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#	207-988
Drug Name:	Zurampic (Lesinurad) 200mg 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 PDUFA goal date: December 29, 2015
Review Priority:	Standard
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Keywords: subgroup analyses

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1 EXECUTIVE SUMMARY

This review examined existing data to assess the treatment effect of Zurampic 200mg on the serum uric acid (sUA) level < 6.0 mg/dL responder rate at month 6 within each sex, age, race, and ethnicity subgroup and whether the treatment effect of Zurampic 200mg on sUA level < 6.0 mg/dL responder rate at month 6 differs by sex, age, race, or ethnicity. We acknowledge that the analyses provided in this review are exploratory and the trials were not designed to support such investigations. Despite possible statistical limitations, these investigations were undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data.

We consider results from three studies, two in gout patients receiving background allopurinol (Studies A and B) and one in gout patients receiving background febuxostat (Study C). Our general conclusions on the subgroup analyses were mainly based on the integrated Studies A and B as these two studies were similar in design. In addition, in most cases, the individual study subgroup analysis results were consistent between these two studies. Study C data were analyzed similarly, but due to smaller sample sizes, a potential study design issue, and the lack of evidence of a treatment effect in the overall study population, this study was given less weight. Also, we mainly based our judgment on Zurampic 200mg data as this is the dose approved by the Agency. Data from Zurampic 400mg were used as supportive evidence when needed. In the single Studies A or B, the small sample size of some subgroups (e.g., women) does not provide enough precision to reliably evaluate whether the treatment effect might differ in those subgroups. That being said, in Studies A and B, there was statistical evidence of a treatment effect of Zurampic 200mg relative to placebo on sUA level < 6.0 mg/dL responder rate at month 6 within most of the subgroups examined (by sex, age, race, and ethnicity). In particular, this review concludes, based on the totality of the data, that

- Zurampic 200mg appears to be efficacious compared with placebo with respect to the sUA < 0.6 mg/dL responder rate at month 6 within each age group (below 65 years and 65 years and above). Available data did not give a strong indication that the treatment effect for Zurampic 200mg is larger in one age group than the other.

- Zurampic 200mg appears to be efficacious compared with placebo with respect to the sUA < 0.6 mg/dL responder rate within male patients with gout. Available data for the female patient subgroup is too limited to draw conclusions about whether the treatment effect for Zurampic 200mg exists in females (without borrowing information from male subjects). There was some evidence of a difference between treatment effects in men and women in a single study. However, with the small female patient numbers and the relatively large number of subgroup analyses performed in this review, as well as the lack of consistency in treatment by sex interaction findings across studies and doses, we have little evidence to suggest that the treatment effect truly differs by sex. Based on these considerations and using all available data, including data in males, we suppose that Zurampic 200mg is superior to placebo even in female patients.

- There was evidence of a treatment effect for the White, Black, and Asian subgroups. For smaller racial subgroups (combined in the analyses), while positive estimates were observed, small sample sizes resulted in wide confidence intervals. There was no evidence of a treatment by race interaction in any of the individual or combined analyses.

- There was evidence of a treatment effect for both the Hispanic/Latino and not Hispanic/Latino subgroups. For the smaller Hispanic/Latino subgroup, while positive estimates of similar size were observed, small sample sizes resulted in wide confidence intervals. There was no evidence of a treatment by ethnicity interaction in any of the individual or combined analyses.

Display of data to describe the effect of Zuramipic by sex, age, race, and ethnicity on the proportion of subjects with sUA<6 (sUA<5 for Study C) could reliably be achieved by displaying results from the following.

(1.) Studies A and B combined since they were identically designed with the exception that study A was conducted in the US and study B was a global study.
(2.) Study C alone due to the unique patient population and other design characteristics.

2 INTRODUCTION

This statistical review is written under FDA's 2014 action plan to enhance the collection and availability of demographic subgroup data. The objective of the review is to use existing data to understand the effects of Zurampic 200mg within age, sex, racial, and ethnic subgroups and whether these effects differ across subgroups.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

3.1 Available Data

The applicant proposed and the Agency has approved[1] Zurampic 200mg to be used in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.

The applicant provided results of two phase 3 trials (referred to in this document as study A and B) conducted to evaluate the efficacy and safety of Zurampic in combination with allopurinol versus allopurinol alone in gout patients who have had an inadequate hypouricemic response

[1] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207988Orig1s000ltr.pdf

to allopurinol, and one phase 3 trial (referred to in this document as C) conducted similarly, with allopurinol replaced by febuxostat in gout patients with tophi at baseline.

The three studies were all randomized, placebo controlled, double-blind, multicenter trials. Among them study A was conducted in the US; studies B and C were both multinational studies. Key features of these studies are summarized in Table 1. In all studies, the primary efficacy endpoint to evaluate the contribution of Zurampic was the proportion of subjects with an sUA level < 6.0 mg/dL (or 5.0 mg/dL in study C with tophi patients) at month 6. Readers of this review may refer to my primary statistical review for additional details on the design and results of these studies.

Table 1: Study Designs

Study	Patient Population	Treatment Duration (Months)	Treatment Groups	Randomized patients
Allopurinol Background				
Study A **RDEA594-301**	Inadequate responders to allopurinol: -Had a history of at least 2 gout flares in the prior year -Already on a stable medically appropriate dose of allopurinol for at least 8 weeks at screening -Had sUA levels repeatedly greater than the recommended treatment goal	12	**Zurampic**: 200mg once daily **Zurampic**: 400mg once daily **Placebo**	202 202 203
Study B **RDEA594-302**		12	**Zurampic**: 200mg once daily **Zurampic**: 400mg once daily **Placebo**	204 201 206
Febuxostat Background				
Study C **RDEA594-304**	Subjects with: -Tophaceous gout -Elevated sUA	12	**Zurampic**: 200mg once daily **Zurampic**: 400mg once daily **Placebo**	106 109 109

Consistent with product labeling, these three phase 3 trials are the basis of the efficacy portion of the "drug snapshot" and the evaluation of whether treatment effects vary across subgroups. The primary efficacy results from the phase 3 studies showing comparisons between Zurampic and placebo with respect to sUA level reduction in the overall study population are summarized in Table 2.

Table 2: Results of Primary Efficacy Analyses in Studies A, B, and C: Proportion of Subjects with an sUA Level < 6 mg/dL (< 5 mg/dL for study C) at Month 6 (Non-Responder Imputation for Dropouts)

Study	Treatment Groups	Treatment Difference (Zurampic – Placebo)	
		Difference in Proportion	95% CI
Allopurinol Background			
Study A RDEA594-301	**Zurampic**: 200mg once daily	0.26	(0.17, 0.36)
Study B RDEA594-302	**Zurampic**: 200mg once daily	0.32	(0.23, 0.41)
Febuxostat Background			
Study C RDEA594-304	**Zurampic**: 200mg once daily	0.10	(-0.03, 0.23)

3.2 Statistical Methods for Assessing Differences in Treatment Effect across Subgroups

To assess the overall efficacy of a product, that is, the treatment effect in the overall population, we typically rely on replicated results from more than one study, each of which may represent a different patient population, dose regimen or background therapy. With this review and its supporting analyses, our objective is to characterize the differences in treatment effect across subgroups. In this pursuit, we rely on two statistical tools: combining data from individual studies to gain precision of characterization or power of comparison, and tests of treatment by subgroup interactions to detect potential treatment effect differences across subgroups. In planning analyses to assess differences in treatment effect across subgroups, the merits of combining studies to provide increased power for small subgroups were weighed against the merits of analyzing all studies separately so as not to miss possible clinical settings where differences in treatment effect across subgroups differ for different populations, dose regimens or background therapy. When the decision of combining studies is made, at the same time of interpreting the combined treatment effect by subgroup, we will also look at individual studies to identify possible sources that may result in differences across studies or populations in terms of differences in treatment effect across subgroups. While we acknowledge that differences in the treatment effect across differing populations or background medications are possible, even likely, we note that consistency in the treatment effect across studies is not

needed to justify combining studies for the purpose of identifying subgroups where the treatment effect differs. The objective of this review and these analyses is different from assessing the overall efficacy of the product. It is to characterize the differences in treatment effect across subgroups. The important assumption of this type of combined analysis is that if there are differences in the treatment effect between certain subgroups these differences by subgroup should be similar in studies with different populations or background therapy. For example if the treatment effect for Zurampic in males is larger than that of females in a population such as used in study A, combining study A with a population such as is used in study B is more agreeable if the treatment effect for Zurampic is also larger for males than females in the population used in study B. We believe that in general this type of assumption might be more likely to be true than the assumption that the overall treatment effect is similar across different populations and background therapies.

As introduced in the previous section, Studies A and B were similar in design with the only difference being Study A was conducted in North America and Study B was a global study. Aside from this regional difference, the two studies had the same xanthine oxidase inhibitor allopurinol as background therapy, enrolled patients of the same disease severity category, and were the same in terms of other trial design elements. In addition, the two studies had similar estimated overall effect sizes (proportional difference of 26% vs. 32%) in terms of sUA level reduction responder rate and were the main basis for the approval of Zurampic 200mg by the FDA. With these considerations in mind, data from the two allopurinol add-on studies (Studies A and B) were combined for examination of consistency of treatment effect across subgroups.

As a result of the afore-mentioned considerations about combining studies, subgroup results for the individual Studies A and B were also examined to help explore consistency in any findings across studies.

Study C was not included in the combined analysis of Studies A and B for several reasons. The study population of Study C was different than those of Studies A and B. Instead of enrolling patients who had inadequate urate control with a stable xanthine oxidase inhibitor, Study C enrolled patients whose disease status reached a more severe level, as only patients who had tophi at screening were entered into this study. In addition, a stable xanthine oxidase inhibitor was not required at screening, and patients were titrated on febuxostat to a stable dose in the run-in period. This may potentially explain why around 50% of patients reached target sUA level criteria at baseline, which may in turn contribute to the failure of the study to demonstrate overall efficacy of Zurampic 200mg over placebo on the background of febuxostat. Still, there were trends toward benefit for other measures of sUA reduction for Zurampic 200mg in Study C (including a similar mean reduction of around 1 mg/dL to that of Studies A and B), so there is likely some utility in exploring subgroup analyses from this study.

Due to the fact that the dose of Zurampic 200mg was approved for the add-on therapy to treat hyperuricemia associated with gout, subgroup analyses of the combined Studies A and B and each individual study (A-C) were considered mainly for Zurampic 200mg. When subgroup and treatment interaction results were not consistent between studies on the Zurampic 200mg dose data, subgroup analysis results based on Zurampic 400mg data were also examined for trend and consistency.

In the original application, the treatment effect of Zurampic 200mg (difference in proportion of subjects with an sUA level < 6.0 mg/dL in studies A and B or 5.0 mg/dL in study C between treatment groups) for the individual trials was calculated from the binomial treatment proportions. The corresponding confidence intervals, the Wald asymptotic confidence limits for the difference of proportions, were calculated based on the normal approximation to the binomial distribution. For Studies A and B, the difference in sUA response rates between the Zurampic 200mg 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 C, Day -7 renal function and sUA level at Day -7 were used as stratifying factors.

In this review, for each individual study, the treatment effect of Zurampic 200mg relative to placebo within subgroups was estimated by calculating the proportional difference for each subgroup separately. The difference in treatment effect between subgroups was tested by a treatment by subgroup interaction. When performing the test for treatment by subgroup interaction, I used a logistic regression model by including the stratifying factors used in the original CMH test and the factor subgroup and a term for treatment by subgroup interaction.

In all cases where Studies A and B were combined, the treatment effect of Zurampic 200mg relative to placebo within subgroups was estimated by combining the data from the individual studies. The test for treatment by subgroup interaction was performed using the same model and approach as described for the individual trials with the exception that the model was extended with interaction terms with study for each factor and covariate as used in the model for individual trials (e.g. including subgroup by study interaction, treatment by study interaction and stratification factor by study interactions). This approach was taken to allow the relationship between covariates and the outcome to differ between the studies.

We acknowledge that these analyses are exploratory and the trials were not designed to support such investigations. In general, these comparisons may be limited by multiplicity on one hand and low power considerations on the other. Despite these possible statistical limitations associated with multiplicity and low power, these investigations are undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data. In cases in which an analysis identifies possible subgroup differences, we evaluated a number of additional factors, such as study consistency and consistency across doses (utilizing Zurampic 400mg data) to help explore

whether low p-values for subgroup interaction tests might represent a true difference or a false positive.

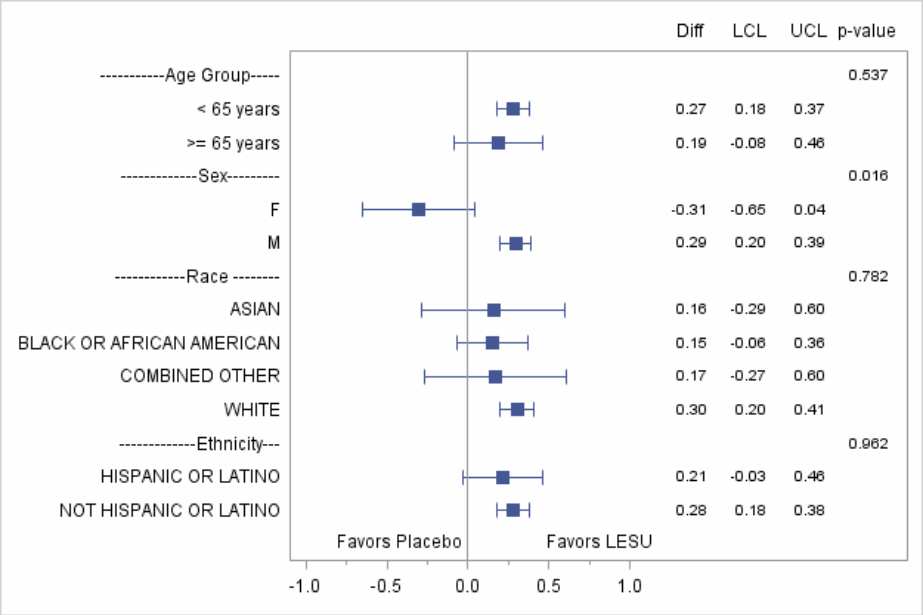
3.3 Results by Sex, Race, Age, and Ethnicity

This section provides estimates of the difference between Zurampic 200mg and placebo in the proportion of subjects with an sUA level < 6.0 (5.0 in Study C) mg/dL at Month 6 by sex, race, age, and ethnicity subgroups. Approximate 95% confidence intervals for treatment differences within each subgroup were constructed using normal approximation to the binomial distribution. Tests for the treatment-by-subgroup interaction are also provided. Table 4 displays the patient demographics by treatment arm. Figures 1 through 4 display results for each study considered individually as well as the combinations of studies A and B. Analogous results are displayed for lesinurad 400mg in the Appendix.

Table 3: Patient Demographics by Treatment (ITT)

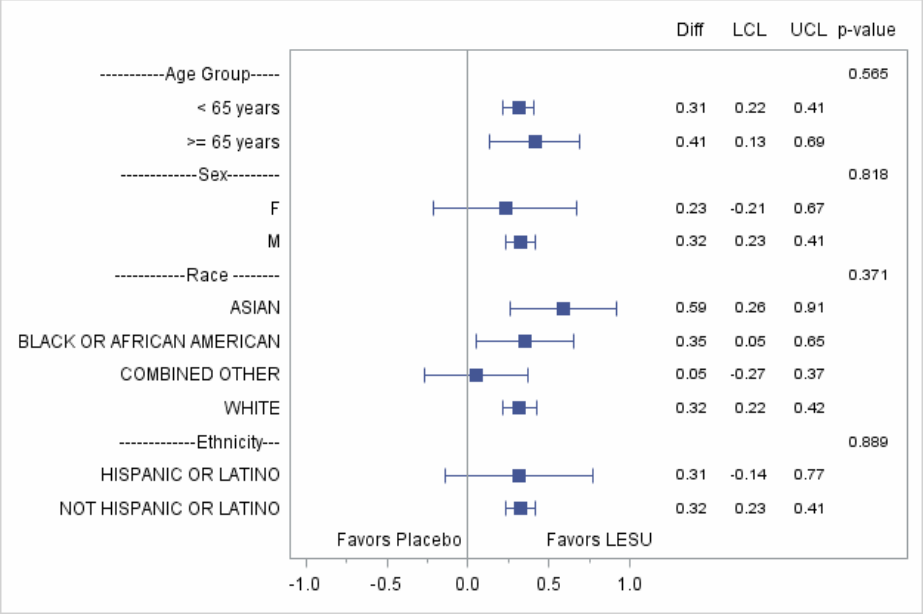
Subgroup	Category	Study A		Study B		Study C	
		Placebo N (%)	Zurampic 200mg N(%)	Placebo N (%)	Zurampic 200mg N(%)	Placebo N (%)	Zurampic 200mg N(%)
Total	N	201	201	206	204	109	106
Age	< 65 YEARS	169 (84%)	181 (90%)	185 (90%)	184 (90%)	89 (82%)	89 (84%)
	>= 65 YEARS	32 (16%)	20 (10%)	21 (10%)	20 (10%)	20 (18%)	17 (16%)
Sex	F	12 (6%)	9 (4%)	10 (5%)	7 (3%)	2 (2%)	6 (6%)
	M	189 (94%)	192 (96%)	196 (95%)	197 (97%)	107 (98%)	100 (94%)
Race	ASIAN	10 (5%)	9 (4%)	14 (7%)	10 (5%)	6 (6%)	8 (8%)
	BLACK OR AFRICAN AMERICAN	29 (14%)	31 (15%)	22 (11%)	15 (7%)	8 (7%)	14 (13%)
	WHITE	153 (76%)	151 (75%)	155 (75%)	167 (82%)	94 (86%)	80 (75%)
	COMBINED OTHER	9 (4%)	10 (5%)	15 (7%)	12 (6%)	1 (<1%)	4 (4%)
	AMERICAN INDIAN OR ALASKA NATIVE	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
	MAORI	0	0	1 (<1%)	4 (2%)	0	0
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDERS	5 (2%)	4 (2%)	5 (2%)	3 (1%)	0	1 (<1%)
	OTHER	3 (1%)	4 (2%)	8 (4%)	4 (2%)	1 (<1%)	2 (2%)
Ethnicity	HISPANIC OR LATINO	19 (9%)	27 (13%)	7 (3%)	10 (5%)	9 (8%)	7 (7%)
	NOT HISPANIC OR LATINO	182 (91%)	174 (87%)	199 (97%)	194 (95%)	100 (92%)	99 (93%)

Figure 1: Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (Study A: Zurampic 200mg minus Placebo, Non-Responder Imputation)



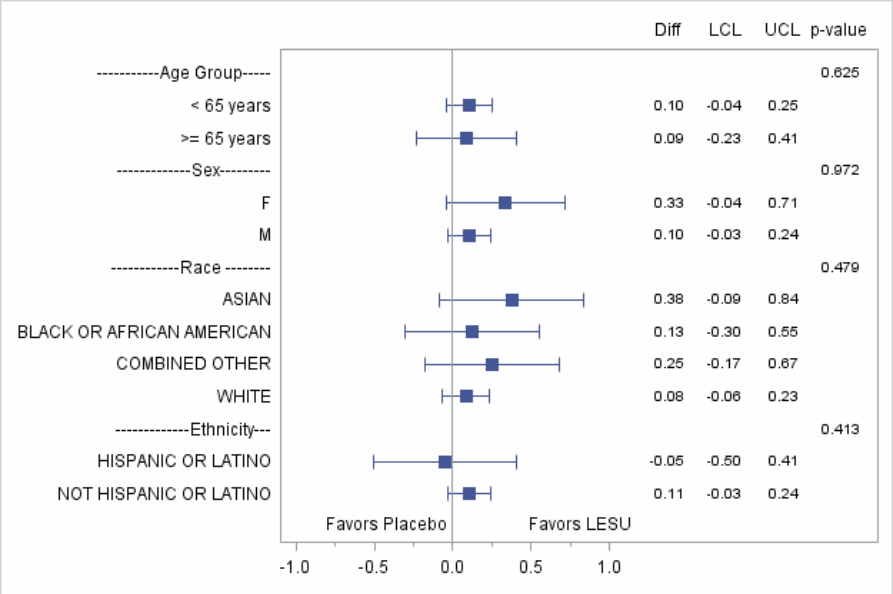
sUA: serum uric acid; Diff: Difference in proportion; LCL: lower confidence limit; UCL: upper confidence limit; p-vaule: statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for treatment-by-subgroup interaction); F: female; M: Male; LESU: lesinurad (Zurampic).

Figure 2: **Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (Study B: Zurampic 200mg minus Placebo, Non-Responder Imputation)**



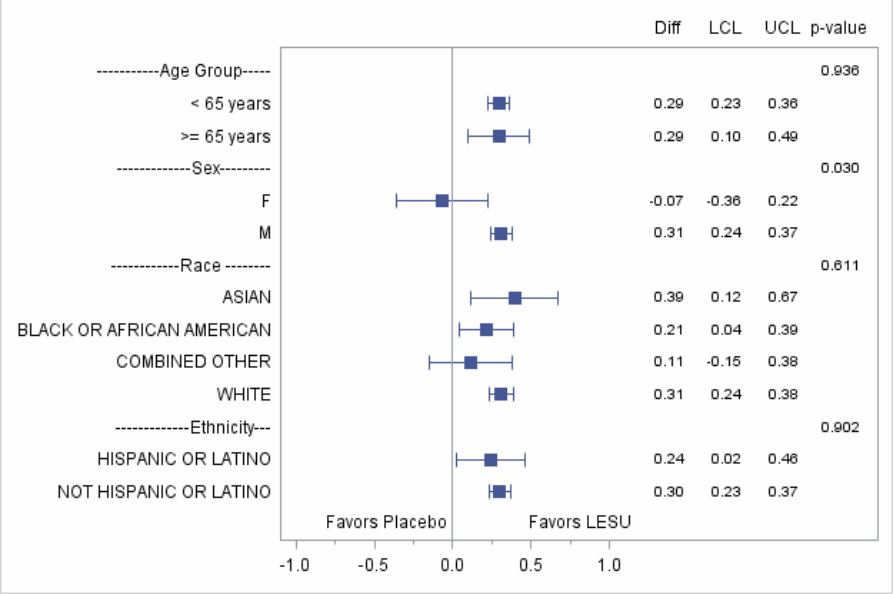
sUA: serum uric acid; Diff: Difference in proportion; LCL: lower confidence limit; UCL: upper confidence limit; p-vaule: statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for treatment-by-subgroup interaction); F: female; M: Male; LESU: lesinurad (Zurampic).

Figure 3: **Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 5.0 mg/dL (Study C: Zurampic 200mg minus Placebo, Non-Responder Imputation)**



sUA: serum uric acid; Diff: Difference in proportion; LCL: lower confidence limit; UCL: upper confidence limit; p-vaule: statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for treatment-by-subgroup interaction); F: female; M: Male; LESU: lesinurad (Zurampic).

Figure 4: **Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (Pooled Studies A and B: Zurampic 200mg Minus Placebo, Non-Responder Imputation)**



sUA: serum uric acid; Diff: Difference in proportion; LCL: lower confidence limit; UCL: upper confidence limit; p-vaule: statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for treatment-by-subgroup interaction); F: female; M: Male; LESU: lesinurad (Zurampic).

Table 4: Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (< 5.0 mg/dL in Study C)
(By Age Group: Zurampic 200mg Minus Placebo, Non-Responder Imputation)

Study	Age Group	Placebo		Zurampic 200mg		Difference (95% CI) in Proportion of sUA Responders (Zurampic 200mg - Placebo)	Test for Treatment by Age Group Interaction (p-value)
		N	Number (%) of Subjects with sUA Level < 6.0 mg/dL at Month 6	N	Number (%) of Subjects with sUA Level < 6.0 mg/dL at Month 6		
Study A	< 65 years	169	46(27.2)	181	99(54.7)	0.27(0.18, 0.37)	0.537
	>= 65 years	32	10(31.3)	20	10(50.0)	0.19(-0.08, 0.46)	
Study B	< 65 years	185	43(23.2)	184	100(54.3)	0.31(0.22, 0.41)	0.565
	>= 65 years	21	5(23.8)	20	13(65.0)	0.41(0.13, 0.69)	
Pooled Studies A and B	< 65 years	354	89(25.1)	365	199(54.5)	0.29(0.23, 0.36)	0.936
	>= 65 years	53	15(28.3)	40	23(57.5)	0.29(0.10, 0.49)	
Study C	< 65 years	89	41(46.1)	89	50(56.2)	0.10(-0.04, 0.25)	0.625
	>= 65 years	20	10(50.0)	17	10(58.8)	0.09(-0.23, 0.41)	

Examination of treatment effect by age group: The combined analysis of Studies A and B showed no evidence of an interaction and produced the same point estimates of effect in the two age subgroups. In addition, in the combined analysis, there is evidence that for gout patients on background allopurinol Zurampic 200mg is effective compared to placebo with respect to the proportion of subjects with an sUA level < 6.0 mg/dL at month 6 in both age groups. Consistent with the conclusions of the combined analysis, within Study A, the estimated effect of Zurampic 200mg over placebo is positive in both age groups although in the older patient group the confidence interval for the difference between treatment groups includes 0. This lack of statistical significance is potentially due to the small sample size in this age group. Also consistent with the combined analysis, within the individual Studies A and B, there is no statistical evidence suggesting that the effect of Zurampic relative to placebo may be different between the two age groups as the p-values associated with the treatment-by-age interaction are about 0.5.

There also was no evidence of a treatment by age interaction in Study C. There was no evidence of treatment effects in the age subgroups in Study C, which is consistent with the lack of evidence of an overall study effect, but trends were in the direction favorable to Zurampic and of a similar magnitude in the two subgroups. Similar results were observed for the 400mg dose in these studies.

In summary, with evidence of effects in both subgroups in integrated studies A and B, consistent estimates in Study C with trends toward benefit, and no evidence of interactions from any analyses, the totality of the data suggests that Zurampic is efficacious compared with placebo in both patient age groups and does not suggest any striking differences in effects between older and younger patients.

Table 5: Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (< 5.0 mg/dL in Study C)
(By Sex: Zurampic 200mg Minus Placebo, Non-Responder Imputation)

Study	Sex	Placebo		Zurampic 200mg		Difference (95% CI) in Proportion of sUA Responders (Zurampic 200mg - Placebo)	Test for Treatment by Sex Interaction (p-value)
		N	Number (%) of Subjects with sUA Level < 6.0 mg/dL at Month 6	N	Number (%) of Subjects with sUA Level < 6.0 mg/dL at Month 6		
Study A	F	12	5(41.7)	9	1(11.1)	-0.31(-0.65, 0.04)	0.016
	M	189	51(27.0)	192	108(56.3)	0.29(0.20, 0.39)	
Study B	F	10	2(20.0)	7	3(42.9)	0.23(-0.21, 0.67)	0.818
	M	196	46(23.5)	197	110(55.8)	0.32(0.23, 0.41)	
Pooled Studies A and B	F	22	7(31.8)	16	4(25.0)	-0.07(-0.36, 0.22)	0.030
	M	385	97(25.2)	389	218(56.0)	0.31(0.24, 0.37)	
Study C	F	2	0	6	2(33.3)	0.33(-0.04, 0.71)	0.972
	M	107	51(47.7)	100	58(58.0)	0.10(-0.03, 0.24)	

Examination of treatment effect by sex: Among the three phase 3 studies, about 95% of the subjects were male. In both Study A and Study B, there was evidence of a treatment effect on serum uric reduction in males. There was considerable uncertainty in the evaluation in females due to small sample sizes. Compared with men, women are less likely to develop gout in the premenopausal period due to the uricosuric effect of female hormones; this explains largely the gender imbalance of subject numbers in enrollment. The small female sample sizes resulted in some statistical difficulties due to small responders counts: for example, there were zero female responders on the placebo arm in study C (Table 6) and a female responder count of

only 1 in the Zurampic 200mg arm in study A, which could be partially attributed to 3 early discontinuations among the 9 total subjects that were imputed as non-responders.

Despite the small numbers of females in these studies, there was some evidence in Study A of a treatment by sex interaction (p=0.016). Borderline evidence (p=0.03) was also seen based on the integrated analysis of Studies A and B. However, this finding in the combined analysis was primarily driven by the Study A interaction test results, and such an interaction was not replicated in either Study B or Study C. With the limited female data in mind, in the face of the inconsistency of subgroup analysis results among the three studies, and with reference the Zurampic 400mg interaction tests results, as any true differences in efficacy by subgroup might be expected to exist for both doses, we conclude that the suggestion of a differing treatment effect by sex in study A may not represent a finding of a true treatment by sex interaction.

In study C, the zero frequency in female patients in placebo group resulted in a quasi-complete separation of data points such that the maximum likelihood iterations did not converge. The result shown for the interaction test are based on the last maximum likelihood iteration (p=0.972) the validity of which is questionable. In terms of point estimates and corresponding confidence intervals, the by sex group responder rate results are consistent with the overall study results, showing a numerically positive but not statistically significant trend. There was no statistical evidence of subgroup differences between the two sexes.

Data from Zurampic 400mg data showed that in general the two genders had consistent treatment effects with no significant interaction effects among the 3 studies, individually or combined. Of note, from the febuxostat background study C, while the overall effect of Zurampic 400mg was statistically significant and 200mg was not, both doses showed a numerically higher treatment effect in females as compared with males, which is different from the trend found from the integrated 200mg dose allopurinol background studies and reinforces the conclusion that the differences in treatment effect by sex are likely a result of natural variation and not indicative of a true treatment by sex interaction.

The totality of the above data shows that there was consistent evidence of a treatment effect in males. There was some evidence (p-value=0.03) of an interaction by sex in integrated Studies A and B, with trends toward less efficacy in females. However, with the small female patient numbers and the relatively large number of subgroup analyses performed in this review, as well as the lack of consistency in findings across studies and doses, it remains unclear whether the treatment effect differs by sex.

Table 6: Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (< 5.0 mg/dL in Study C)
(By Race: Zurampic 200mg Minus Placebo, Non-Responder Imputation)

Study	Race	Placebo		Zurampic 200mg		Difference (95% CI) in Proportion of sUA Responders (Zurampic 200mg - Placebo)	Test for Treatment by Race Interaction (p-value)
		N	Number (%) of Subjects with sUA Level < 6.0 mg/dL at Month 6	N	Number (%) of Subjects with sUA Level < 6.0 mg/dL at Month 6		
Study A	ASIAN	10	4(40.0)	9	5(55.6)	0.16(-0.29, 0.60)	0.782
	BLACK OR AFRICAN AMERICAN	29	5(17.2)	31	10(32.3)	0.15(-0.06, 0.36)	
	COMBINED OTHER	9	3 (33.3)	10	5(50.0)	0.17(0.22, 0.60)	
	WHITE	153	44(28.8)	151	89(58.9)	0.30(0.20, 0.41)	
Study B	ASIAN	14	3(21.4)	10	8(80.0)	0.59(0.26, 0.91)	0.371
	BLACK OR AFRICAN AMERICAN	22	4(18.2)	15	8(53.3)	0.35(0.05, 0.65)	
	COMBINED OTHER	15	3 (20.0)	12	3 (25.0)	0.05(-0.27, 0.37)	
	WHITE	155	38(24.5)	167	94(56.3)	0.32(0.22, 0.42)	
Pooled Studies A and B	ASIAN	24	7(29.2)	19	13(68.4)	0.39(0.12, 0.67)	0.611
	BLACK OR AFRICAN AMERICAN	51	9(17.6)	46	18(39.1)	0.21(0.04, 0.39)	
	COMBINED OTHER	24	6(25.0)	22	8(36.4)	0.11(-0.15, 0.38)	
	WHITE	308	82(26.6)	318	183(57.5)	0.31(0.24, 0.38)	
Study C	ASIAN	6	3(50.0)	8	7(87.5)	0.38(-0.09, 0.84)	0.479
	BLACK OR AFRICAN AMERICAN	8	3(37.5)	14	7(50.0)	0.13(-0.30, 0.55)	
	COMBINED OTHER	1	0	4	1 (25.0)	0.25(-0.17, 0.67)	
	WHITE	94	45(47.9)	80	45(56.3)	0.08(-0.06, 0.23)	

Examination of treatment effect by race: There were a total of 7 racial subgroups across the studies, with some groups of very small sample sizes. Some subgroup sizes were too small to allow for a reliable evaluation, so we combined some racial subgroups as catalogued in Table 3 into a Combined Other group.

From the integrated analysis of Studies A and B, there was evidence of a treatment effect for the White, Black, and Asian subgroups. In individual Study A or B, in general, there was evidence of treatment effects or trends toward benefit for the White, Black, Asian, and Other subgroups. For smaller subgroups, while positive estimates were observed, small sample sizes resulted in wide confidence intervals. Trends toward benefit were observed in all racial subgroups in Study C, but the small sample sizes resulted in wide confidence intervals (that included zero) in all racial groups. There was no evidence of a treatment by race interaction in any of the individual or combined analyses. Results were similar for the 400mg dose. The totality of the data therefore suggests that Zurampic is effective in Whites, Blacks, and Asians, and no large differences in efficacy across racial subgroups were identified.

Table 7: Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (< 5.0 mg/dL in Study C)
(By Ethnicity: Zurampic 200mg Minus Placebo, Non-Responder Imputation)

Study	Ethnicity	Placebo		Zurampic 200mg		Difference (95% CI) in Proportion of sUA Responders (Zurampic 200mg - Placebo)	Test for Treatment by Ethnicity Interaction (p-value)
		N	Number (%) of Subjects with sUA Level < 6.0 mg/dL at Month 6	N	Number (%) of Subjects with sUA Level < 6.0 mg/dL at Month 6		
Study A	HISPANIC OR LATINO	19	3(15.8)	27	10(37.0)	0.21(-0.03, 0.46)	0.962
	NOT HISPANIC OR LATINO	182	53(29.1)	174	99(56.9)	0.28(0.18, 0.38)	
Study B	HISPANIC OR LATINO	7	2(28.6)	10	6(60.0)	0.31(-0.14, 0.77)	0.889
	NOT HISPANIC OR LATINO	199	46(23.1)	194	107(55.2)	0.32(0.23, 0.41)	
Pooled Studies A and B	HISPANIC OR LATINO	26	5(19.2)	37	16(43.2)	0.24(0.02, 0.46)	0.902
	NOT HISPANIC OR LATINO	381	99(26.0)	368	206(56.0)	0.30(0.23, 0.37)	
Study C	HISPANIC OR LATINO	9	3(33.3)	7	2(28.6)	-0.05(-0.50, 0.41)	0.413
	NOT HISPANIC OR LATINO	100	48(48.0)	99	58(58.6)	0.11(-0.03, 0.24)	

Examination of treatment effect by ethnicity:
Results and conclusions from analyses across the ethnic subgroups were similar to those across racial subgroups. From the pooled analysis of Studies A and B, there was evidence of a treatment effect for both the ethnic subgroups. When looking at Study A or B, a treatment effect was observed in patients who were not Hispanic or Latino. For the Hispanic or Latino subgroup, while positive estimates were observed, small samples resulted in wider confidence intervals that included zero. In Study C, a trend toward benefit was observed in the not Hispanic or Latino group but not in the Hispanic or Latino group, although the sample size in this subgroup was very small.

Subgroup analysis results from Lesinurad 400mg supported the efficacy of both subgroups with the only exception of a wide confidence interval for the Hispanic or Latino subgroup in Study B. Across studies and dosages, there was no evidence based on interaction tests of differences in treatment effects across the ethnic subgroups.

4. SUMMARY AND CONCLUSIONS

This review examined existing data to assess the treatment effect of Zurampic 200mg on sUA level < 6.0 mg/dL responder rate at month 6 within each sex, age, race, and ethnicity subgroup and whether the treatment effect of Zurampic 200mg on sUA level < 6.0 mg/dL responder rate at month 6 differs by sex, age, race, or ethnicity. We acknowledge that the analyses provided in this review are exploratory and the trials were not designed to support such investigations. Despite possible statistical limitations, these investigations were undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data.

This review concludes that

- Zurampic 200mg appears to be efficacious compared with placebo with respect to the sUA < 0.6 mg/dL responder rate at month 6 within each age group (below 65 years and 65 years and above). Available data did not give a strong indication that the treatment effect for Zurampic 200mg is larger in one age group than the other.

- Zurampic 200mg appears to be efficacious compared with placebo with respect to the sUA < 0.6 mg/dL responder rate within male patients with gout. Available data for the female patient subgroup is too limited to draw conclusions about whether the treatment effect for Zurampic 200mg exists in females (without borrowing information from male subjects). There was some evidence of a difference between treatment effects in men and women in a single study. However, with the small female patient numbers and the relatively large number of subgroup analyses performed in this review, as well as the lack of consistency in treatment by sex interaction findings across studies and doses, we have little evidence to suggest that the treatment effect truly differs by

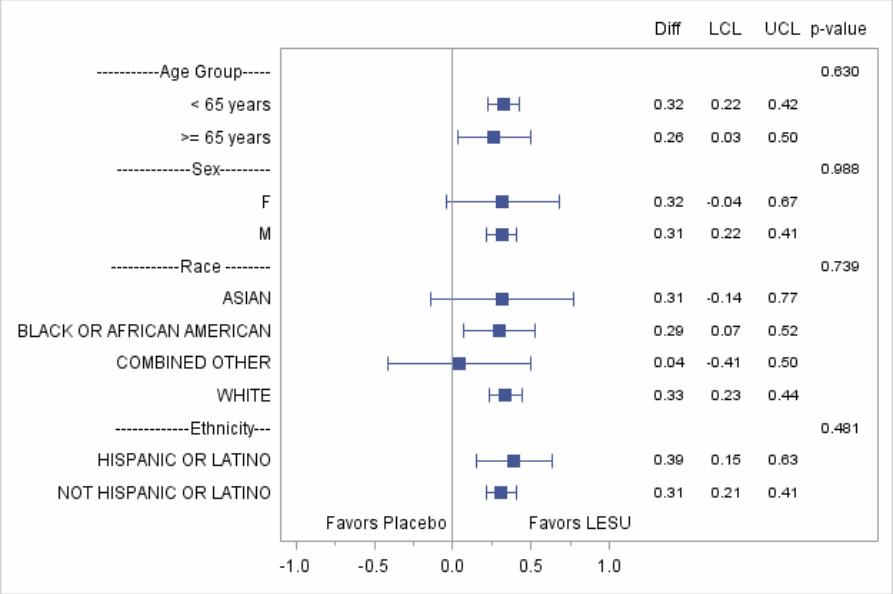
sex. Based on these considerations and using all available data, including data in males, we suppose that Zurampic 200mg is superior to placebo even in female patients.

- There was evidence of a treatment effect for the White, Black, and Asian subgroups. For smaller racial subgroups (combined in the analyses), while positive estimates were observed, small sample sizes resulted in wide confidence intervals. There was no evidence of a treatment by race interaction in any of the individual or combined analyses.

- There was evidence of a treatment effect for both the Hispanic/Latino and not Hispanic/Latino subgroups. For the smaller Hispanic/Latino subgroup, while positive estimates of similar size were observed, small sample sizes resulted in wide confidence intervals. There was no evidence of a treatment by ethnicity interaction in any of the individual or combined analyses.

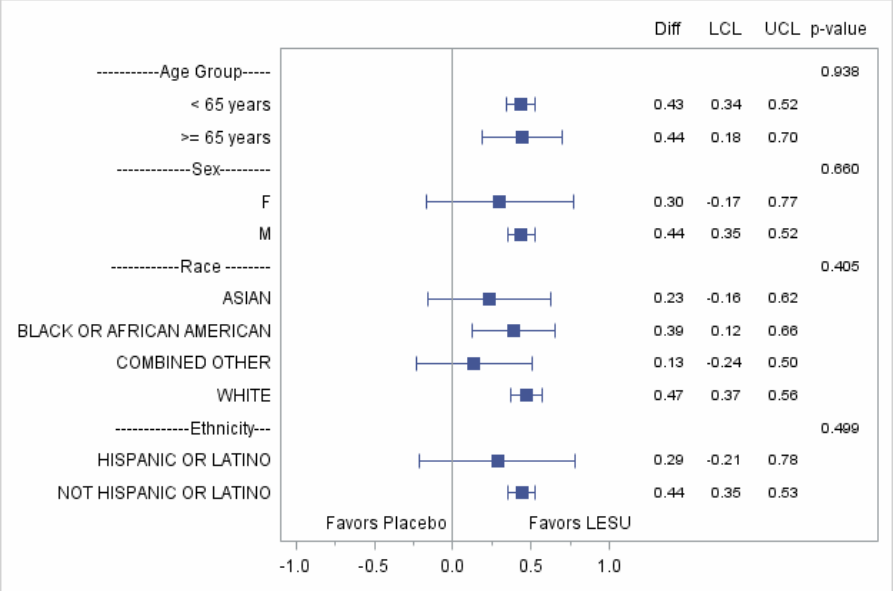
Appendix: Subgroup Analysis Results Comparing Zurampic 400mg with Placebo

Figure 5: Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (Study A: Zurampic 400mg minus Placebo, Non-Responder Imputation)



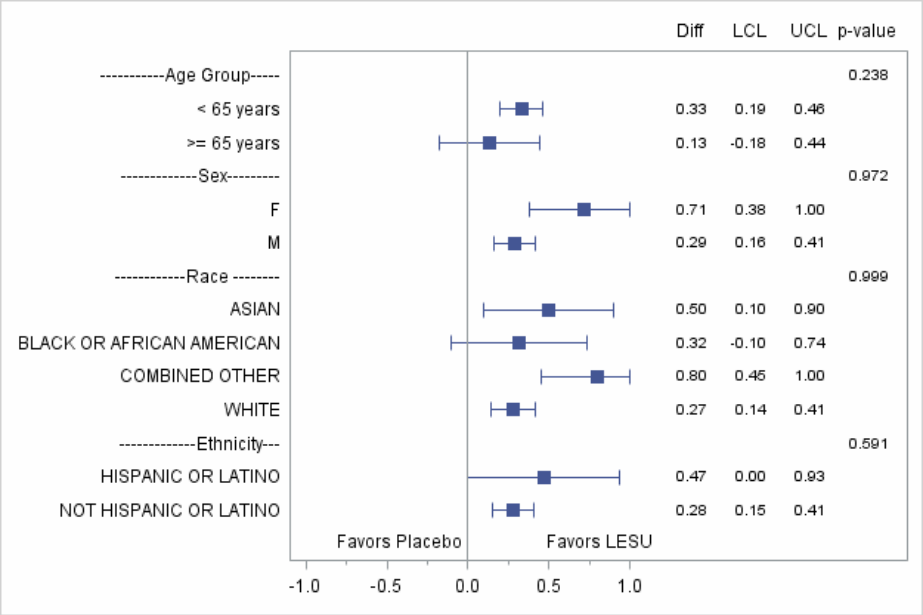
sUA: serum uric acid; Diff: Difference in proportion; LCL: lower confidence limit; UCL: upper confidence limit; p-vaule: statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for treatment-by-subgroup interaction); F: female; M: Male; LESU: lesinurad (Zurampic).

Figure 6: Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (Study B: Zurampic 400mg minus Placebo, Non-Responder Imputation)



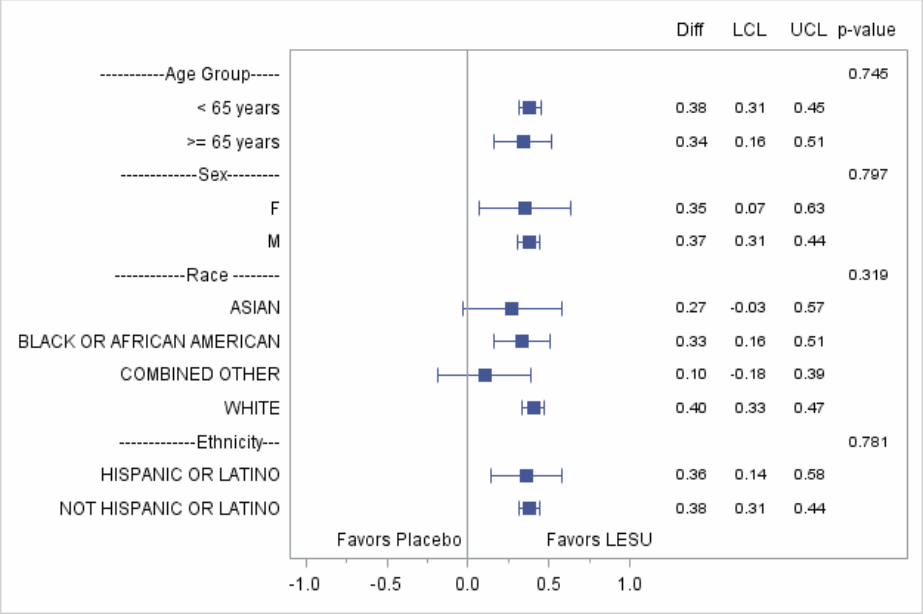
sUA: serum uric acid; Diff: Difference in proportion; LCL: lower confidence limit; UCL: upper confidence limit; p-vaule: statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for treatment-by-subgroup interaction); F: female; M: Male; LESU: lesinurad (Zurampic).

Figure 7: Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 5.0 mg/dL (Study C: Zurampic 400mg minus Placebo, Non-Responder Imputation)



sUA: serum uric acid; Diff: Difference in proportion; LCL: lower confidence limit; UCL: upper confidence limit; p-vaule: statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for treatment-by-subgroup interaction); F: female; M: Male; LESU: lesinurad (Zurampic).

Figure 8: Difference (95% Confidence Interval) of Proportion for Subjects with Month 6 sUA Levels < 6.0 mg/dL (Pooled Studies A and B: Zurampic 400mg minus Placebo, Non-Responder Imputation)



sUA: serum uric acid; Diff: Difference in proportion; LCL: lower confidence limit; UCL: upper confidence limit; p-vaule: statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for treatment-by-subgroup interaction); F: female; M: Male; LESU: lesinurad (Zurampic).

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/s/

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03/04/2016

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03/04/2016