction between treatment and subgroup factor. One close to significant observation was found in study 302 with region. The estimated mean and confidence interval of the treatment arm LESU400 + ALLO was almost separated from those of the placebo arm. Study 301 was conducted only in the US. Results from study 304 do not show such a strong signal.

Analyses on change from baseline sUA are in a sense sensitivity analyses to support the interpretation of the analysis results on the responder endpoint. By using the continuous measurement of sUA level, a more robust estimate of the subgroup treatment effects and corresponding interaction tests can be derived. No evidence of heterogeneity of treatment efficacy exists in the baseline demographic subgroups examined.

4.2 Baseline Disease Characteristics

Subgroup analyses were also conducted on both the primary endpoint, the dichotomized sUA response and the change from baseline sUA level for the following baseline disease characteristic factors: baseline renal function (eCrCl), background Allopurinol dose (in studies 301 and 302), and baseline sUA.

Lesinurad is believed to be a selective uric acid reabsorption inhibitor and its activity is dependent on the renal function of the patients (See Dr. Jianmeng Chen's OCP review). The Applicant summarized treatment effects on sUA by subgroups dichotomized with varying cut-point of baseline renal function (eCrCl) values. In this review, we chose, in consultation with the FDA medical and clinical pharmacology teams, the following cut-points and corresponding intervals to categorize severe renal impairment group (eCrCl <45 mL/min), moderate renal impairment group (45 to <60 mL/min) and mild to normal renal function group (>=60). Note that in the Applicant's reports, >90 mL/min was used as an additional category to differentiate normal and not normal renal function.

Consistency of treatment effect among baseline background ULT (Allopurinol) dose groups (< 300, =300, >300) in study 301 and 302 were also investigated.

The medical team is also concerned with the observation that in study 304 that around 50% of subjects had reached the urate lowering target at the baseline visit. Treatment effect of further urate lowering and consistency of treatment effect across these patient groups is explored with subgroup analysis for baseline sUA level (<5, >=5).

The analysis methods are the same as described in section 4.1. In all the three studies 301, 302 and 304, there were no statistically significant treatment by baseline renal function interactions. Note that the relative small severe baseline renal impairment group sample sizes result in sampling zero in the case of severe baseline renal impairment (eCrCl < 45 mL/min) non-responder count (Table 23) in study 304. An exact test for the interaction effect was performed instead of just reporting the Wald Statistics from maximum likelihood estimation. In studies 301 and 302, there were no statistically significant treatment by background allopurinol dose interaction.

In study 304, for subgroup analysis for baseline sUA group, the subgroup analysis on the responder endpoint, the treatment by baseline sUA group interaction is not statistically significant (p-value=0.108). However, in the subgroup analysis on change from baseline sUA level, there is a statistically significant (p-value=0.048) interaction between treatment and baseline sUA group. If we focus on the comparison between LESU 200 + FBX and FBX, the responder analysis give a better treatment effect in the baseline sUA group of >=5.0 mg/dL; the change from baseline measure give a better treatment effect in the baseline sUA group of <5.0 mg/dL.

The directions of the estimated effects are conflicting within the comparison (LESU200+FBX over FBX) between the two endpoints. However, a close examination of the estimates and associated confidence intervals in comparisons on LESU400+FBX over FBX showed consistent trends.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

5.1.1 Missing Data and Sensitivity Analysis

5.1.1.1 Tipping Point Analysis for Responder Rate

The primary analyses of sUA Responder rate were conducted, as pre-specified, on the ITT population in which subjects with missing month 6 serum uric acid data were imputed as non-responders (NRI), without differentiation between the different reasons for drop out, across the treatment arms. This is considered a fair representation of the efficacy of the study treatment in that patients who chose to prematurely discontinue study treatment have in fact indicated that they are not willing to continue taking the study medication in exchange for what level of efficacy is being received (i.e., that the study treatment is ineffective for that patient). Nonetheless, in the review, tipping point analyses are provided to gauge the extent to which the demonstration of a treatment effect is dependent on the NRI. The tipping point approach is a method that estimates the treatment effect under varying assumptions about the outcomes of the dropouts in each treatment group. By exploring the whole range of possible and meaningful outcomes for the dropouts and imputing with different rate under different arms, we may assess how extreme the off-study-treatment unobserved data would have to have been to negate the treatment effects estimated from the observed data. If this "tipping point" is so extreme that it is not clinically plausible, one may conclude that demonstration of efficacy is reliable despite the missing data.

From study 301 and 304, early study treatment discontinuation and therefore early study withdrawal as the protocol did not distinguish between the two was slightly more common in the LESU groups at approximately 18-19% as opposed to 13-14% in the Placebo groups. The most common reasons for early withdrawal were "withdraw consent," "adverse event," "non-compliance."

Table 27 and Table 28 provide estimates of the treatment effect (proportional difference and 97.5% confidence interval) and p-values associated with a test of whether the proportion difference from LESU 200 + XOI relative to XOI alone in the responder rate, respectively. These analyses incorporate both observed data and imputed data. Imputed data are generated with varying assumptions about the rate of responder for each treatment group (from total non-responder to total responder) in patients who withdrew from the study early during the time for which they should have been observed but were not. Results on the diagonal indicate analyses based on assumptions that require equal post-discontinuation exacerbation rates in each treatment group. Areas below those cells assume that the post-discontinuation responder rates in the XOI alone arm would have been higher than that of the LESU + XOI arm. Areas above the diagonal represent the cases where the unobserved responder rates for the LESU + XOI arm are assumed to be higher than that of the XOI alone arm. Pink shaded regions include the cases where the assumptions regarding the post-discontinuation data are sufficient to "tip" the analysis of the proportional difference for the responder rate (including observed and unobserved imputed data) so that the result numerically favoring the LESU + XOI group is no longer associated with a p-value less than 0.025.

In order for the hypothesis test to fail to demonstrate an advantage of LESU200+XOI over XOI alone in Study 301, the responder rate of the XOI only arm would need to be higher by an absolute difference of at least 86% in the XOI dropouts than in the LESU200+XOI dropouts. As a point of reference, the responder rate in the observed data was 54% and 28% for the LESU200+XOI and XOI alone, respectively. The post-discontinuation responder rate for XOI patients would have to be more than three times as high as the observed responder rate whiles the post-discontinuation mean exacerbation rate for the LESU200+XOI patients would have to be 0 to reach the tipping point for the test of the proportional difference being equal to one. Given the similar proportions of patients and distributions of reasons for early withdrawal on the two treatment arms, an assumption of such large differences between the outcomes in dropouts on the two arms seems implausible. Therefore, these tipping point analyses largely support the findings of the key efficacy analyses of the observed data presented in Section 3.2.5, Table 13. The situation in study 302 is more extreme while nowhere on the spectrum of assumption can the conclusion be tipped.

Table 28: Tipping Point Analysis Output – Study 301

Difference in Proportion (97.5% CI)		Number of LESU 200 mg Patients Imputed as Responder (Nmiss=37)						
		0 (0%)	1 (3%)	2 (5%)	3 (8%)	4 (11%)	5 (16%)	6 (19%)
Number of Placebo Group Patients Imputed as Responder Nmiss=36	0 (0%)	**0.26 (0.16, 0.37)**	…	…	…	…	…	…
	…	…	…	…	…	…	…	…
	29 (81%)	0.12 (0.01, 0.23)	0.12 (0.01, 0.24)	0.13 (0.02, 0.24)	0.13 (0.02, 0.25)	0.14 (0.03, 0.25)	0.14 (0.03, 0.25)	0.15 (0.04, 0.26)
	30 (83%)	0.11 (0.00, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.24)	0.13 (0.02, 0.24)	0.13 (0.02, 0.25)	0.14 (0.03, 0.25)	0.14 (0.03, 0.25)
	31 (86%)	0.11 (-0.00, 0.22)	0.11 (0.00, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.24)	0.13 (0.02, 0.24)	0.13 (0.02, 0.25)	0.14 (0.03, 0.25)
	32 (89%)	0.10 (-0.01, 0.22)	0.11 (-0.00, 0.22)	0.11 (0.00, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.24)	0.13 (0.02, 0.24)	0.13 (0.02, 0.25)
	33 (83%)	0.10 (-0.01, 0.21)	0.10 (-0.01, 0.22)	0.11 (-0.00, 0.22)	0.11 (0.00, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.24)	0.13 (0.02, 0.24)
	34 (92%)	0.09 (-0.02, 0.21)	0.10 (-0.01, 0.21)	0.10 (-0.01, 0.22)	0.11 (-0.00, 0.22)	0.11 (0.00, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.24)
	35 (97%)	0.09 (-0.02, 0.20)	0.09 (-0.02, 0.21)	0.10 (-0.01, 0.21)	0.10 (-0.01, 0.22)	0.11 (-0.00, 0.22)	0.11 (0.00, 0.23)	0.12 (0.01, 0.23)
	36(100%)	0.08 (-0.03, 0.20)	0.09 (-0.02, 0.20)	0.09 (-0.02, 0.21)	0.10 (-0.01, 0.21)	0.10 (-0.01, 0.22)	0.11 (-0.00, 0.22)	0.11 (0.00, 0.23)

Table 29: Tipping Point Analysis Output – Study 302

Difference in Proportion (97.5% CI)		Number of LESU 200 mg Patients Imputed as Responder (Nmiss=31)						
		0	1	2	3	4	5	6
Number of Placebo Group Patients Imputed as Responder Nmiss=31	0	**0.32 (0.22, 0.42)**	…	…	…	…	…	…
	…	…	…	…	…	…	…	…
	24	0.20 (0.10, 0.31)	0.21 (0.10, 0.32)	0.21 (0.11, 0.32)	0.22 (0.11, 0.33)	0.22 (0.12, 0.33)	0.23 (0.12, 0.34)	0.23 (0.13, 0.34)
	25	0.20 (0.09, 0.31)	0.20 (0.10, 0.31)	0.21 (0.10, 0.32)	0.21 (0.11, 0.32)	0.22 (0.11, 0.33)	0.22 (0.12, 0.33)	0.23 (0.12, 0.34)
	26	0.19 (0.09, 0.30)	0.20 (0.09, 0.31)	0.20 (0.10, 0.31)	0.21 (0.10, 0.32)	0.21 (0.11, 0.32)	0.22 (0.11, 0.33)	0.22 (0.12, 0.33)
	27	0.19 (0.08, 0.30)	0.19 (0.09, 0.30)	0.20 (0.09, 0.31)	0.20 (0.10, 0.31)	0.21 (0.10, 0.32)	0.21 (0.11, 0.32)	0.22 (0.11, 0.33)
	28	0.18 (0.08, 0.29)	0.19 (0.08, 0.30)	0.19 (0.09, 0.30)	0.20 (0.09, 0.31)	0.20 (0.10, 0.31)	0.21 (0.10, 0.32)	0.21 (0.11, 0.32)
	29	0.18 (0.07, 0.29)	0.19 (0.08, 0.29)	0.19 (0.08, 0.30)	0.19 (0.09, 0.30)	0.20 (0.09, 0.31)	0.20 (0.10, 0.31)	0.21 (0.10, 0.32)
	30	0.18 (0.07, 0.28)	0.18 (0.07, 0.29)	0.19 (0.08, 0.29)	0.19 (0.08, 0.30)	0.19 (0.09, 0.30)	0.20 (0.09, 0.31)	0.20 (0.10, 0.31)
	31	0.17 (0.06, 0.28)	0.18 (0.07, 0.28)	0.18 (0.07, 0.29)	0.19 (0.08, 0.29)	0.19 (0.08, 0.30)	0.19 (0.09, 0.30)	0.20 (0.09, 0.31)

The situation in Study 304 is different. Since the efficacy analyses with NRI do not do not demonstrate a statistically significant effect in favor of LESU, tipping point analyses illustrating under which assumptions the statistical significance of the treatment effect would be lost are not relevant or provided.

5.1.1.2 Cumulative Responder Plot for the Month 6 sUA Level

The primary analyses are based on the responder rate corresponding to criteria from the international guidelines (i.e., with success defined as sUA<6 mg/dL by Month 6). In this section, we explore the sensitivity of the demonstration of the treatment effect to this particular definition by considering all other possible thresholds for definition of success thru the cumulative responder plot of the sUA levels.

Figure 8 and Figure 9 provide continuous responder curves (i.e., cumulative responder plot) for studies 301 and 302, respectively. These presentations are developed as follows. Each patient is classified as having been successfully or unsuccessfully treated according to whether or not the patient reached a certain threshold for the sUA level at the study primary time-point (month 6).

This dichotomization of the absolute sUA value is repeated across a range of possible thresholds, in this case from 0 to the maximum sUA value under each study. Patients with missing or very high value of sUA data at the primary time-point are classified as unsuccessfully treated for all thresholds. In the continuous responder curve, the x-axis displays the thresholds required to classify a patient as a successfully treated patient. The y-axis represents the proportion of ITT patients who achieved the corresponding threshold. For example, using study 301, in which the proportion of subject that reached the goal of sUA<6.0 at month 6 is 80% for the LESU 400 + XOI arm, 66% for LESU 200 + XOI arm and 35% for the XOI only arm. In Figure 9, at the vertical reference line of absolute sUA value of 5.0, is 60% for the LESU 400 + XOI arm, 30% for LESU 200 + XOI arm and 6% for the XOI only arm.

As shown in both the figures, the proportion of successfully treated subjects never reaches the full 100% of subjects even for very high thresholds of success since patients with missing data were classified as unsuccessfully treated for all thresholds. Generally, across the studies, no-where the proportions were bigger in the XOI alone arm compared to the LESU + XOI arms. Also evident from the figures is that for studies 301 and 302, there is separation between the treatment groups (better for LESU than placebo) in the proportion of subject successfully treated across a range of thresholds for the definition of success. These plots provide descriptive evidence that the effect of LESU over placebo on the proportion of patients who are sUA responders is not dependent on the specific threshold of 6 mg/dL.

Figure 8: Cumulative Responder Plot for Month 6 sUA Level (Study 301)

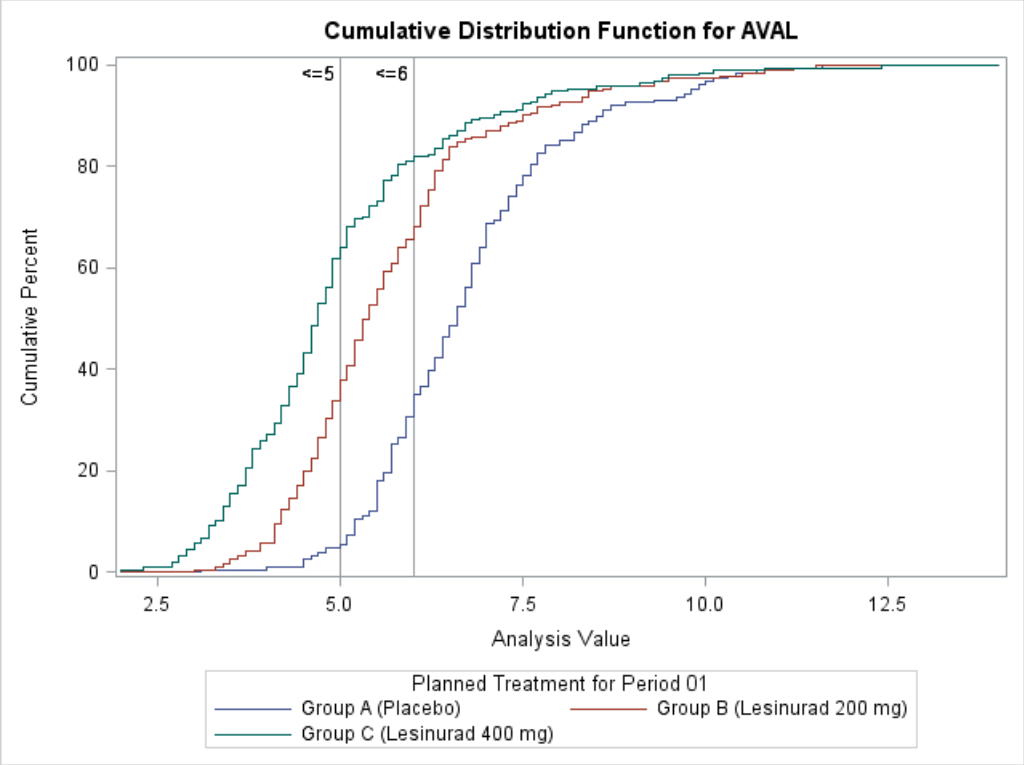
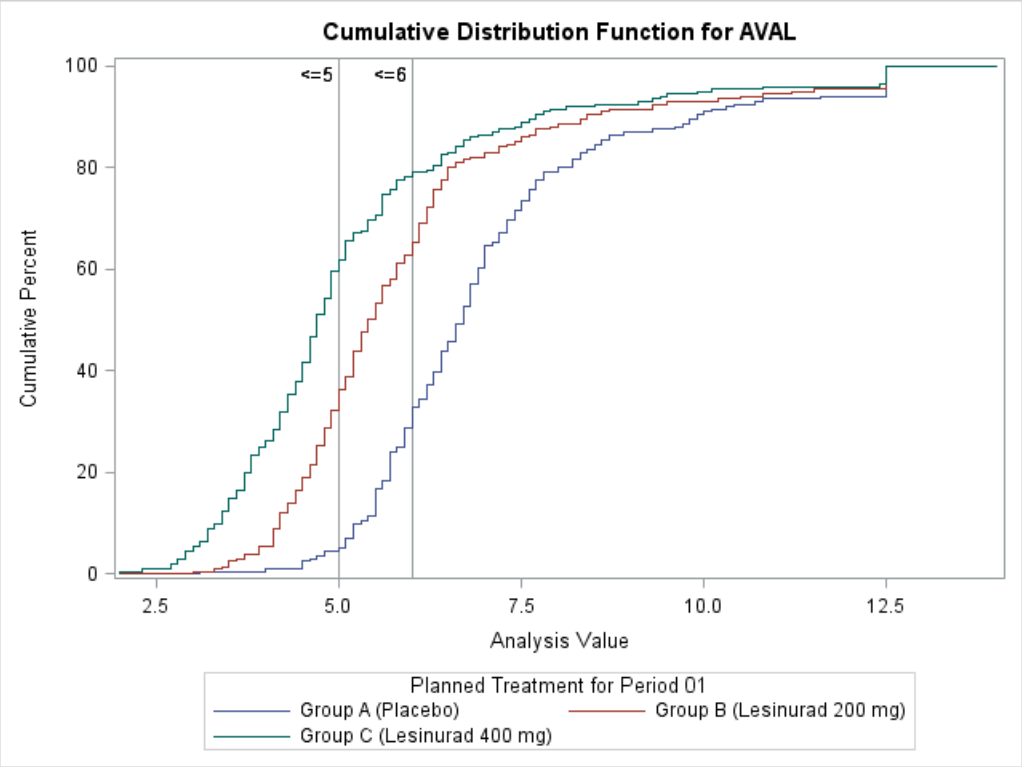


Figure 9: Cumulative Responder Plot for Month 6 sUA Level (Study 302)



5.1.2 Subgroup Analysis

These studies were not pre-planned for subgroup analyses in terms of sample sizes. Also, the very nature of the disease results in few females and few young patients being included. In consequence, quasi-complete separation, which occurs when the level of a categorical predictor variable perfectly predicts the response, is found in two subgroup analyses. In study 304, there is a frequency of 0 (for the cell of placebo treated none responders) in the contingency table of treatment by responder under the female group. This empty cell results in that the treatment of placebo perfectly predicts response (sUA responder) in the female subgroup. As for logistic regression model fitting, this quasi-complete separation causes convergence problem in iterative algorithm for maximum likelihood estimation. As a result, exact tests are utilized in these cases.

5.2 Collective Evidence

As summarized in Table 32, effectiveness of two different dosages was examined: LESU 200 mg + XOI and LESU 400 mg + XOI. The review focused on three phase 3 studies. Statistically significant and reliable (despite for example missing data, threshold used for definition of success in sUA, etc.) demonstration of efficacy of LESU over placebo was achieved for sUA in most cases as is indicated by the checkmark in Table 32. However, no statistically significant benefits of LESU over placebo were identified for any of the key secondary efficacy endpoints, gout flare and tophi resolution, in any study or at any dose as is indicated by the X in Table 32.

Table 30: Summary of the Key Efficacy Test Results

Study	Region	Treatment Arms	LESU 200 vs. Placebo			LESU 400 vs. Placebo		
			sUA	Gout Flare	Tophi	sUA	Gout Flare	Tophi
Replicate Combination Studies (12Months)								
301	US	LESU200mg+ALLO	✓	X	X	✓	X	X
302	Global	LESU400mg+ALLO PBO+ALLO	✓	X	X	✓	X	X
Study for Subjects with Tophaceous Gout (Greater Severity) (12 Months)								
304	Global	LESU200mg+FBX LESU400mg+FBX PBO+FBX	X	X	X	✓	X	X

5.3 Conclusions and Recommendations

Ardea Biosciences, Inc. has proposed Lesinurad (RDEA594) 200 mg once daily (qd), an add-on therapy to a xanthine oxidase inhibitor (XOI) for the chronic treatment of hyperuricemia associated with gout.

Effectiveness and safety of two different dosages of Lesinurad (LESU) were examined with this submission: LESU200mg + XOI and LESU400mg + XOI. The review focused on three phase 3 studies to investigate the efficacy of Lesinurad in terms of serum uric acid (sUA) level, gout flare rate and tophi resolution.

The contribution of LESU over placebo in the presence of background allopurinol (ALLO) for all major endpoints was directly examined. In support of the efficacy of LESU in the presence of ALLO use, after 6 months of treatment, patients assigned to receive LESU 200 and LESU 400 showed statistically greater improvement in pre-defined sUA responder rate than patients assigned to receive placebo. However, statistical significance was not reached in the clinical endpoints, tophi resolution and gout flare rate. In the presence of ALLO use, neither dose of LESU was found to be statistically significant better than placebo in terms of these endpoints.

For the efficacy of LESU over placebo in the presence of background febuxostat (FBX) use, after 6 months of treatment, patients assigned to receive LESU 200 did not show statistically greater improvement in pre-defined sUA responder rate than patients assigned to receive placebo.

Subgroup analyses were conducted to investigate the level of consistency or heterogeneity of the treatment effect across subgroups of interest, including demographic factors age, sex, race, region, and baseline disease characteristics including background allopurinol dose, baseline renal impairment, and baseline sUA group. Possibly due to the small number of females included in the study of a male pre-dominant disease and lack of multiplicity control, among the series of subgroup analysis conducted, there are two statistically significant findings, one of sex, one of baseline sUA level. While the one with sex may due to chance, the one found with sUA level in study investigating the add-on effect to Febuxostat is reasonable. However, as the primary efficacy was not established in this study, interpretation is complicated.

This submission supports effectiveness of LESU200mg in the presence of ALLO for once daily treatment of hyperuricemia associated with gout [redacted] (b) (4) in terms of the primary efficacy endpoint, sUA responder rate at month 6. However, no statistically significant benefit for lesinurad over placebo in terms of any of the secondary clinical efficacy endpoints was found.

6 APPENDICES

Table 31: Study 301, Differences of Proportion of Subjects with Month 6 sUA Levels < 6.0 mg/dL (NRI, ITT), and Difference of Least Square Means (LOCF, ITT) by Subgroup Factors

Subgroup	Difference of Proportion (sUA < 6.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
	LESU400 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value	LESU400 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value
--------Age Group--------		.	.		0.812	.	.	.	.	0.902
< 65 years	0.323	0.239	0.407	337		-1.26	-1.65	-.870	333	.
>= 65 years	0.263	0.068	0.459	65		-1.12	-1.77	-.477	62	.
----------Sex----------		.	.		0.034	.	.	.	.	0.158
F	0.317	0.017	0.617	27		-1.22	-2.57	0.130	26	.
M	0.311	0.231	0.391	375		-1.22	-1.58	-.862	369	.
-------Race Group--------		.	.		0.520	.	.	.	.	0.314
Non-White	0.239	0.079	0.399	93		-.784	-1.63	0.067	91	.
White	0.334	0.246	0.422	309		-1.36	-1.73	-.994	304	.
--Baseline Allopurinol---		.	.		0.866	.	.	.	.	0.471
300	0.323	0.242	0.404	359		-1.20	-1.57	-.833	355	.
< 300	0.250	-.064	0.564	24		-1.76	-2.81	-.709	23	.
> 300	0.282	-.105	0.669	19		-1.79	-3.95	0.361	17	.
-Baseline Renal Function-		.	.		0.422	.	.	.	.	0.315
<45	0.233	-.037	0.504	35		-1.17	-2.44	0.095	33	.
45 to <60	0.188	-.050	0.426	46		-1.00	-1.84	-.160	45	.
>= 60	0.335	0.249	0.421	319		-1.22	-1.62	-.833	315	.

Table 32: Study 302, Differences of Proportion of Subjects with Month 6 sUA Levels < 6.0 mg/dL (NRI, ITT), and Difference of Least Square Means (LOCF, ITT) by Subgroup Factors

Subgroup	Difference of Proportion (sUA < 6.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
	LESU400 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value	LESU400 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value
--------Age Group--------		.	.		0.813	.	.	.	.	0.606
< 65 years	0.430	0.353	0.508	360		-1.41	-1.77	-1.06	352	.
>= 65 years	0.442	0.225	0.659	46		-.938	-1.75	-.126	45	.
----------Sex----------		.	.		0.907	.	.	.	.	0.961
F	0.300	-.095	0.695	16		-1.18	-3.28	0.922	15	.
M	0.435	0.361	0.510	390		-1.36	-1.70	-1.03	382	.
-------Race Group--------		.	.		0.279	.	.	.	.	0.394
Non-White	0.291	0.131	0.451	90		-.962	-1.76	-.165	89	.
White	0.467	0.386	0.549	315		-1.45	-1.81	-1.09	307	.
--------Region ---------		.	.		0.420	.	.	.	.	0.061
Non-USA	0.380	0.275	0.485	205		-.983	-1.51	-.459	202	.
USA	0.488	0.387	0.590	201		-1.77	-2.17	-1.37	195	.
--Baseline Allopurinol---		.	.		0.519	.	.	.	.	0.727
300	0.442	0.363	0.521	345		-1.41	-1.75	-1.06	337	.
< 300	0.479	0.210	0.747	26		-1.54	-2.75	-.322	26	.
> 300	0.267	-.003	0.536	35		-.979	-2.59	0.636	34	.
-Baseline Renal Function-		.	.		0.901	.	.	.	.	0.611
<45	0.567	0.214	0.920	16		-.767	-2.77	1.240	16	.
45 to <60	0.352	0.139	0.566	53		-.751	-1.45	-.048	52	.
>= 60	0.434	0.354	0.515	335		-1.46	-1.84	-1.09	328	.

Table 33: Study 304, Differences of Proportion of Subjects with Month 6 sUA Levels < 5.0 mg/dL (NRI, ITT), and Difference of Least Square Means (LOCF, ITT) by Subgroup Factors

Subgroup	Difference of Proportion (sUA < 5.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
	LESU400 + FBX v. FBX	LL	UL	N	Interaction Test p-value	LESU400 + FBX v. FBX	LL	UL	N	Interaction Test p-value
--------Age Group--------	.	.	.		0.374	.	.	.	.	0.059
< 65 years	0.328	0.216	0.440	179		-1.87	-2.40	-1.34	173	.
>= 65 years	0.132	-.127	0.390	39		-2.00	-3.24	-.756	39	.
----------Sex----------	.	.	.		0.832*	.	.	.	.	0.880
F	0.714	0.433	0.995	9		-2.75	-6.30	0.806	9	.
M	0.288	0.183	0.393	209		-1.89	-2.39	-1.40	203	.
-------Race Group--------	.	.	.		0.782	.	.	.	.	0.455
Non-White	0.392	0.143	0.640	39		-2.62	-3.90	-1.34	36	.
White	0.274	0.160	0.389	179		-1.76	-2.30	-1.23	176	.
--------Region ---------	.	.	.		0.813	.	.	.	.	0.541
Non-USA	0.327	0.122	0.531	55		-1.55	-2.55	-.545	55	.
USA	0.281	0.161	0.401	163		-2.00	-2.56	-1.44	157	.
-Baseline Renal Function-	.	.	.		0.673**	.	.	.	.	0.626
<45	0.750	0.498	1.000	12		-1.70	-4.48	1.076	12	.
45 to <60	0.119	-.158	0.396	35		-1.37	-2.65	-.086	35	.
>= 60	0.305	0.190	0.421	171		-1.91	-2.46	-1.36	165	.
-Baseline sUA Group-	.	.	.		0.108	.	.	.	.	0.048
< 5.0 mg/dL	0.138	0.006	0.270	116		-1.57	-2.19	-.945	114	.
>= 5.0 mg/dL	0.471	0.327	0.614	102		-2.27	-3.02	-1.52	98	.

*: Due to the existence of quasi-complete separation, an exact test was performed for Sex by Treatment interaction effect, the score statistic associated exact p-value is 0.81.

**: For the Baseline Renal Function by Treatment interaction effect, the score statistic associated exact p-value is 0.40.

Table 34: Pooled Studies 301 and 302, Differences of Proportion of Subjects with Month 6 sUA Levels < 6.0 mg/dL (NRI, ITT), and Difference of Least Square Means (LOCF, ITT) by Subgroup Factors

Subgroup	Difference of Proportion (sUA < 6.0 mg/dL)					Difference of Least Square Mean (mg/dL)				
	LESU400 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value	LESU400 + ALLO v. ALLO	LL	UL	N	Interaction Test p-value
--------Age Group--------		.	.		0.888	.	.	.	.	0.575
< 65 years	0.378	0.321	0.436	697		-1.34	-1.60	-1.08	685	.
>= 65 years	0.338	0.192	0.484	111		-1.04	-1.54	-.534	107	.
----------Sex----------		.	.		0.060	.	.	.	.	0.366
F	0.348	0.113	0.584	43		-1.27	-2.37	-.158	41	.
M	0.374	0.320	0.429	765		-1.30	-1.54	-1.05	751	.
-------Race Group--------		.	.		0.392	.	.	.	.	0.194
Non-White	0.266	0.153	0.379	183		-.885	-1.46	-.306	180	.
White	0.401	0.341	0.462	624		-1.41	-1.67	-1.15	611	.
--------Region ---------		.	.		0.888	.	.	.	.	0.382
Non-USA	0.380	0.275	0.485	205		-.983	-1.51	-.459	202	.
USA	0.371	0.309	0.433	603		-1.40	-1.66	-1.13	590	.
--Baseline Allopurinol---		.	.		0.834	.	.	.	.	0.823
300	0.381	0.324	0.438	704		-1.30	-1.56	-1.05	692	.
< 300	0.374	0.169	0.579	50		-1.66	-2.48	-.846	49	.
> 300	0.258	0.042	0.475	54		-.863	-2.11	0.385	51	.
-Baseline Renal Function-		.	.		0.569	.	.	.	.	0.441
<45	0.338	0.120	0.556	51		-1.35	-2.39	-.311	49	.
45 to <60	0.272	0.113	0.430	99		-.913	-1.45	-.379	97	.
>= 60	0.386	0.327	0.445	654		-1.35	-1.61	-1.08	643	.

Figure 10: Study 301, Differences of Proportion, LESU 400 + ALLO vs. ALLO for Subjects with Month 6 sUA Levels < 6.0 mg/dL, by Subgroup Factors (None Responder Imputation, ITT)

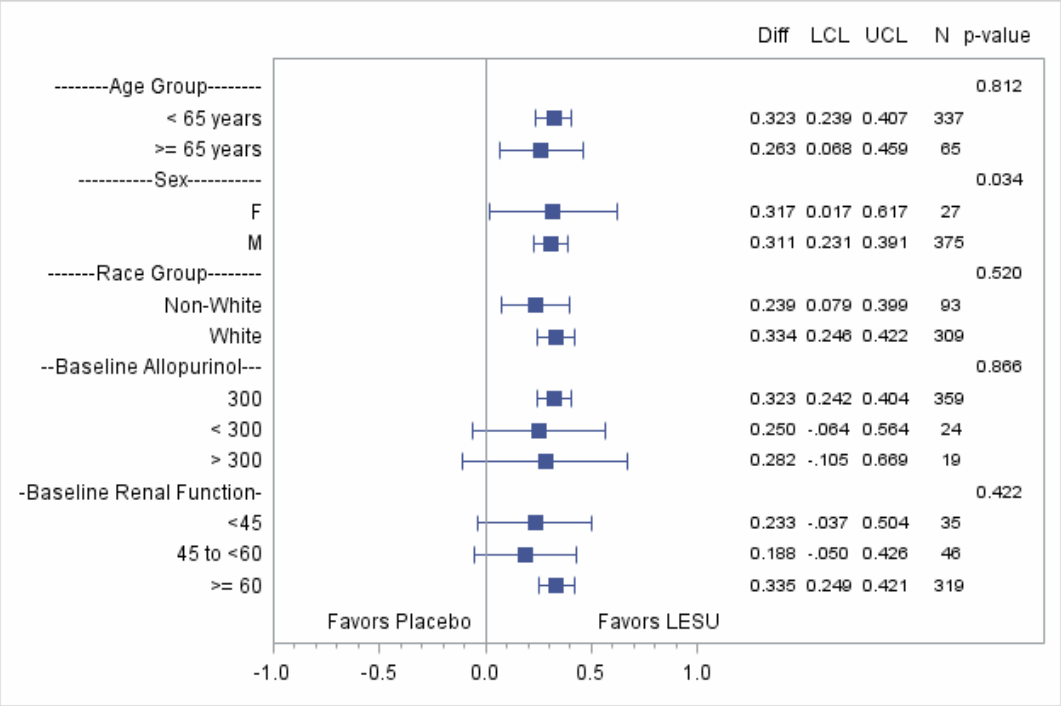


Figure 11: Study 302, Differences of Proportion, LESU 400 + ALLO vs. ALLO for Subjects with Month 6 sUA Levels < 6.0 mg/dL, by Subgroup Factors (None Responder Imputation, ITT)

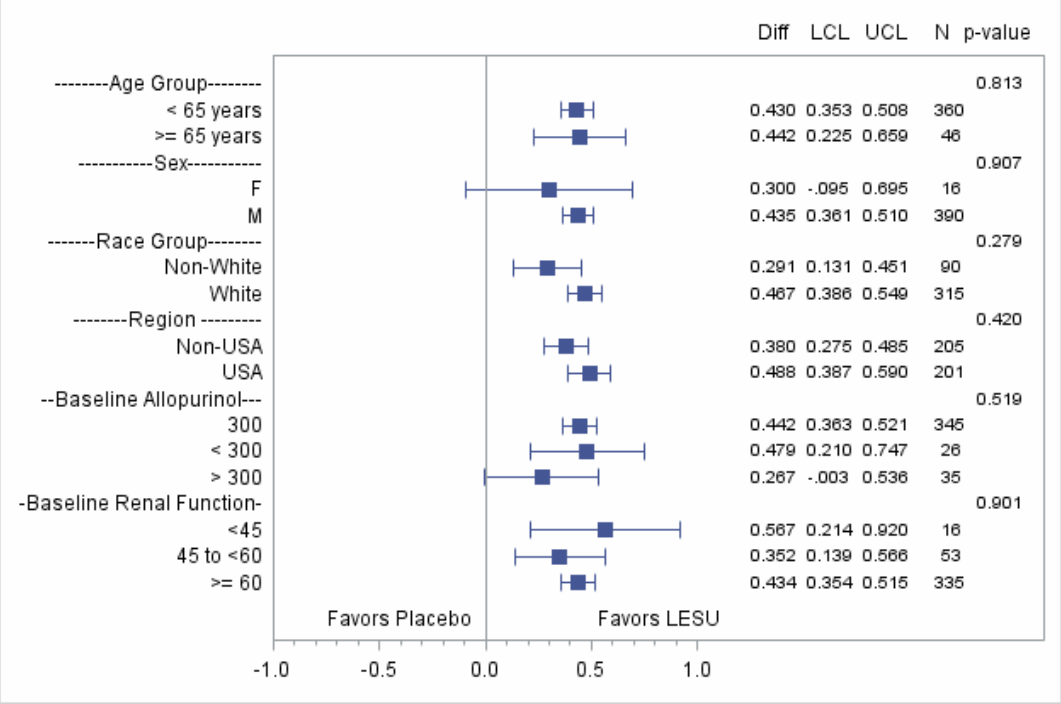


Figure 12: Study 304, Differences of Proportion, LESU 400 + ALLO vs. ALLO for Subjects with Month 6 sUA Levels < 5.0 mg/dL, by Subgroup Factors (None Responder Imputation, ITT)

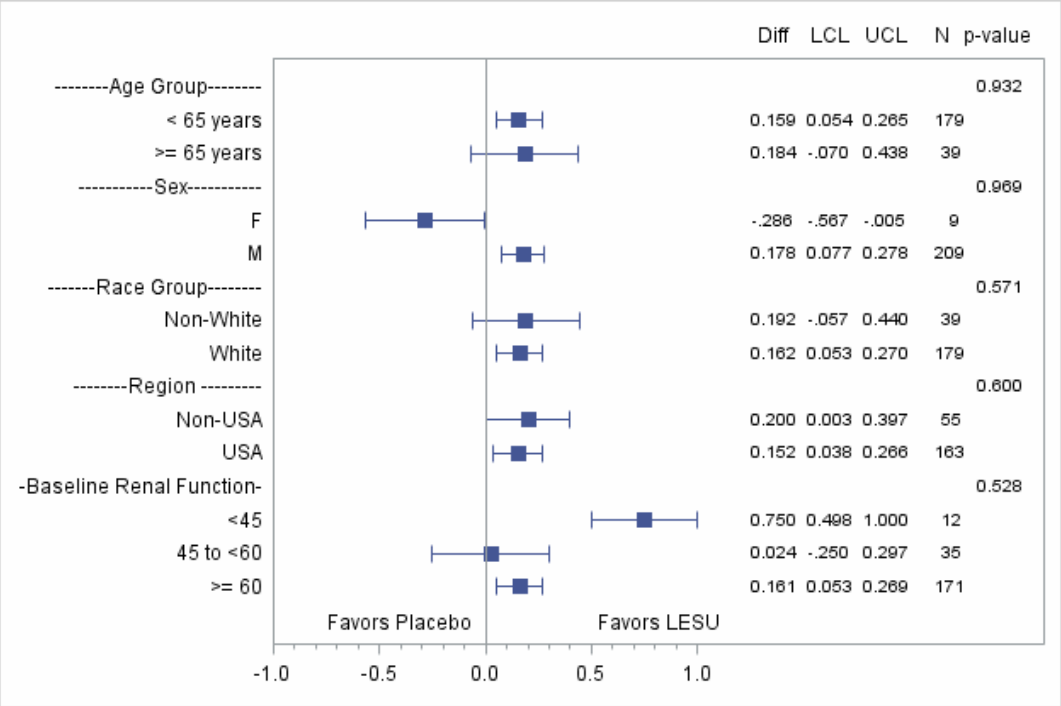


Figure 13: Studies 301 and 302, Differences of Proportion, LESU 400 + ALLO vs. ALLO for Subjects with Month 6 sUA Levels < 5.0 mg/dL, by Subgroup Factors (None Responder Imputation, ITT)

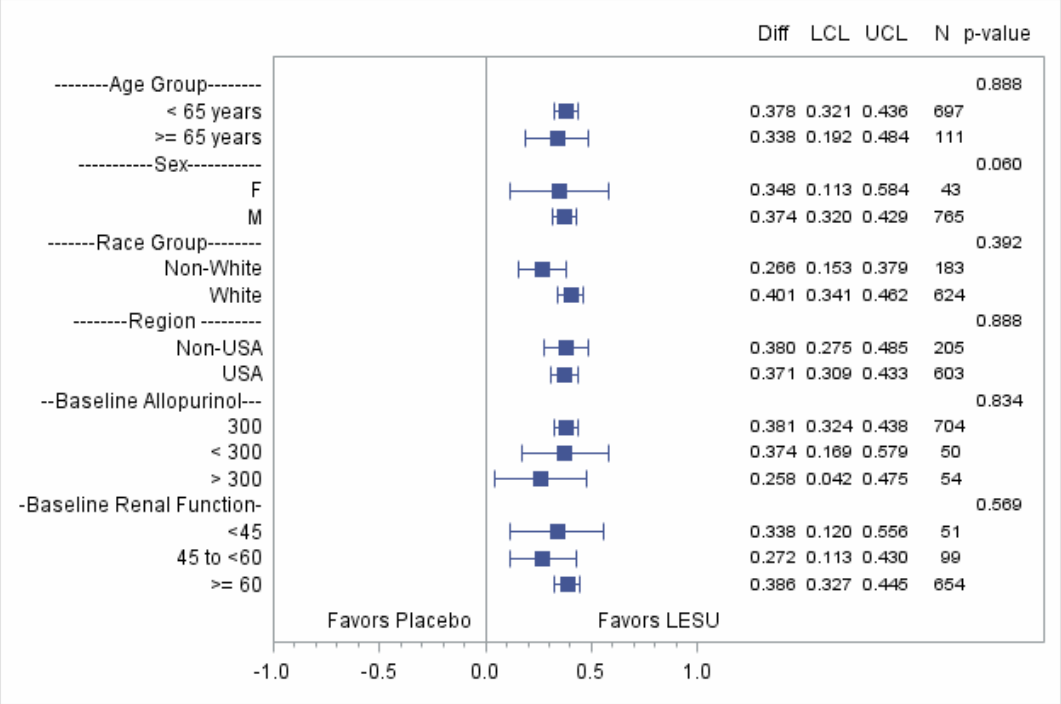


Figure 14: Study 301, Estimated Mean Differences, LESU 200 + ALLO vs. ALLO, of Change from Baseline Month 6 sUA Levels, by Subgroup Factors (LOCF, ITT)

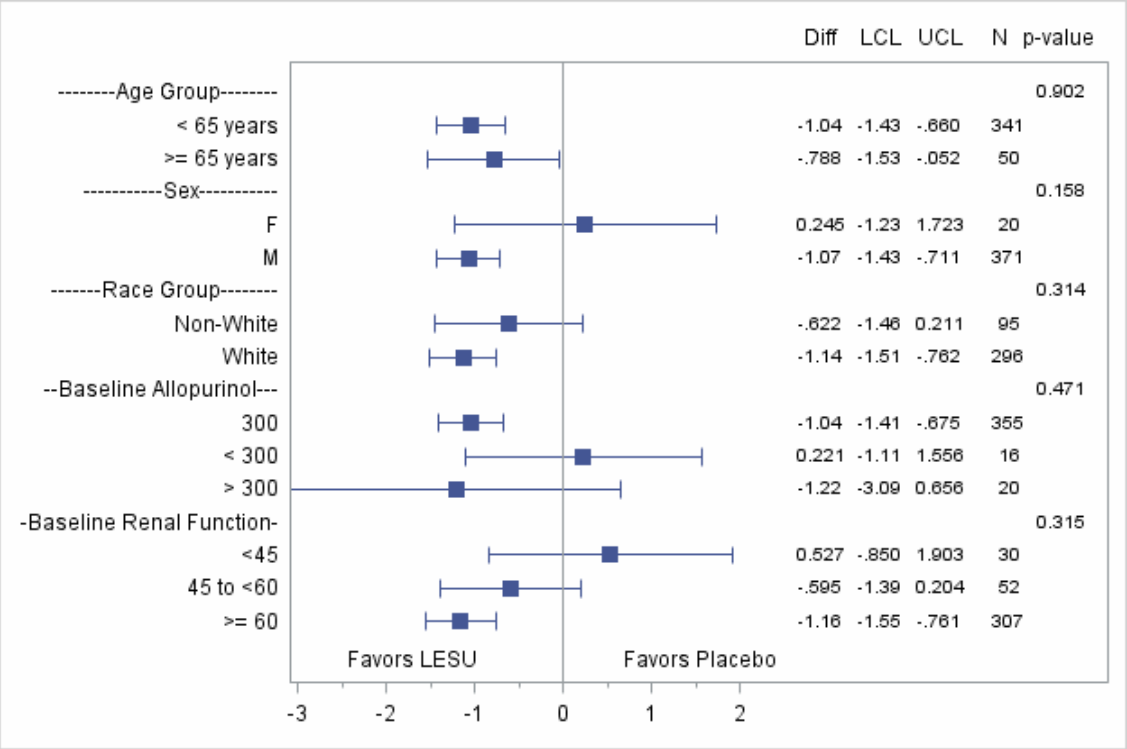


Figure 15: Study 301, Estimated Mean Differences, LESU 400 + ALLO vs. ALLO, of Change from Baseline Month 6 sUA Levels, by Subgroup Factors (LOCF, ITT)

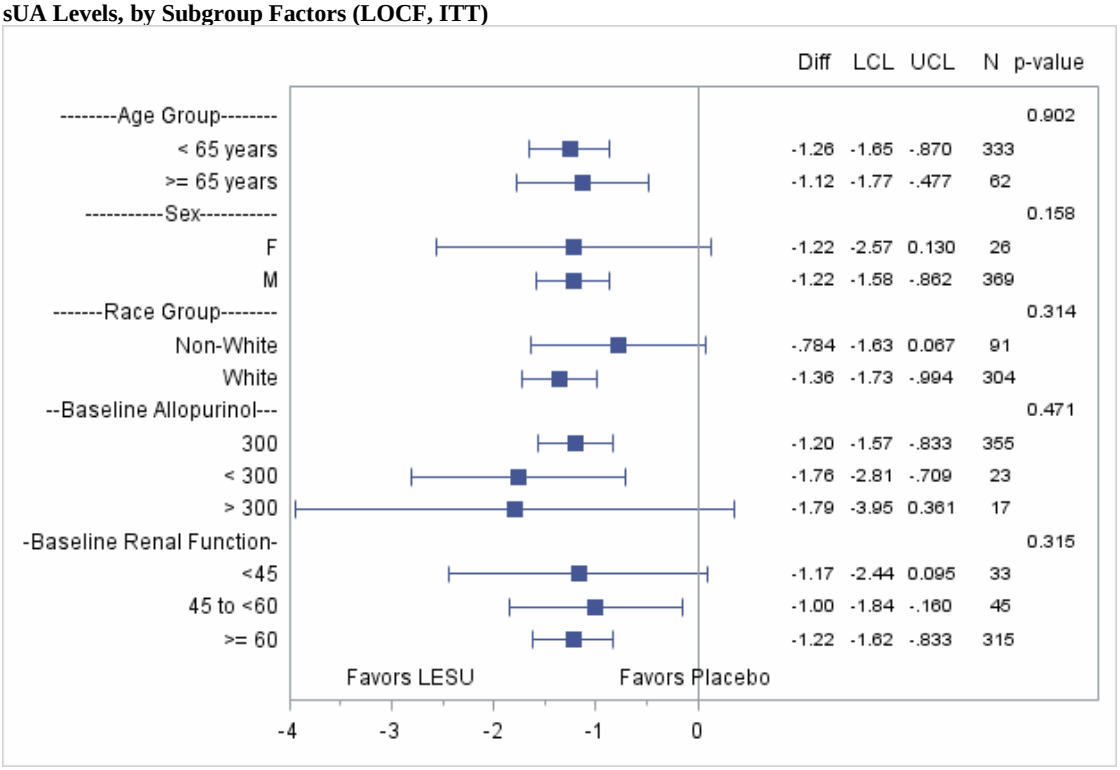


Figure 16: Study 302, Estimated Mean Differences, LESU 200 + ALLO vs. ALLO, of Change from Baseline Month 6 sUA Levels, by Subgroup Factors (LOCF, ITT)

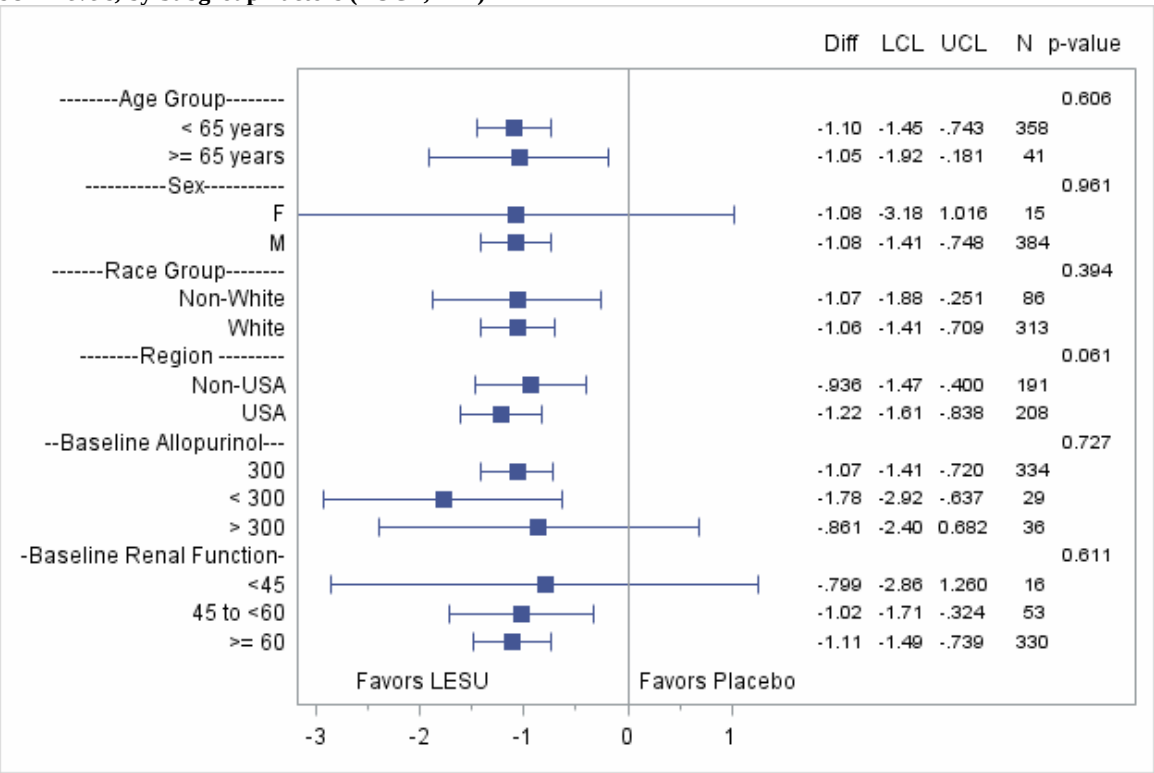


Figure 17: Study 302, Estimated Mean Differences, LESU 400 + ALLO vs. ALLO, of Change from Baseline Month 6 sUA Levels, by Subgroup Factors (LOCF, ITT)

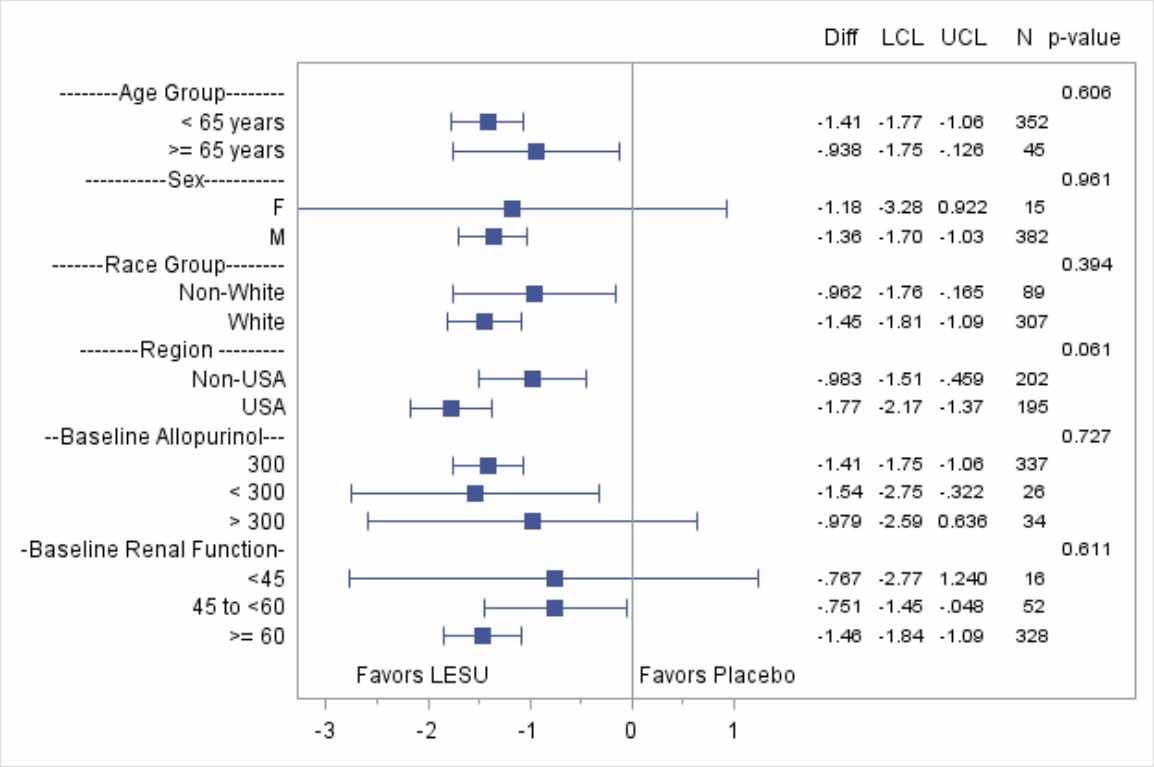


Figure 18: Study 304, Estimated Mean Differences, LESU 200 + ALLO vs. ALLO, of Change from Baseline Month 6 sUA Levels, by Subgroup Factors (LOCF, ITT)

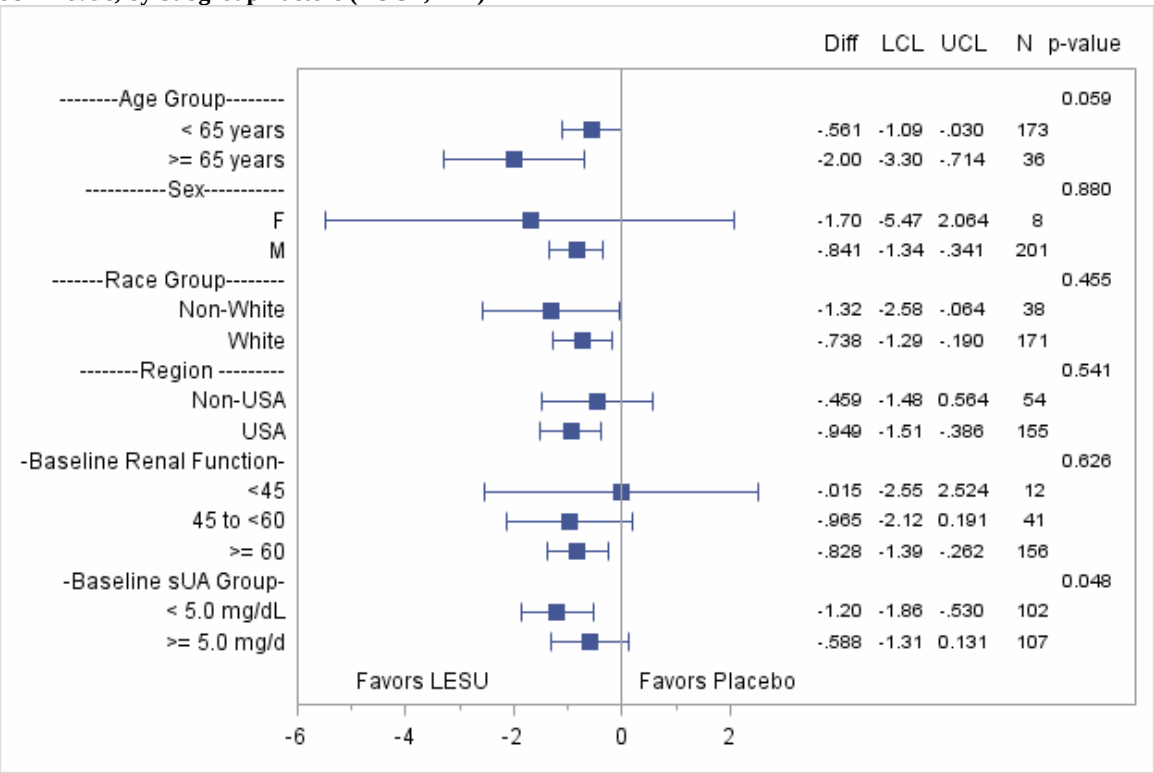


Figure 19: Study 304, Estimated Mean Differences, LESU 400 + ALLO vs. ALLO, of Change from Baseline Month 6 sUA Levels, by Subgroup Factors (LOCF, ITT)

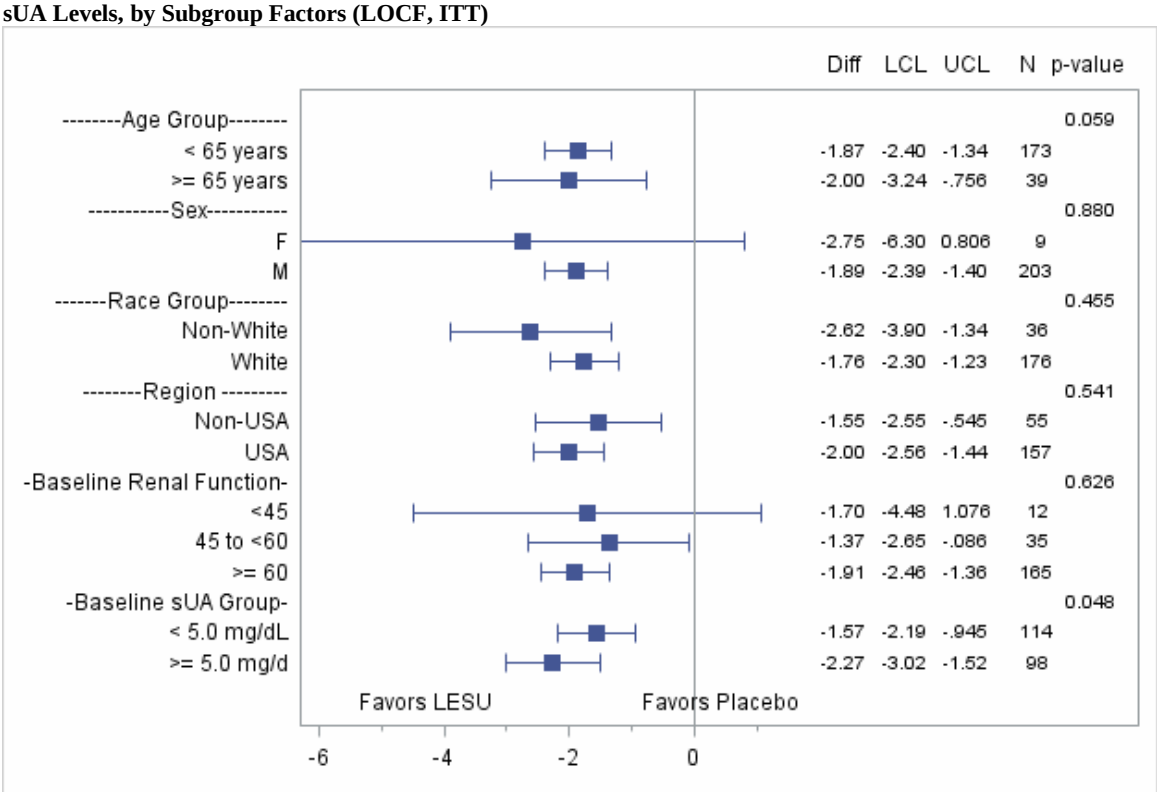


Figure 20: Pooled Studies 301 and 302, Estimated Mean Differences, LESU 200 + ALLO vs. ALLO, of Change from Baseline Month 6 sUA Levels, by Subgroup Factors (LOCF, ITT)

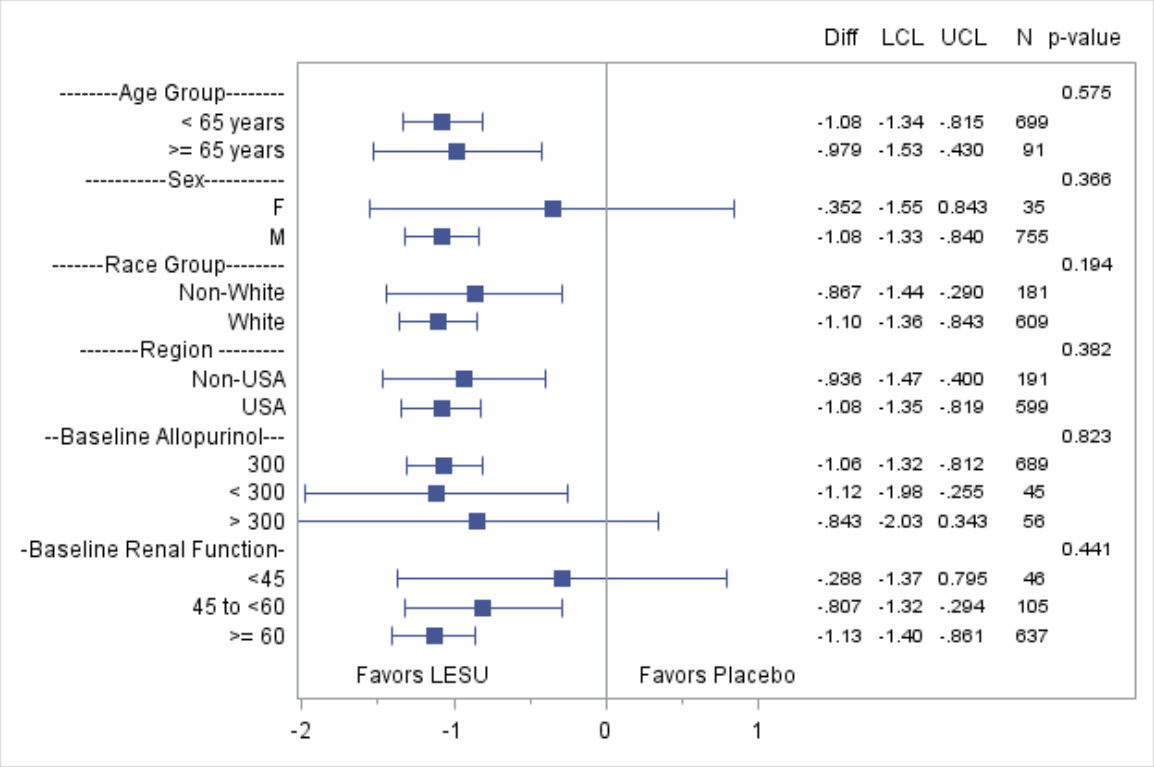
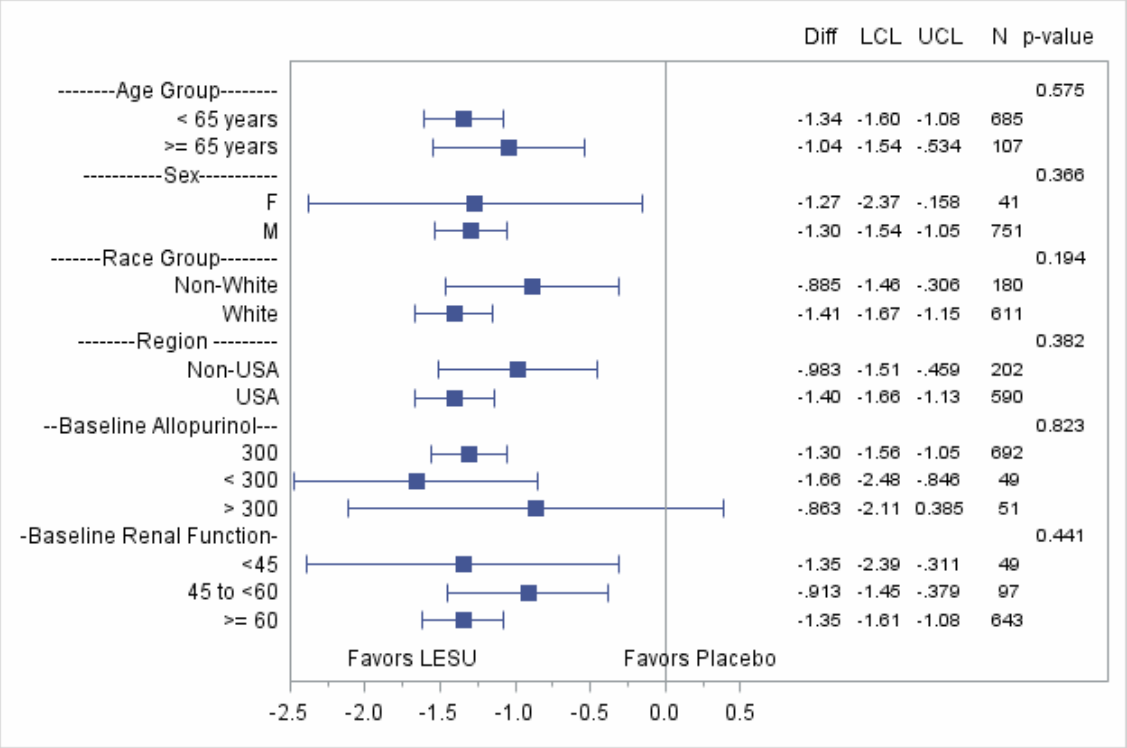


Figure 21: Pooled Studies 301 and 302, Estimated Mean Differences, LESU 400 + ALLO vs. ALLO, of Change from Baseline Month 6 sUA Levels, by Subgroup Factors (LOCF, ITT)



7 Bibliography

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/s/

YU WANG
10/08/2015

RUTHANNA C DAVI
10/08/2015

STATISTICS FILING CHECKLIST FOR NDA 207988

NDA Number: 207988 **Applicant:** Ardea Bioscience, Inc. **Stamp Date:** December 29, 2014

Drug Name: Lesinurad **NDA Type:** Standard

On **initial** overview of the NDA application for RTF: **Studies 301, 302 and 304**

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Comment:

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR NDA 207988

Brief Summary of Pivotal Studies

The clinical development program focuses on 3 randomized, placebo controlled, double blind, multicenter, 12 months studies as summarized in the table below. The replicate studies 301 and 302 investigated the effect of Lesinurad as an add-on therapy compared with placebo for patients whose gout symptoms could not stabilized with Allopurinol. Study 304 targets a generally severe, longstanding, symptomatic gout patient population who had tophi at screening with Lesinurad as an add-on therapy to Febuxostat compared with placebo on Febuxostat.

Design Summary of Key Phase III Studies

Study	Region	Treatment Arms*	Primary Endpoint
Replicate Combination Studies (12Months)			
301 (CLEAR1)	US (N=607)	Lesinurab200mg+ Allopurinol Lesinurab400mg+ Allopurinol Placebo+ Allopurinol	Proportion by M6 achieving the sUA target level of <6.0 mg/dL
302 (CLEAR2)	Global (N=611)		
Study for Subjects with Tophaceous Gout (Greater Severity) (12Months)			
304 (CRYSTAL)	Global (N=330)	Lesinurab200mg+ Febuxostat Lesinurab400mg+ Febuxostat Placebo+ Febuxostat	Proportion by M6 achieving the sUA target level of <5.0 mg/dL

Subjects were randomized at a 1:1:1 ratio to the three arms under each study. Patients are followed-up for 12 months while the primary efficacy time point is month 6. The primary efficacy endpoint is a surrogate biomarker: serum Uric Acid (sUA) level. While the two CLEAR studies targeted a sUA level at 6.0 mg/dL, the CRYSTAL study targeted a stricter level 5.0 mg/dL due to the clinical goal of gout resolution. The primary analysis of the responder rate is a CMH test stratified by renal function at Day 7 and tophus status at screening. Multiple comparisons of two dose strengths with placebo were controlled with Bonferroni correction of Type I error rate. The secondary efficacy endpoints include proportion of subjects who experienced complete or partial tophus resolution, mean rate of gout flares from month 6 to month 12. The mean rate of gout flares were analyzed by a linear model assuming negative binomial distribution of flare count.

For the primary analyses, a non-responder imputation was used to handle missing data handling.

Among the three studies, studies 301 and 302 demonstrated efficacy in the primary responder analyses, study 304 failed to meet its primary endpoint.

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/s/

YU WANG
02/20/2015

DAVID M PETULLO
02/20/2015
I concur.