CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA#:	NDA 209805
Drug Name:	Ertugliflozin and Sitagliptin Fixed Dose Combination Tablets
Indication(s):	As an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus when treatment with both ertugliflozin and sitagliptin is appropriate.
Applicant:	Merck Sharp and Dohme Corporation
Date(s):	Submitted Date: 12/19/2016 PDUFA Goal Date: 12/19/2017 Primary Review Completion Date: 08/28/2017
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Alexander Cambon
Concurring Reviewers:	Yun Wang, Acting Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Frank Pucino/William Chong
Project Manager:	Elizabeth Godwin

Keywords: active control/non-inferiority, analysis of covariance, sensitivity analyses, missing data, drop-outs, jump to reference, return to baseline

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Reference ID: 4145163

1 EXECUTIVE SUMMARY

Merck Sharp and Dohme is seeking approval for efficacy and safety of fixed dose combination (FDC) ertugliflozin and sitagliptin tablets (E+S) for treatment of adults with type 2 diabetes mellitus (T2DM). Ertugliflozin is a new molecular entity (NME), and the new drug application for ertugliflozin (NDA 209803) was submitted simultaneously with this NDA. Sitagliptin (brand name Januvia) has been previously approved for treatment of T2DM. The proposed indication for E + S is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both ertugliflozin and sitagliptin is appropriate. The sponsor submitted this NDA on December 19, 2016.

Brief Overview of Clinical Studies

This efficacy statistical review encompasses three confirmatory safety and efficacy trials, including one active-controlled study (P005) and two placebo-controlled studies with different background therapies (P006 and P017). Study P005 was a full factorial study with metformin (M) background comparing E+S to E alone and to S alone. Study P006 was a placebo study with metformin and sitagliptin background (M+S), and P017 was a placebo study with diet and exercise (DE) background comparing E+S to placebo. In all these studies, two doses of ertugliflozin were used: ertugliflozin 5 mg (E5) and ertugliflozin 15 mg (E15). For sitagliptin, a 100 mg dose was used (S100). These three studies were used to support this NDA 209805. Change in HbA1c (%) from baseline was the primary efficacy endpoint for all three studies. More detail on study design for these three studies including sample size and background medication can be found in this section of the Statistical Review for ertugliflozin (NDA 209803) dated August 25, 2017, and in Table 1 of the same review.

Statistical Issues

Statistical issues concerning missing data, dropouts, and rescue rates are described in Section 3.2.2.3 in the statistical review for NDA 209803, and Section 5.1 in this review. Sensitivity analyses used to address these issues did not alter our conclusions.

Conclusions and Recommendations

The primary endpoint for all three studies used to support this NDA is reduction in HbA1c (%). The primary endpoint analysis for factorial study P005 demonstrates the statistically significant contribution of each of the individual components E and S, to the combination E+S (i.e. E+S is superior to both E alone and to S alone). The primary endpoint analysis for study P017 demonstrates the superiority of E+S against placebo. Study P006 further demonstrates the statistically significant contribution of the E component to E+S. Please refer to Sections 3.2.4 in the statistical review for NDA 209803, and Section 5 in this review for further details. This NDA is approvable from the statistical point of view.

Reference ID: 4145163

2 INTRODUCTION

2.1 Overview

This submission included three confirmatory safety and efficacy trials. The primary endpoint for each of these is HbA1c (%) change from baseline. The sponsor is seeking approval for efficacy and safety of FDC ertugliflozin and sitagliptin tablets (E+S) to improve glycemic control in adults with T2DM.

Refer to Table 1, Section 2.1.3 of the Statistical Review for NDA 209803 for further details of study design for studies P005, P006, and P017, including background medication and sample size for each of the three studies.

2.1.1 Class and Indication

FDC ertugliflozin and sitagliptin tablets (E+S - proposed proprietary name Steglujan), is a combination of an oral sodium glucose co-transporter 2 (SGLT2) inhibitor with a DPP-4 inhibitor. An example of an approved FDC drug involving an SGLT2 and a DPP-4 inhibitor is Glyxambi, a combination of empagliflozin (trade name Jardiance, an SGLT2 inhibitor), and linagliptin (trade name Tradjenta, a DPP-4 inhibitor). SGLT2 inhibitors prevent kidneys from reabsorbing glucose back into the blood. The excess glucose in the blood is then removed from the body via urine. DPP-4 inhibitors increase incretin levels, which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels. The proposed indication for E+S is to improve glycemic control in adults with Type 2 diabetes mellitus (T2DM).

2.1.2 Select Submission History and Communication to Sponsor

Refer to Statistical Review of NDA 209803 for submission and communication history, including select history of IND submissions and comments concerning preventing and addressing missing data.

2.1.3 Specific Studies Reviewed

Three of the seven studies in Table 1 of the Statistical Review of NDA 209803 (ertugliflozin - E) are used to support this review for E+S. These are the factorial study (P005), Study P017, and Study P006. Efficacy results of all three of these studies are included in tables in Section 14 of the draft label for this NDA (E+S).

2.2 Data Sources

The data and final study report for NDA 209805 were submitted electronically as an eCTD submission. The submission, organized as an .enx file, is archived at the following link.

\\CDSESUB1\EVSPROD\NDA209805\209805.enx

Reference ID: 4145163

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The SDTM and ADaM data sets are located in the proper sections of the submission, and analysis reviewer guides are provided which define variables and their locations.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The primary and secondary efficacy endpoints for the three studies are shown in Table 2 of the Statistical Review for NDA 209803. All endpoints for the three studies are assessed at 26 weeks. Secondary endpoints typically include Fasting Plasma Glucose (FPG), HbA1c < 7%, Body Weight, and Systolic Blood Pressure (SBP). Study P017 includes the secondary endpoints of Post Meal Glucose (PMG) and Diastolic Blood Pressure (DBP).

Refer to this section in the Statistical Review for NDA 209803 for further details.

3.2.2 Statistical Methodologies

Refer to this Section in the Statistical review for NDA 209803 for details on the sponsor's and statistical reviewer's analyses approach, and issues we have with missing values and retrieve dropouts.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Refer to this section in the Statistical Review for NDA 209803.

3.2.4 Results and Conclusions

Refer to this section in the Statistical Review for NDA 209803 for analyses results for all three studies: P005, P006 and P017, and my conclusions.

3.3 Evaluation of Safety

Please see the clinical review of Dr. Frank Pucino for NDA 209803 for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Race, Age, and Geographic Region

Please see this section in the Statistical Review for NDA 209803 for the three studies.

Reference ID: 4145163

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

The following statistical issues were identified in this application. Sensitivity analyses used to address these issues did not alter our conclusion that efficacy was demonstrated.

- Missing data, which ranged from 7% to 21% across the arms in the three studies, were strongly associated with treatment discontinuation.
- There were very few retrieved dropouts.
- The sponsor's primary analysis treated observations after initiation of rescue therapy as missing.
- Data after treatment discontinuation were completely excluded (i.e. not included in the analysis set) in the sponsor's initially submitted primary and sensitivity analyses.
- The placebo study P017, which had a background of diet and exercise only, had high rescue rates on the placebo arm (31%).

5.2 Collective Evidence

The primary efficacy endpoint was change from baseline in HbA1c (%) in the three studies reviewed for this NDA. The full factorial study demonstrates superiority of E5/E15 + S100 compared to S100 alone, as well as superiority of E5/E15+S100 compared to E5/E15 alone, against a background of M. This in turn demonstrates the efficacy contribution of each of the two components (E and S) to the combination of E+S and, in so doing, satisfies a key requirement of the combination drug law in CFR 21 Section 300.50. Study P006 demonstrates the statistically significant contribution of the E component (E5/E15) when added to a background of S100+M; (superiority of E+S+M vs. S+M). Study P017 demonstrates the efficacy of the combination E+S (E5/E15 +S100) against a background of diet and exercise only.

These findings were consistent using the sponsor's primary analysis, and also across our sensitivity analyses which addressed possible shortcomings in the primary analyses.

5.3 Conclusions and Recommendations

In my view, the collective evidence from this review supports the claim of using E+S to improve glycemic control in adults with T2DM, when treatment with both ertugliflozin and sitagliptin is appropriate. This NDA is approvable from the statistical point of view.

5.4 Labeling Recommendations

Please see this section in the Statistical Review for NDA 209803 for the three studies.

Reference ID: 4145163

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/s/

ALEXANDER CAMBON
08/28/2017

MARK D ROTHMANN
08/28/2017
Signing for Yun Wang

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#:	NDA 209806
Drug Name:	Ertugliflozin and Metformin Fixed Dose Combination Tablets
Indication(s):	As an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus (b) (4)
Applicant:	Merck Sharp and Dohme Corporation
Date(s):	Submitted Date: 12/19/2016 PDUFA Goal Date: 12/19/2017 Primary Review Completion Date: 08/28/2017
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Alexander Cambon
Concurring Reviewers:	Yun Wang, Acting Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Frank Pucino/William Chong
Project Manager:	Elizabeth Godwin

Keywords: active control/non-inferiority, analysis of covariance, sensitivity analyses, missing data, drop-outs, jump to reference, return to baseline

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Reference ID: 4145183

1 EXECUTIVE SUMMARY

Merck Sharp and Dohme is seeking approval for efficacy and safety of fixed dose combination (FDC) ertugliflozin/metformin hydrochloride tablets (E + M) for treatment of adults with type 2 diabetes mellitus (T2DM). Ertugliflozin is a new molecular entity (NME), and the new drug application for ertugliflozin (NDA 209803) was submitted simultaneously with this NDA on December 19, 2016. Metformin (brand name Glucophage) has been previously approved for treatment of T2DM and is considered a first line therapy. The proposed indication for E + M is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (b) (4)

Brief Overview of Clinical Studies

This efficacy statistical review encompasses four confirmatory safety and efficacy trials, including two active-controlled studies (P005 and P002) and two placebo-controlled studies (P006 and P007). All these studies had a background that included metformin. Change in HbA1c (%) from baseline was the primary efficacy endpoint for all four studies. In all these studies, two doses of ertugliflozin were used: ertugliflozin 5 mg (E5) and ertugliflozin 15 mg (E15). More detail on study design including sample size and background medication can be found in this section of the Statistical Review for NDA 209803 dated August 25, 2017 and in Table 1 of the same review.

Statistical Issues

Statistical issues concerning missing data, dropouts, and rescue rates are described in Section 3.2.2.3 in the statistical review for NDA 209803, and Section 5.1 in this review. Sensitivity analyses used to address these issues did not alter our conclusions.

Conclusions and Recommendations

The primary endpoint for all three studies used to support this NDA is reduction in HbA1c (%). Three of the four studies demonstrate the statistical superiority of the combination therapy compared to individual component (E+M vs M) and added contribution of the individual component of E vs. a background that includes M. Non-inferiority study P002 demonstrated the non-inferiority of E15 compared to glimepiride (E15+M vs. glimepiride +M). The contribution of M to E+M (E+M vs. E) was not assessed statistically. Please refer to Sections 3.2.4 in the statistical review for NDA 209803, and Section 5 in this review for further details. This statistical review supports the use of ertugliflozin as add-on therapy to metformin.

2 INTRODUCTION

2.1 Overview

This submission included four confirmatory safety and efficacy trials. The primary endpoint for each of these is HbA1c (%) change from baseline. The sponsor is seeking approval for efficacy and safety of FDC ertugliflozin and metformin tablets (E+M) to improve glycemic control in adults with T2DM.

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Refer to Table 1, Section 2.1.3 of the Statistical Review for NDA 209803 for further details of study design for studies P005, P002, P006, and P007, including background medication and sample size for each of the four studies.

2.1.1 Class and Indication

FDC ertugliflozin and metformin tablets (E+M - proposed proprietary name Segluromet) is a combination of an oral sodium glucose co-transporter 2 (SGLT2) inhibitor with metformin, a biguanide. Examples of approved FDC drugs combining an SGLT2 inhibitor with metformin include:

1) Synjardy (empagliflozin +metformin).
2) Invokamet (canagliflozin + metformin)
3) Xiduo (dapagliflozin + metformin)

SGLT2 inhibitors prevent kidneys from reabsorbing glucose back into the blood. The excess glucose in the blood is then removed from the body via urine. Metformin decreases high blood sugar, primarily by suppressing liver glucose production. The proposed indication for E+M is to improve glycemic control in adults with T2DM.

2.1.2 Select Submission History and Communication to Sponsor

Refer to Statistical Review of NDA 209803 for submission and communication history, including select history of IND submissions and comments concerning preventing and addressing missing data.

2.1.3 Specific Studies Reviewed

Four of the seven studies in Table 1 of the Statistical Review of NDA 209803 (ertugliflozin - E) are used to support this review for E+M. These are the factorial study (P005), the non-inferiority study (P002), and placebo studies P007 and P006. Efficacy results of all four of these studies are included (b) (4) in Section 14 of the draft label for this NDA.

2.2 Data Sources

The data and final study report for NDA 209806 were submitted electronically as an eCTD submission. The submission, organized as an .enx file, is archived at the following link.

\\CDSESUB1\EVSPROD\NDA209806\209806.enx

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The SDTM and ADaM data sets are located in the proper sections of the submission, and analysis reviewer guides are provided which define variables and their locations.

Reference ID: 4145183

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The primary and secondary efficacy endpoints for the four studies are shown in Table 2 of the Statistical Review for NDA 209803. Secondary endpoints typically include Fasting Plasma Glucose (FPG), HbA1c < 7%, Body Weight, and Systolic Blood Pressure (SBP). Study P007 includes the secondary endpoint of Diastolic Blood Pressure (DBP).

Refer to this section in the Statistical Review for NDA 209803 for further details.

3.2.2 Statistical Methodologies

Refer to this Section in the Statistical review for NDA 209803 for details on the sponsor's and statistical reviewer's analyses approach, and issues we have with missing values and retrieve dropouts.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Refer to this section in the Statistical Review for NDA 209803.

3.2.4 Results and Conclusions

Refer to this section in the Statistical Review for NDA 209803 for analyses results for all four studies: P002, P005, P006 and P007, and my conclusions.

3.3 Evaluation of Safety

Please see the clinical review of Dr. Frank Pucino for NDA 209803 for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Race, Age, and Geographic Region

Please see this section in the Statistical Review for NDA 209803 for all four studies.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

The following statistical issues were identified in this application. Sensitivity analyses used to address these issues did not alter our conclusion that efficacy was demonstrated.

Reference ID: 4145183

- Missing data, which ranged from 5% to 20% across the arms in the four studies, were strongly associated with treatment discontinuation.
- There were very few retrieved dropouts.
- The sponsor's primary analysis treated observations after initiation of rescue therapy as missing.
- Data after treatment discontinuation were completely excluded (i.e. not included in the analysis set) in the sponsor's initially submitted primary and sensitivity analyses.

5.2 Collective Evidence

The primary efficacy endpoint was change from baseline in HbA1c (%) in the four studies reviewed for this NDA. The primary endpoint analysis for study P007 demonstrated superiority of the combination therapy (E+M vs. M) and added contribution of the individual component of E against a background of M. Placebo study P006 demonstrated the superiority of the combination therapy (E+M+S vs. M+S) and added contribution of E against a background of M and Sitagliptin 100 mg. Active control study P005 also demonstrated the superiority of E+M+S vs. M+S. The primary endpoint analysis for active control study P002 demonstrated the non-inferiority of E compared to glimepiride (G) (non-inferiority of E+M vs. G+M) for glycemic control among patients receiving background therapy of M; These findings were consistent using the sponsor's primary analysis, and also across our sensitivity analyses which addressed possible shortcomings in the primary analyses.

Each of these four studies demonstrated the efficacy contribution of the component E to the combination of E+M. The combination drug law in CFR 21 Section 300.50 requires that each component of an FDC combination drug be demonstrated. The contribution of the component M to E+M was not assessed statistically in this submission in any of the studies. It should be noted that in at least two other approved combination drugs involving an SGLT2 inhibitor and metformin, a factorial study was used to demonstrate the statistically significant contribution of each component. See for example NDA 204353, S014 (Invokamet – Canagliflozin XR and Metformin, Table 9 in the label – https://www.accessdata.fda.gov/drugsatfda docs/label/2017/204353s014lbl.pdf) and NDA 206111, S009 (Synjardy – Empagliflozin and Metformin, Table 8 in the label - https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206111s009lbl.pdf). A similar factorial study was not found for the combination drug Xiduo (NDA 205649 - dapagliflozin and metformin).

5.3 Conclusions and Recommendations

In my view, the collective evidence from this statistical review supports the use of ertugliflozin as an add-on therapy to metformin to improve glycemic control in adults with T2DM. This NDA is approvable from the statistical point of view with this claim.

5.4 Labeling Recommendations

Please see this section in the Statistical Review for NDA 209803 for the three studies.

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/s/

ALEXANDER CAMBON
08/28/2017

MARK D ROTHMANN
08/28/2017
Signing for Yun Wang

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#:	NDA 209803
Drug Name:	Ertugliflozin
Indication(s):	As an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus
Applicant:	Merck Sharp and Dohme Corporation
Date(s):	Submitted Date: 12/19/2016 PDUFA Goal Date: 12/19/2017 Primary Review Completion Date: 08/25/2017
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Alexander Cambon
Concurring Reviewers:	Yun Wang, Acting Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Frank Pucino/William Chong
Project Manager:	Elizabeth Godwin

Keywords: active control/non-inferiority, analysis of covariance, sensitivity analyses, missing data, drop-outs, jump to reference, return to baseline

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1 EXECUTIVE SUMMARY

Merck Sharp and Dohme is seeking approval for efficacy and safety of ertugliflozin for treatment of adults with type 2 diabetes mellitus (T2DM). The proposed indication for ertugliflozin is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The sponsor submitted the new drug application (NDA) on December 19, 2016.

Brief Overview of Clinical Studies

This efficacy statistical review encompasses seven confirmatory safety and efficacy trials, including two active-controlled studies and five placebo-controlled studies with different background therapies. All seven studies were used to support this NDA 209803 (ertugliflozin tablet - E). Change in HbA1c (%) from baseline was the primary efficacy endpoint for all seven studies. Study P002 was a 52-week non-inferiority study comparing ertugliflozin 15 mg (E15) and ertugliflozin 5 mg (E5) to glimepiride, a sulfonylurea. Therefore, change in HbA1c at 52 weeks was the primary efficacy endpoint for Study P002. All the other six studies had change in HbA1c (%) at 26 weeks as efficacy endpoints. Study P005 was a five-arm full factorial study comparing E15/E5 + sitagliptin 100 mg (S100) to S100 alone and to E15/E5 alone. Four of the placebo studies compared E15/E5 to placebo (P003, P007, P006, and P001), and one (P017) compared E15/E5 + S100 to placebo. Study P001 was a renal impairment study. More detail on study design including sample size and background medication can be found in Table 1. Some of these studies, including the full factorial study, were also used to support fixed dose combination (FDC) ertugliflozin and sitagliptin tablet (E + S), submitted under NDA 209805, and FDC ertugliflozin and metformin tablet (E + M) submitted under NDA 209806.

Statistical Issues

Statistical issues concerning missing data, dropouts, and rescue rates are described in Section 3.2.2.3 and Section 5.1. Sensitivity analyses used to address these issues did not alter our conclusions.

Conclusions and Recommendations

The primary endpoint for studies all studies is reduction in HbA1c (%). The primary endpoint analyses for all studies except for P001 demonstrate the superiority of ertugliflozin for treatment of adults with T2DM compared to active control or placebo (please refer to Sections 3.2.4 and 5 for further details). This NDA is approvable from the statistical point of view.

2 INTRODUCTION

2.1 Overview

This submission included seven confirmatory safety and efficacy trials. The primary endpoint for each of these is HbA1c (%) change from baseline. The sponsor is seeking approval for efficacy and safety of ertugliflozin to improve glycemic control in adults with T2DM.

Reference ID: 4144831

Table 1 below in Section 2.1.3 gives further details of study design, including background medication, sample size, and rescue medication for each of the seven studies.

2.1.1 Class and Indication

Ertugliflozin (proposed proprietary name Steglatro) is an oral sodium glucose co-transporter 2 (SGLT2) inhibitor. Examples of approved SGLT2 inhibitors include canagliflozin (Invokana, Invokamet), empagliflozin (Jardiance), and dapagliflozin (Farxiga). These inhibitors prevent kidneys from reabsorbing glucose back into the blood. The excess glucose in the blood is then removed from the body via urine. The proposed indication for ertugliflozin (E) is to improve glycemic control in adults with Type 2 diabetes mellitus (T2DM). This is also the proposed indication for Fixed Dose Combination (FDC) ertugliflozin and sitagliptin tablet (E+S - proposed proprietary name Steglujan) and FDC ertugliflozin and metformin tablet (E + M - proposed proprietary name Segluromet).

2.1.2 Select Submission History and Communication to Sponsor

On September 28, 2009, Pfizer submitted IND 106447. The product was at that time referred to as PF-04971729. The End-of-Phase 2 meeting was held on December 17, 2012. The Pre-NDA meeting was held on September 6, 2016. The Pre-NDA meeting request was not only for E, but for FDC's E + S (IND 122330 – Pre-IND Meeting Request April 14, 2014) and E + M (IND 122329). On December 19, 2016, all three NDA's were simultaneously submitted.

Comments concerning prevention of missing data were communicated by the Agency to the Sponsor in January of 2014 under IND 106447:

> The number of subjects not measured for the primary endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results.

Further Agency comments concerning prevention of missing data dated were communicated to the Sponsor in October 2014 under IND 106447:

> Considerable efforts should be made in order to avoid any missing data. Measurements on HbA1c at key time-points should be taken for all study subjects regardless of adherence to therapy or study protocol. A sizable amount of missing data will impact our confidence in study findings. Another reason to minimize missing data is that the missing data assumption for the proposed cLDA model may not allow for a reliable estimate of the average difference between treatment groups on the primary study endpoint. Our concern is that statistical behavior of the missing data will not be the same as the observed data since missing data tends to be associated with changes in adherence to randomized therapy. It is therefore critical that extensive efforts are made to prevent missing data. To this end, we note that your protocol encourages patients to attend the landmark visits if they prematurely discontinuation treatment. The protocol should
>
> (1) describe the procedures that will be in place to prevent missing data which should include training the site investigator,
>
> (2) collect the reason for missing data, when it does occur, and

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(3) describe the assumptions that went into the choice of the primary analysis method.

See the 2010 report on missing data by the National Academy of Sciences, The Prevention and Treatment of Missing Data in Clinical Trials, for additional discussion.

We also recommend that the informed consent forms for your phase 3 trials clearly differentiate treatment discontinuation from study withdrawal, and that the forms include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early.

Agency comments addressing missing data were communicated to the Sponsor in June 2015 under IND 106447:

None of the sponsor's eight phase 3 trials were designed to support an analysis that follows the ITT principle since subjects were not followed for efficacy after stopping treatment (Table 1). Subjects that stopped study drug and did not withdraw consent were only contacted by phone and they were not to continue scheduled study visits for continued efficacy assessments.

[Table 1 not included]

…

(b) (4)

We are particularly interested in results from analyses that evaluate the de facto or intention-to-treat (ITT) estimand (i.e., the difference in mean HbA1c change between treatment groups at the landmark visit regardless of adherence). The designs of your trials do not support reliably estimating this effect since efficacy data were not collected at scheduled visits after patients stopped treatment early. The missing at random assumption may be reasonable for the likely small subset of patients with missing data who were able to adhere to treatment for the entire study duration. However, for the group who were unable to adhere we do not believe the assumption will be satisfied. Your trials have HbA1c data after treatment discontinuation missing by design, making the plausibility of MAR low because adherence is almost surely related to the outcome. You have proposed sensitivity analyses that attempt to estimate the ITT quantity, with some relying on particularly strong and untestable assumptions (e.g., nonfuture dependence pattern mixture model and copy difference from control pattern mixture model). Of the proposed analyses, the jump to control approach may provide the most reasonable estimate of the ITT effect. This approach still has its limitations because it relies on untestable assumptions about the experience of patients after stopping treatment, and you will not have data after patients stop treatment to evaluate whether the imputation strategy may or may not lead to conservative inferences. To supplement these analyses, we request you perform and present findings from a tipping-point investigation for the ITT effect to assess whether missing data could have adversely impacted the study conclusion.

Agency Comments from December 2015 concerning the Statistical Analysis Plan (SAP) for the ISE (Integrated Summary of Efficacy) and ISS (Integrated Summary for Safety). The comments included a statement that they applied to the individual studies as well as the ISE.

> For ISE, we do not agree that the data collected after the initiation of rescue therapy or after bariatric surgery should be treated as missing. Analyses should be performed on the overall population and for the interested subgroups that include all available post-baseline observations regardless of treatment discontinuation, initiation of rescue therapy or other procedures. This also applies to the analysis of individual trials.

Agency Comments from pre-NDA meeting minutes (Finalized September 30, 2016):

> We are interested in estimating the treatment effect based on the intent-to-treat (de facto) estimand, which considers the actual measurements of subjects regardless of adherence to treatment or use of subsequent therapy, including use of glycemic rescue therapy, bariatric surgery, or bone mineral density rescue therapy. The corresponding analyses should account for missing data in the primary endpoint in a fashion consistent with what the measurement would have been, had it been measured and should address missing data based on that information most relevant to what the measurement would have been had it been measured. The cLDA (constrained Longitudinal Data Analysis) method likely does not appropriately address missing data as they both treat the behavior of missing data for those patients who are off-treatment to be the same as that of observed data for those patients who are on-treatment in the same treatment arm. We would recommend addressing missing data on the primary endpoint by having the missing data from subjects who do not adhere to therapy represented by the data from those subjects on the same arm that also did not adhere to therapy but had the measurement for the primary endpoint. Analysis results based on the de facto estimand will likely be the results put on the product label.

2.1.3 Specific Studies Reviewed

The seven studies in Table 1 below are all included in this review. Efficacy results of all these studies are included (b) (4) in Section 14 of the draft label for this NDA (ertugliflozin tablet) except for studies P001 and P017. However study P001 and Study P017 are still included in this review since efficacy results are described in the text in Section 14 of the draft label. Study P017 is also included in a Section 14 table for FDC E+S (NDA 209805).

Studies P005 and P006, in addition to being included in Section 14 (b) (4) for NDA 209803, are also in Section 14 tables for NDA 209805 (E+S). Studies P005, P002, P007 and P006 are in Section 14 (b) (4) of the draft label for NDA 209806 (E+M). These three NDA's were submitted together at the same time by the sponsor.

Table 1: Details of Study Design

Study	Study Design	Treatment Period	Follow-up Period	Treatment Arm	Sample Size	Study Population
P005	R, AC, PG, DB, MN; Background* - M; Full factorial study comparing E5/E15 +S100 vs S100 alone and vs. E5/E15 alone.	26 weeks	26 weeks	E5 : E15: S100: E5+S100: E15+S100:	244 247 242 237 241	M/F ≥ 18 years, T2DM
P002	R, AC, PG, DB, MN Background* - M Non-Inferiority Study comparing E5/E15 to Glim.	52 weeks	52 weeks	E5: E15: Glim:	447 440 437	M/F ≥ 18 years T2DM
P006	R, PC, PG, DB, MN Background*: M+S	26 weeks	26 weeks	E5 : E15: Placebo:	156 154 153	M/F ≥ 18 years, T2DM
P007	R, PC, PG, DB, MN Background*: M BMD Assessment	26 weeks	78 weeks	E5: E15: Placebo:	205 201 207	M/F ≥ 18 years, T2DM Large cohort post-menopausal women
P003	R, PC, PG, DB, MN Background*:	26 weeks	26 weeks	E5: E15: Placebo:	155 151 153	M/F ≥ 18 years, T2DM
P017	R, PC, PG, DB, MN Background*:	26 weeks	NA	E5+S100: E15+S100: Placebo:	98 96 96	M/F ≥ 18 years, T2DM
P001	R, PC, PG, DB, MN Background*: Approximately 90% of subjects on insulin and/or sulfonylurea	26 weeks	26 weeks	E5: E15: Placebo:	154 151 152	M/F ≥ 18 years, T2DM Stage 3 CKD with inadequate glyc. control on BG antihyp. therapy

Abbreviations: R-Randomized ; AC-Active controlled; PC- Placebo controlled; DB-Double Blind; PG-Parallel Group; MN-Multi-national; M/F – Male and Female subjects; T2DM – Type 2 Diabetes Mellitus; E5- ertugliflozin 5mg; E15- ertugliflozin 15mg; S100- sitagliptin 100 mg; M-metformin; BMD-Bone Mineral Density; Glim.-glimepiride; CKD-Chronic Kidney Disease; glyc.-glycemic; antihyp.-antihyperglycemic; BG-background*All studies include background of diet and exercise regimen

2.2 Data Sources

The data and final study report for NDA 209803 were submitted electronically as an eCTD submission. The submission, organized as an .enx file, is archived at the following link.

\\CDSESUB1\EVSPROD\NDA209803\209803.enx

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The SDTM and ADaM data sets are located in the proper sections of the submission, and analysis reviewer guides are provided which define variables and their locations.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The primary and secondary efficacy endpoints for the seven studies are shown in Table 2 below. All endpoints are assessed at 26 weeks except for study P002, where endpoints are assessed at 52 weeks. The European Medical Agency "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus", dated 2012, states that

> Confirmatory studies are typically 6 months in duration but at least one trial, preferably active controlled, should demonstrate maintenance of effect over at least 12 months.

In addition, the 2008 Draft Guidance for Industry-Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention (https://www.fda.gov/downloads/Drugs/.../Guidances/ucm071624.pdf) states:

> …Longer term controlled data also allow for better assessments of the comparative durability of effects on glycemia…

Secondary endpoints typically include Fasting Plasma Glucose (FPG), HbA1c < 7%, Body Weight, and Systolic Blood Pressure (SBP). Diastolic Blood Pressure (DBP) is also included in three of the studies. The non-inferiority study includes a secondary endpoint of hypoglycemia. Study P017 includes the secondary endpoint Post Meal Glucose (PMG).

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Table 2: Primary and Secondary Endpoints Listed in Hierarchical Testing Order

Study	Endpoint Type	Description
P005	Primary	Change from baseline in HbA1c: E15+S100 vs. S100
	Primary	Change from baseline in HbA1c: E15+S100 vs. E15
	Secondary	Change from baseline in HbA1c: E5+S100 vs. S100
	Secondary	Change from baseline in HbA1c: E5+S100 vs. E5
	Secondary	Change from baseline in Body Weight: E15+S100 vs. S100
	Secondary	Change from baseline in Body Weight: E5+S100 vs. S100
	Secondary	Change from baseline in FPG: E15+S100 vs. S100
	Secondary	Change from baseline in FPG: E15+S100 vs. E15
	Secondary	Change from baseline in FPG: E5+S100 vs. S100
	Secondary	Change from baseline in FPG: E5+S100 vs. E5
	Secondary	Change from baseline in SBP: E15+S100 vs. S100
	Secondary	Change from baseline in SBP: E5+S100 vs. S100
	Secondary	HbA1c<7% : E15+S100 vs. S100
	Secondary	HbA1c<7%: E15+S100 vs. E15
	Secondary	HbA1c<7%: E5+S100 vs. S100
	Secondary	HbA1c<7%: E5+S100 vs. E5
	Secondary†	Change from baseline in β cell function: E15+S100 vs. E15
	Secondary†	Change from baseline in β cell function: E15+S100 vs. S100
	Secondary‡	Change from baseline in β cell function: E5+S100 vs. E5
	Secondary‡	Change from baseline in β cell function: E5+S100 vs. S100
P002		**All Endpoints for Study P002 are assessed at 52 weeks**
	Primary	Change from baseline in HbA1c: E15 vs. Glim. (NI margin=0.3)
	Secondary	Hypoglycemia: E15 vs. Glim.
	Secondary	Change from baseline in Body Weight: E15 vs. Glim.
	Secondary	Change from baseline in HbA1c: E5 vs. Glim. (NI margin=0.3)
	Secondary	Hypoglycemia: E5 vs. Glim.
	Secondary	Change from baseline in Body Weight: E5 vs. Glim.
	Secondary†	Change from baseline in SBP: E15 vs. Glim.
	Secondary†	Change from baseline in SBP: E5 vs. Glim
	Secondary	Change from baseline in HbA1c: E15 vs. Glim - Superiority
	Secondary	Change from baseline in HbA1c: E5 vs. Glim - Superiority
P006	Primary	Change from baseline in HbA1c: E15 vs. Placebo
	Primary	Change from baseline in HbA1c: E5 vs. Placebo
	Key Secondary	Change from baseline in FPG: E15 vs. Placebo
	Key Secondary	Change from baseline in FPG: E5 vs. Placebo
	Key Secondary	Change from baseline in Body Weight : E15 vs. Placebo
	Key Secondary	Change from baseline in Body Weight : E5 vs. Placebo
	Key Secondary	HbA1c <7% : E15 mg vs. Placebo
	Key Secondary	HbA1c <7% : E5 mg vs. Placebo
	Key Secondary	Change from baseline in SBP: E15 vs. Placebo
	Key Secondary	Change from baseline in SBP : E5 vs. Placebo

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Table 2: Primary and Secondary Endpoints - Continued

P007*	Primary	Change from baseline HbA1c : E15 vs. Placebo
	Primary	Change from baseline HbA1c : E5 vs. Placebo
	Key Secondary	Change from baseline in FPG : E15 vs. Placebo
	Key Secondary	Change from baseline in FPG : E5 vs. Placebo
	Key Secondary	Change from baseline in Body Weight: E15 vs. Placebo
	Key Secondary	Change from baseline in Body Weight: E5 vs. Placebo
	Key Secondary	HbA1c <7%: E15 mg vs. Placebo
	Key Secondary	HbA1c <7%: E5 mg vs. Placebo
	Key Secondary	Change from baseline in SBP: E15 vs. Placebo
	Key Secondary	Change from baseline in SBP: E5 vs. Placebo
	Key Secondary	Change from baseline in DBP: E15 vs. Placebo
	Key Secondary	Change from baseline in DBP: E5 vs. Placebo
P017	Primary	Change from baseline HbA1c: E15+S100 vs. Placebo
	Primary	Change from baseline HbA1c: E5+S100 vs. Placebo
	Key Secondary	Change from baseline in FPG: E15+S100 vs. Placebo
	Key Secondary	Change from baseline in FPG: E5+S100 vs. Placebo
	Key Secondary	Change from baseline in 2 Hr. PMG: E15+S100 vs. Placebo
	Key Secondary	Change from baseline in 2 Hr. PMG: E5+S100 vs. Placebo
	Key Secondary	HbA1c <7% : E15+S100 vs. Placebo
	Key Secondary	HbA1c <7% : E5+S100 vs. Placebo
	Key Secondary	Change from baseline in Body Weight: E15+S100 vs. Placebo
	Key Secondary	Change from baseline in Body Weight: E5+S100 vs. Placebo
	Key Secondary	Change from baseline in SBP: E15 +S100 vs. Placebo
	Key Secondary	Change from baseline in SBP: E5+S100 vs. Placebo
	Key Secondary	Change from baseline in DBP: E15+S100 vs. Placebo
	Key Secondary	Change from baseline in DBP: E5+S100 vs. Placebo
P003**	Primary	Change from baseline HbA1c :: E15 vs. Placebo
	Primary	Change from baseline HbA1c : E5 vs. Placebo
	Key Secondary	Change from baseline in FPG : E15 vs. Placebo
	Key Secondary	Change from baseline in FPG : E5 vs. Placebo
	Key Secondary	Change from baseline in Body Weight : E15 vs. Placebo
	Key Secondary	Change from baseline in Body Weight : E5 vs. Placebo
	Key Secondary	HbA1c <7% : E15 mg vs. Placebo
	Key Secondary	HbA1c <7% : E5 mg vs. Placebo
	Key Secondary	Change from baseline in SBP : E15 vs. Placebo
	Key Secondary	Change from baseline in SBP : E5 vs. Placebo
	Key Secondary	Change from baseline in DBP : E15 vs. Placebo
	Key Secondary	Change from baseline in DBP : E5 vs. Placebo

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Table 2: Primary and Secondary Endpoints - Continued

P001	Primary	Change from baseline HbA1c : E15 vs. Placebo
	Primary	Change from baseline HbA1c : E5 vs. Placebo
	-	**All Secondary endpoints for P001 apply only to eGFR ≥ 45 stratum**
	Secondary	Change from baseline HbA1c : E15 vs. Placebo
	Secondary	Change from baseline HbA1c : E5 vs. Placebo
	Secondary	Change from baseline in Body Weight : E15 vs. Placebo
	Secondary	Change from baseline in SBP : E15 vs. Placebo
	Secondary	Change from baseline in Body Weight : E5 vs. Placebo
	Secondary	Change from baseline in SBP : E5 vs. Placebo
	Secondary	Change from baseline in FPG : E15 vs. Placebo
	Secondary	Change from baseline in FPG : E5 vs. Placebo
	Secondary	HbA1c <7%: E15 vs. Placebo
	Secondary	HbA1c <7%: E5 vs. Placebo

All endpoints are assessed at 26 weeks except for the 52 week (for Phase A) non-inferiority study P002.
Abbreviations; NI – Non-Inferiority; Glim.-glimepiride; FPG-Fasting Plasma Glucose; PMG-Post Meal Glucose; Novo-NovoLog; PPG - Post Prandial Glucose
*for P007:taken from sponsor's Statistical Analysis Plan Amendment (Version 3), Section 4.2, page 12, dated February 10, 2016; -Data Lock date was not found in the Synopsis or in the Clinical Study Report.;– the latest "Date of Last Exposure in Phase A" for a subject in the study was January 24, 2016; section 9.8 in the Clinical Study Report details changes in the Amendment and states they were before database lock; in response to IR request, sponsor stated database lock was 3/8/2016;
** for P003 -(Taken from sponsor's Statistical Analysis Plan (Amended Version 3), Section 4.2, page 12, dated January 27, 2016; -Data Lock was not found in Synopsis or Clinical Study Report; the latest "Date of Last Exposure in Phase A" for a subject in the study was January 14, 2016; in response to IR request, sponsor stated database lock was 2/11/2016; Section 9.8 of the Study Report states:

> An amendment to the SAP (Version 1.0; dated 22 November 2013) was issued on 07 December 2015 (Version 1.1). An amended Version 3 was issued on 27 January 2016. There was no version 2 of the SAP. All amendments to the SAP were finalized prior to database lock and unblinding.

Multiple Testing Procedure

All seven studies use a hierarchical testing strategy to control Type 1 Error rate at $\alpha \leq 0.025$, one-sided. The order of the hierarchical testing for each study is shown in Table 2. Within the hierarchical testing for Study P002, the Hochberg procedure is used for the SBP endpoints: E15 vs. glimepiride and E5 vs. glimepiride. If previous endpoints in the hierarchical testing order are all significant at $p < 0.025$ one-sided, then testing for the two SBP endpoints proceeds as follows:

1) The two p-values for the SBP tests are ordered from largest to smallest.
2) If the highest of the two p-values is $< \alpha_1=0.025$ (one-sided), then SBP for both E5 and E15 vs. glimepiride are declared significant, and hierarchical testing proceeds to the next test (superiority for HbA1c).
3) If the highest p-value is ≥ 0.025 one-sided, but the other p-value is $< \alpha_2=0.0125$ one-sided, then only the endpoint with p-value < 0.0125 is declared statistically significant. The hierarchical testing stops, and no further endpoints are tested.
4) If neither of the two SBP endpoints is declared significant in steps 2 and 3 above, then the hierarchical testing stops, and no further endpoints are tested.

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Finalized SAP Date and Database Lock

For studies P007 and P003, I was not able to find the time of database lock in the report synopses. In response to an information request, the sponsor specified the date of database lock for both studies, and the latest SAP revisions for these studies were all prior to the date of database lock specified. See Table 2 notes for more details.

For study P002, the multiple testing procedure is as described in Figure 8 Section 8.2.5 of the sponsor's SAP dated September 25, 2013, which is well before cut-off and also before first date of randomization for the study. The revised SAP (revision dated February 26, 2015) has the revised multiple testing hierarchy which is described in Figure 2 of the SAP. The revision was also before the database lock for study P002, which was May 25, 2015.

3.2.1.2 Non-Inferiority Margin

For the primary endpoints in Study P002 (52-week reduction in HbA1c (%) – E15 vs. glimepiride, and E5 vs. glimepiride), a non-inferiority margin of 0.3 was used. A non-inferiority margin of 0.30 was also used for the SGLT2 inhibitor empagliflozin/Jardiance (NDA 204629). A margin of 0.35 was used for SGLT2 inhibitor dapagliflozin/Farxiga (NDA 202293).

3.2.2 Statistical Methodologies

3.2.2.1 Sponsor Approach:

The sponsor's primary analysis population for the primary cLDA analysis is the "Full Analysis Set" (FAS) population which is defined as all randomized subjects who

- receive at least one dose of study treatment;
- have a baseline measurement or a post-randomization measurement for the analysis endpoint subsequent to at least one dose of study treatment.

The sponsor's data analysis set excludes measurements obtained after discontinuation of study treatment. This is true both for the primary analysis and the sensitivity analyses.

The sponsor's defined primary analysis for continuous endpoints, including the primary endpoint of reduction in HbA1c (%), was a constrained longitudinal data analysis (cLDA). This analysis treated observations obtained after initiation of rescue medication as missing.

Covariates in the model, both for the primary and sensitivity analyses, included baseline HbA1c (%) and baseline estimated glomerular filtration rate (eGFR). For study P002, prior antihyperglycemic therapy status was included as a factor. For study P006, actual stratification status based on having had prior antihyperglycemic therapy that included a sulfonylurea was included as a factor.

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Sponsor Sensitivity Analyses

The sponsor also incorporated sensitivity analyses which used the same analysis method as for the primary analysis (cLDA), but including measurements obtained after rescue medication. For this analysis, subjects who started rescue medication had their measurements included only up to the time of study treatment discontinuation.

In addition the sponsor incorporated jump-to-reference (J2R) and tipping point sensitivity analyses which both included and excluded measures obtained after initiation of rescue medication. Measurements obtained after study treatment discontinuation were still left out of the analysis set, as they were for the sponsor's primary analysis. For the J2R excluding rescue analyses, subjects on the experimental arms who initiated rescue therapy were assumed to switch to the comparator arm. This is done using the method of Carpenter et al. (2013), and code for J2R and tipping point analyses was taken from the website specified in that manuscript (www.missingdata.org.uk).

3.2.2.2 Statistical Reviewer Approach:

The preferred analysis population is all randomized subjects who have a baseline measurement and have been exposed to treatment. The analysis set should include all measures obtained after initiation of rescue therapy and study treatment discontinuation.

In general, subjects who discontinue study treatment cannot be expected to have the same outcomes as subjects who complete study treatment. Similarly subjects who initiate rescue medication cannot be expected to have the same outcomes as subjects who do not initiate rescue therapy. Therefore, in order to represent what actually occurred, it is necessary to include measures after initiation of rescue therapy as well as measures after study treatment discontinuation. This approach is also consistent with the IR requests sent to the sponsor during the IND and pre-NDA periods (see Section 2.1.2).

My preferred analysis includes measures after study treatment discontinuation and after initiation of alternative therapy. To assure that final assessments occur reasonably close to the planned final assessment week, a 26 +/- 4 week window was specified for the final assessment for the 26 week studies, and a 52 +/- 8 week window was specified for the 52-week non-inferiority study. If no non-missing assessment is available for a subject in the final assessment window, it is treated as missing for the final assessment. The missing observation is then imputed multiple times according to the methods specified below. Since there are not enough retrieved dropouts to utilize a retrieved dropout analysis (see Section 3.2.2.3), alternative multiple imputation methods such as J2R and return to baseline (RTB) are needed.

With the J2R approach, subjects with missing final assessments on the experimental arms are assumed to take on (i.e. switch to) the profile of subjects on the comparator arm. This approach may be appropriate when subjects have missing data due to treatment discontinuation, and these subjects are given alternative therapy. The comparator arm is used to represent the effect of the alternative therapy on the subjects who have the missing data. For non-inferiority studies, a

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penalty term is often used for subjects with missing data on the experimental arm to prevent an equalizing effect of the alternative therapy on the experimental and comparator arms.

An RTB approach assumes that subjects who have missing data return to their baseline measurement. This approach may be appropriate when missing data is due to treatment discontinuation, and the effect of any alternative therapy (or continued background therapy) is only expected to prevent a further deterioration from baseline.

While the assumptions in these two approaches are not verifiable, they seem reasonable for this application.

Sensitivity analyses requested in the IR include the following:

1) An ANCOVA return to baseline (RTB) analysis for each study.
2) In addition, for the non-inferiority study P002, an ANCOVA using RTB on the experimental arms and missing at random (MAR) on the control arm.
3) A J2R analysis for each study. For the non-inferiority study, a 0.3 penalty is added for the HbA1c (%) assessment for the experimental arms. A 0.6 penalty is also used.

In addition, my analyses included the following.

1) An ANCOVA analysis (using no intermediate measures) where subjects with missing final assessments on the experimental arm are assumed to wash out to the comparator arm. For the non-inferiority study, a 0.3 penalty is added for the subjects with missing data on the experimental arms (who are assumed to switch to the comparator arm).
2) For the non-inferiority study, an ANCOVA analysis similar to #1 above, but assuming missing at random (MAR) on the comparator arm and using a 0.3 % penalty for the experimental arms (for HbA1c).

3.2.2.3 Characterization of Missing Data

Characterization of Sponsor's Submitted Data and Variable Definitions

For variable AVISITN in the sponsor's submission, the value of ADY (Analysis Relative Day) for AVISITN=26, does not fall within a specified window of week 26. Assessments after treatment discontinuation, regardless of time of discontinuation, are assigned an AVISITN value of 999. The actual ADY for AVISITN=26 (or 52 for the non-inferiority study) is always prior to the time a subject discontinues treatment, regardless of the number of weeks from date of first exposure to treatment. For example, if a subject discontinues treatment at 6 weeks after first exposure to treatment, then the ADY corresponding to AVISITN=26/52 would be at the last ADY at or before 6 weeks. This is consistent with sponsor final written presentation for the February 16, 2017 Walk-thru or "Applicant Orientation" Meeting.

> To identify the last assessment prior to treatment discontinuation or the last assessment prior to rescue medication, select the population of interest and then sort by subject and

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time (e.g. by SUBJID AVISITN) and then select the last observation for each subject. There are no specific flags for these.

For example, to identify pre vs. post-treatment discontinuation visits use the value of AVISITN. Visits conducted post treatment discontinuation have an AVISITN value of 999. Visits prior to treatment discontinuation have AVISITN values equal to the planned study week: 6, 12, 18, 26, etc. To select the last value prior to rescue, use the endpoint-specific excluding rescue flag (listed in the ADRGs) then select the latest timepoint where AVISITN ne 999 (and visits are in Phase of interest).

For AVISITN=52 for Non-inferiority Study P002 (the 52 week study) there were at least 5 % of 52-Week assessments that were actually made at less than 26 weeks after treatment exposure (ADY < 182 days-) and at least 10 percent that were before 40 weeks (ADY<280).

The distribution of ADY (in weeks) for AVISITN=52 in weeks is shown in Figure 1.

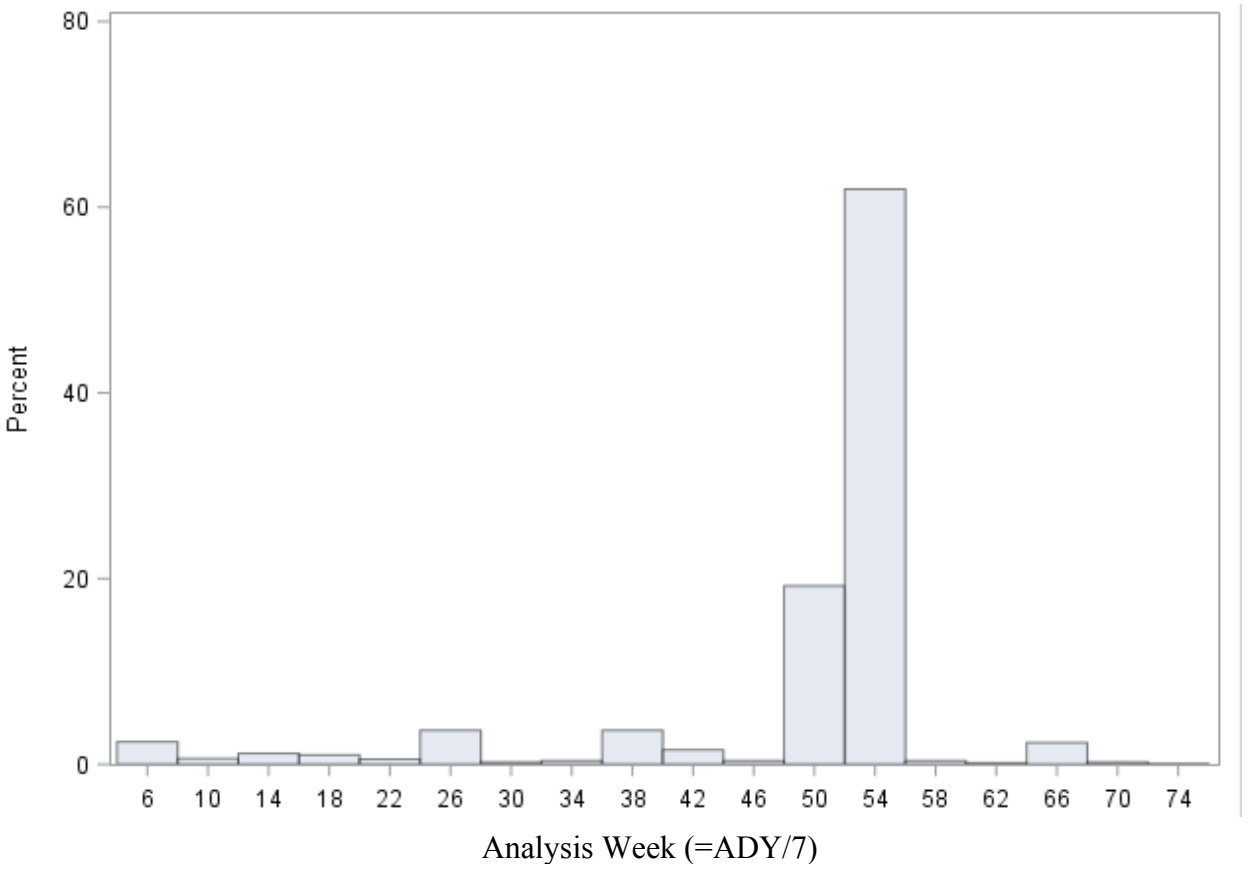

Figure 1: Distribution of Time of Analysis Week 52 (AVISITN=52)-Study P002

The Agency, as part of an information request sent June 26, 2017, asked the sponsor for analyses which have all final assessments within a 26 +/- 4 Week window for the 26 week studies, and (at

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request of sponsor for a wider window for the 52 week study) within a 52 +/- 8 week window for the non-inferiority study. The sponsor complied with these requests.

Missing Rates, Discontinuation Rates, and Rescue Rates

All subjects that had no assessment within a 26 +/- 4 week window (or a 52 +/- 8 week window for the non-inferiority study) are counted as having missing data for the final assessment. Missing rates, study treatment discontinuation rates, and rescue rates for all seven studies are shown in Table 3. The rate of missing primary efficacy data was close to 10% for the factorial Study P005 and from 15% (on the glimepiride arm) to 20% (on the E5 arm) for the 52-week non-inferiority study. The non-inferiority study had the highest overall missing rate of all the studies, probably due to its 52-week length.

The placebo studies, especially the two with a background consisting of a diet and exercise regimen (DER) only (studies P003 and P017 – Table 1) had missing rates, study treatment discontinuation rates, and rescue rates which were much higher on the placebo arm (Table 4). The rescue rates for these studies were especially imbalanced and higher on the placebo arm. Study P017 had a placebo arm rescue rate of almost 31%, and for Study P003 it was 24%. The study with the next weakest background of the placebo studies (P007 – background of DER+M), also had the next highest placebo rescue rate - 16%.

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Table 3: Descriptive statistics for patients having primary efficacy data, and patients discontinuing treatment.

Study	Group	All Patients Random.	Treated, With BL	Missing*	(%)	Had Primary Efficacy Data in Final Ass. Window	(%)	Disc. Treatment Early**	(%)	Started Rescue Med. Before Final Assess. Window***	(%)
P002	E5	448	447	88	19.7%	359	80.3%	76	17.0%	23	5.1%
P002	E15	441	440	71	16.1%	369	83.9%	64	14.5%	13	3.0%
P002	Glim.	437	437	66	15.1%	371	84.9%	60	13.7%	10	2.3%
P005	E5	250	244	18	7.4%	226	92.6%	16	6.6%	15	6.1%
P005	E15	248	247	26	10.5%	221	89.5%	19	7.7%	7	2.8%
P005	S100	247	242	27	11.2%	215	88.8%	22	9.1%	13	5.4%
P005	E5+S100	243	237	20	8.4%	217	91.6%	17	7.2%	5	2.1%
P005	E15+S100	245	241	26	10.8%	215	89.2%	20	8.3%	0	0.0%
P006	Placebo	153	152	14	9.2%	138	90.8%	11	7.2%	20	13.2%
P006	E5	156	155	16	10.3%	139	89.7%	12	7.7%	2	1.3%
P006	E15	154	152	11	7.2%	141	92.8%	10	6.6%	3	2.0%
P007	Placebo	209	207	23	11.1%	184	88.9%	17	8.2%	33	15.9%
P007	E5	207	205	11	5.4%	194	94.6%	6	2.9%	6	2.9%
P007	E15	205	201	14	7.0%	187	93.0%	14	7.0%	3	1.5%
P017	Placebo	97	96	20	20.8%	76	79.2%	21	21.9%	30	31.3%
P017	E5+S100	98	98	7	7.1%	91	92.9%	7	7.1%	6	6.1%
P017	E15+S100	96	96	10	10.4%	86	89.6%	8	8.3%	0	0.0%
P003	Placebo	153	153	35	22.9%	118	77.1%	33	21.6%	37	24.2%
P003	E5	156	155	16	10.3%	139	89.7%	22	14.2%	3	1.9%
P003	E15	152	151	24	15.9%	127	84.1%	23	15.2%	4	2.6%
P001	Placebo	154	152	27	17.8%	125	82.2%	14	9.2%	9	5.9%
P001	E5	158	154	21	13.6%	133	86.4%	16	10.4%	13	8.4%
P001	E15	156	151	25	16.6%	126	83.4%	14	9.3%	5	3.3%

*The final assessment for a subject was considered missing if they had no assessment within 26 +/- 4 weeks for the 26 week studies, and within 52 +/- 8 weeks for the non-inferiority study.** For 52-Week study (P002), number (%) discontinuing treatment is defined as at < 44 weeks after randomization. For all other studies, treatment discontinuation is defined as < 22 weeks.; *** Assessment window is defined previously - +/- 4 weeks for 26 week studies and 52 +/- 8 weeks for non-inferiority study;
Abbreviations: Glim. – glimepiride. E5- ertugliflozin 5mg; E15- ertugliflozin 15mg; S100- sitagliptin 100 mg; Ass. – Assessment; Rand. – Randomized; Disc. – Discontinued; Med.-Medication

Few Retrieved Dropouts

For Study P005, only one of the five arms (the S100 arm) had more than one subject who discontinued treatment before 22 weeks but still had a non-missing final assessment as defined by the final assessment window (Appendices, Table S1). For the 52-week non-inferiority study P002 (Table S2), there were only 2 of 76 subjects on the E5 arm, 3 of 64 subjects on the E15 arm, and 5 of 60 subjects on the glimepiride arm, who discontinued treatment before 44 weeks and still had a final assessment. This trend was also present for the placebo studies (Tables S3-S7). Because of the sparsity of retrieved dropouts, there was limited information to conduct an analysis which incorporated this information.

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3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The distributions of baseline demographic characteristics for the seven studies are shown in Tables 4-10 below. In general these characteristics seem evenly distributed between treatment arms for each of the seven studies. In particular, baseline HbA1c and eGFR levels seem reasonably similar between arms for each study.

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Table 4: Demographics and Baseline Characteristics by Treatment Arm - Study P005

Treatment Group	E5	E15	S100	E5+S100	E15+S100
N per Group	**244**	**247**	**242**	**237**	**241**
Sex, n (%)					
F	120 (49)	113 (46)	91 (38)	117 (49)	116 (48)
M	124 (51)	134 (54)	151 (62)	120 (51)	125 (52)
Race, n (%)					
Asian	20 (8)	21 (9)	28 (12)	22 (9)	35 (15)
Black	7 (3)	6 (2)	9 (4)	12 (5)	10 (4)
White	202 (83)	205 (83)	191 (79)	191 (81)	186 (77)
Ethnicity, n (%)					
Hispanic or Latino	86 (35)	88 (36)	77 (32)	84 (35)	85 (35)
Age					
Mean (95%CI)	55.3 (54.1 - 56.6)	55.4 (54.2 - 56.6)	54.8 (53.4 - 56.1)	55.0 (53.7 - 56.4)	55.1 (53.8 - 56.3)
Median (min - max)	56.5 (21.0 - 85.0)	56.0 (26.0 - 77.0)	56.0 (26.0 - 79.0)	56.0 (24.0 - 80.0)	56.0 (30.0 - 83.0)
>=65, n (%)	36 (15)	43 (17)	40 (17)	42 (18)	33 (14)
Region, n (%)					
Asia	21 (9)	20 (8)	24 (10)	18 (8)	29 (12)
Australia/New Zealand	4 (2)	3 (1)	8 (3)	3 (1)	2 (1)
Europe (incl. Russia)	102 (42)	105 (43)	102 (42)	100 (42)	93 (39)
North Am. (excl. Central America)	71 (29)	77 (31)	75 (31)	74 (31)	75 (31)
South America	42 (17)	42 (17)	37 (15)	42 (18)	42 (17)
Baseline HbA1c (%)					
Mean (95%CI)	8.6 (8.4 - 8.7)	8.6 (8.4 - 8.7)	8.5 (8.4 - 8.6)	8.6 (8.4 - 8.7)	8.6 (8.4 - 8.7)
Median (min - max)	8.4 (5.4 - 12.3)	8.4 (5.8 - 11.6)	8.3 (5.1 - 11.5)	8.4 (5.6 - 11.9)	8.4 (6.5 - 11.7)
Baseline Estimated GFR (mL/min/1.73m[2])					
Mean (95%CI)	92.0 (89.4 - 94.6)	92.6 (90.0 - 95.3)	92.7 (90.4 - 95.0)	91.9 (89.3 - 94.5)	92.7 (90.2 - 95.1)
Median (min - max)	89 (35 - 17)	90 (52 - 196)	91 (53 - 150)	88 (53 - 174)	90 (54 - 155)
Baseline BMI (kg/m)					
Mean (95%CI)	31.7 (30.9 - 32.5)	31.5 (30.8 - 32.2)	31.7 (30.8 - 32.5)	32.5 (31.6 - 33.4)	31.9 (31.0 - 32.7)
Median (min - max)	30.6 (18.4 - 55.4)	30.3 (19.2 - 50.7)	30.7 (20.5 - 64.6)	30.9 (21.8 - 56.9)	31.1 (19.1 - 59.6)
Duration of Diabetes					
Mean (95%CI)	7.1 (6.4 - 7.8)	7.4 (6.7 - 8.0)	6.1 (5.4 - 6.7)	7.0 (6.3 - 7.7)	6.9 (6.2 - 7.5)
Median (min - max)	5.8 (0.2 - 26.0)	6.3 (0.3 - 33.7)	5.0 (0.2 - 33.8)	5.6 (0.2 - 35.5)	5.7 (0.2 - 24.1)

CI-Confidence Intervals

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Table 5: Demographics and Baseline Characteristics by Treatment Arm - Study P002

Treatment Group	**E5**	**E15**	**Glim**
N per Group	**447**	**440**	**437**
Sex, n (%)			
F	221 (49)	249 (57)	213 (49)
M	226 (51)	191 (43)	224 (51)
Race, n (%)			
Asian	80 (18)	85 (19)	73 (17)
Black	17 (4)	19 (4)	25 (6)
White	332 (74)	316 (72)	318 (73)
Ethnicity, n (%)			
Hispanic or Latino	92 (21)	92 (21)	89 (20)
Age			
Mean (95%CI)	58.8 (57.9 - 59.7)	58.0 (57.1 - 58.9)	57.8 (56.9 - 58.7)
Median (min - max)	60.0 (31.0 - 86.0)	58.0 (22.0 - 82.0)	59.0 (26.0 - 81.0)
>=65, n (%)	121 (27)	112 (25)	103 (24)
Region, n (%)			
Asia	54 (12)	64 (15)	56 (13)
Europe (inc. Russia)	201 (45)	194 (44)	202 (46)
North Am. (excl. Cent. Am.)	131 (29)	128 (29)	124 (28)
South America	46 (10)	43 (10)	44 (10)
South Africa	15 (3)	11 (3)	11 (3)
Baseline HbA1c (%)			
Mean (95%CI)	7.8 (7.8 - 7.9)	7.8 (7.7 - 7.9)	7.8 (7.7 - 7.8)
Median (min - max)	7.7 (5.9 - 10.5)	7.7 (6.6 - 9.7)	7.7 (5.8 - 10.9)
Baseline GFR (mL/min/1.73m)			
Mean (95%CI)	88.3 (86.5 - 90.0)	86.7 (85.0 - 88.4)	86.6 (84.9 - 88.3)
Median (min - max)	86.0 (46.0 - 162.0)	86.0 (41.0 - 158.0)	85.0 (28.0 - 149.0)
Baseline BMI (kg/m)			
Mean (95%CI)	31.7 (31.2 - 32.2)	31.3 (30.7 - 31.9)	31.2 (30.6 - 31.8)
Median (min - max)	31.2 (17.4 - 51.2)	30.4 (18.8 - 61.2)	30.1 (19.1 - 77.9)
Duration of Diabetes at Baseline (years)			
Mean (95%CI)	7.4 (6.9 - 7.9)	7.5 (7.0 - 8.0)	7.5 (7.0 - 8.1)
Median (min - max)	6.5 (0.2 - 35.0)	6.1 (0.2 - 29.7)	6.3 (0.2 - 49.6)

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Table 6: Demographics and Baseline Characteristics by Treatment Arm-Study P006

Treatment Group	**Placebo**	**E5**	**E15**
N per Group	**152**	**155**	**152**
Sex, n (%)			
F	52 (34)	75 (48)	70 (46)
M	100 (66)	80 (52)	82 (54)
Race, n (%)			
Asian	32 (21)	33 (21)	27 (18)
Black	3 (2)	2 (1)	4 (3)
White	108 (71)	113 (73)	115 (76)
Ethnicity, n (%)			
Hispanic or Latino	24 (16)	23 (15)	25 (16)
Age			
Mean (95%CI)	58.3 (56.8 - 59.7)	59.2 (57.7 - 60.6)	59.7 (58.3 - 61.1)
Median (min - max)	59.5 (36.0 - 80.0)	59.0 (34.0 - 81.0)	60.0 (35.0 - 84.0)
>=65, n (%)	47 (31)	48 (31)	41 (27)
Region, n (%)			
Asia	43 (28)	44 (28)	38 (25)
Europe (inc. Russia)	65 (43)	69 (45)	74 (49)
North Am. (excl. Cent. Am.)	30 (20)	32 (21)	31 (20)
South America	14 (9)	10 (6)	9 (6)
Baseline HbA1c (%)			
Mean (95%CI)	8.0 (7.9 - 8.2)	8.1 (7.9 - 8.2)	8.0 (7.9 - 8.1)
Median (min - max)	7.9 (6.3 - 11.1)	7.9 (5.7 - 10.7)	7.8 (5.8 - 10.6)
Baseline GFR (mL/min/1.73m)			
Mean (95%CI)	89.7 (86.9 - 92.4)	86.9 (84.2 - 89.7)	87.0 (84.5 - 89.5)
Median (min - max)	88.0 (54.0 - 145.0)	84.0 (51.0 - 144.0)	86.5 (54.0 - 137.0)
Baseline BMI (kg/m)			
Mean (95%CI)	30.3 (29.3 - 31.3)	31.1 (30.3 - 32.0)	30.9 (30.0 - 31.9)
Median (min - max)	29.8 (17.5 - 67.1)	30.8 (18.8 - 48.2)	30.4 (19.4 - 53.7)
Duration of Diabetes at Baseline (years)			
Mean (95%CI)	9.4 (8.5 - 10.3)	9.8 (8.9 - 10.8)	9.2 (8.3 - 10.0)
Median (min - max)	8.0 (0.3 - 28.8)	8.7 (0.2 - 29.4)	9.1 (0.2 - 34.3)

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Table 7: Demographics and Baseline Characteristics by Treatment Arm-Study P007

Treatment Group	**Placebo**	**E5**	**E15**
N per Group	**207**	**205**	**201**
Sex, n (%)			
F	109 (53)	110 (54)	108 (54)
M	98 (47)	95 (46)	93 (46)
Race, n (%)			
Asian	30 (14)	34 (17)	35 (17)
Black	18 (9)	22 (11)	23 (11)
White	144 (70)	132 (64)	129 (64)
Ethnicity, n (%)			
Hispanic or Latino	43 (21)	36 (18)	34 (17)
Age			
Mean (95%CI)	56.6 (55.5 - 57.8)	56.6 (55.5 - 57.7)	56.7 (55.4 - 58.0)
Median (min - max)	58.0 (24.0 - 72.0)	58.0 (26.0 - 79.0)	58.0 (29.0 - 79.0)
>=65, n (%)	35 (17)	26 (13)	34 (17)
Region, n (%)			
Asia	26 (13)	27 (13)	32 (16)
Australia	4 (2)	6 (3)	1 (0)
Europe (inc. Russia)	76 (37)	73 (36)	70 (35)
North Am. (excl. Cent. Am.)	55 (27)	60 (29)	53 (26)
South Africa	37 (18)	35 (17)	37 (18)
South America	9 (4)	4 (2)	8 (4)
Baseline HbA1c (%)			
Mean (95%CI)	8.2 (8.0 - 8.3)	8.1 (7.9 - 8.2)	8.1 (8.0 - 8.3)
Median (min - max)	8.0 (5.8 - 11.0)	7.9 (6.2 - 11.3)	7.9 (5.7 - 10.6)
Baseline GFR (mL/min/1.73m)			
Mean (95%CI)	91.1 (88.5 - 93.7)	88.9 (86.5 - 91.3)	91.2 (88.3 - 94.0)
Median (min - max)	91.0 (47.0 - 151.0)	88.0 (55.0 - 144.0)	90.0 (42.0 - 178.0)
Baseline BMI (kg/m)			
Mean (95%CI)	30.7 (30.0 - 31.3)	30.8 (30.2 - 31.5)	31.0 (30.4 - 31.7)
Median (min - max)	30.2 (19.0 - 40.9)	31.0 (18.9 - 40.0)	31.0 (19.4 - 40.4)
Duration of Diabetes at Baseline (years)			
Mean (95%CI)	8.1 (7.2 - 9.0)	7.9 (7.1 - 8.7)	8.1 (7.3 - 8.8)
Median (min - max)	6.6 (0.2 - 38.9)	6.2 (0.2 - 27.9)	7.3 (0.2 - 28.6)

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Table 8: Demographics and Baseline Characteristics by Treatment Arm-Study P003

Treatment Group	**Placebo**	**E5**	**E15**
N per Group	**153**	**155**	**151**
Sex, n (%)			
F	71 (46)	67 (43)	61 (40)
M	82 (54)	88 (57)	90 (60)
Race, n (%)			
Asian	15 (10)	10 (6)	13 (9)
Black	9 (6)	10 (6)	10 (7)
White	126 (82)	133 (86)	126 (83)
Ethnicity, n (%)			
Hispanic or Latino	34 (22)	27 (17)	41 (27)
Age			
Mean (95%CI)	56.1 (54.3 - 57.8)	56.9 (55.1 - 58.7)	56.2 (54.5 - 58.0)
Median (min - max)	56.0 (26.0 - 80.0)	58.0 (28.0 - 87.0)	56.0 (23.0 - 76.0)
>=65, n (%)	38 (25)	41 (26)	41 (27)
Region, n (%)			
Asia	2 (1)	2 (1)	2 (1)
Europe (inc. Russia)	39 (25)	40 (26)	39 (26)
North Am. (excl. Cent. Am.)	101 (66)	106 (68)	100 (66)
South Africa	7 (5)	6 (4)	6 (4)
South America	4 (3)	1 (1)	4 (3)
Baseline HbA1c (%)			
Mean (95%CI)	8.1 (8.0 - 8.3)	8.2 (8.0 - 8.3)	8.4 (8.2 - 8.5)
Median (min - max)	7.9 (6.5 - 11.2)	8.0 (6.6 - 10.6)	8.1 (6.6 - 11.1)
Baseline GFR (mL/min/1.73m)			
Mean (95%CI)	86.2 (83.2 - 89.3)	88.5 (85.6 - 91.4)	88.1 (85.2 - 90.9)
Median (min - max)	83.0 (52.0 - 181.0)	87.0 (47.0 - 157.0)	88.0 (56.0 - 143.0)
Baseline BMI (kg/m)			
Mean (95%CI)	33.3 (32.2 - 34.3)	33.2 (32.1 - 34.4)	32.4 (31.5 - 33.4)
Median (min - max)	32.4 (21.3 - 58.6)	32.8 (22.2 - 67.9)	31.3 (20.4 - 49.3)
Duration of Diabetes at Baseline (years)			
Mean (95%CI)	4.6 (3.9 - 5.3)	5.1 (4.3 - 5.9)	5.2 (4.3 - 6.1)
Median (min - max)	3.3 (0.1 - 24.9)	3.9 (0.0 - 24.2)	3.4 (0.0 - 39.9)

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Table 9: Demographics and Baseline Characteristics by Treatment Arm-Study P017

Treatment Group	**Placebo**	**E5+S100**	**E15+S100**
N per Group	**96**	**98**	**96**
Sex, n (%)			
F	40 (42)	41 (42)	43 (45)
M	56 (58)	57 (58)	53 (55)
Race, n (%)			
Black	4 (4)	2 (2)	7 (7)
White	89 (93)	92 (94)	81 (84)
Ethnicity, n (%)			
Hispanic or Latino	36 (38)	34 (35)	34 (35)
Age			
Mean (95%CI)	54.5 (52.4 - 56.5)	56.4 (54.6 - 58.3)	56.1 (54.1 - 58.1)
Median (min - max)	55.0 (32.0 - 78.0)	56.0 (37.0 - 76.0)	57.0 (35.0 - 78.0)
>=65, n (%)	14 (15)	23 (23)	21 (22)
Region, n (%)			
Europe (inc. Russia)	40 (42)	57 (58)	51 (53)
North Am. (excl. Cent. Am.)	56 (58)	41 (42)	45 (47)
Baseline HbA1c (%)			
Mean (95%CI)	8.9 (8.8 - 9.1)	8.9 (8.7 - 9.1)	9.0 (8.8 - 9.2)
Median (min - max)	8.9 (7.0 - 10.8)	9.0 (6.2 - 10.7)	8.9 (6.2 - 10.9)
Baseline GFR (mL/min/1.73m)			
Mean (95%CI)	92.6 (88.2 - 96.9)	90.0 (86.6 - 93.4)	89.5 (85.9 - 93.1)
Median (min - max)	87.5 (57.0 - 171.0)	89.0 (55.0 - 137.0)	87.0 (58.0 - 142.0)
Baseline BMI (kg/m)			
Mean (95%CI)	32.7 (31.4 - 33.9)	32.0 (30.7 - 33.2)	32.1 (30.9 - 33.2)
Median (min - max)	32.0 (22.3 - 55.1)	31.7 (21.6 - 57.4)	31.3 (20.9 - 57.3)
Duration of Diabetes at Baseline (years)			
Mean (95%CI)	6.8 (5.5 - 8.1)	5.7 (4.7 - 6.7)	6.5 (5.2 - 7.8)
Median (min - max)	4.9 (0.1 - 34.7)	4.6 (0.0 - 21.4)	5.4 (0.1 - 40.4)

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Table 10: Demographics and Baseline Characteristics by Treatment Arm-Study P001

Treatment Group	**Placebo**	**E5+S100**	**E15+S100**
N per Group	**152**	**154**	**151**
Sex, n (%)			
F	80 (53)	72 (47)	78 (52)
M	72 (47)	82 (53)	73 (48)
Race, n (%)			
Asian	9 (6)	15 (10)	20 (13)
Black	4 (3)	5 (3)	9 (6)
White	132 (87)	125 (81)	115 (76)
Ethnicity, n (%)			
Hispanic or Latino	27 (18)	29 (19)	31 (21)
Age			
Mean (95%CI)	67.5 (66.1 - 68.9)	66.6 (65.3 - 67.9)	67.6 (66.3 - 69.0)
Median (min - max)	67.0 (35.0 - 85.0)	67.0 (42.0 - 86.0)	68.0 (45.0 - 87.0)
>=65, n (%)	98 (64)	104 (68)	95 (63)
Region, n (%)			
Asia	23 (15)	23 (15)	32 (21)
Europe (incl. Russia)	69 (45)	52 (34)	60 (40)
North Am. (excl. Cent. Am.)	41 (27)	55 (36)	37 (25)
South Africa	2 (1)	7 (5)	2 (1)
South Am.	17 (11)	17 (11)	20 (13)
Baseline HbA1c (%)			
Mean (95%CI)	8.1 (7.9 - 8.2)	8.2 (8.0 - 8.4)	8.2 (8.0 - 8.3)
Median (min - max)	8.0 (6.0 - 10.4)	8.0 (6.4 - 11.9)	8.0 (6.4 - 10.6)
Baseline GFR (mL/min/1.73m)			
Mean (95%CI)	46.1 (44.6 - 47.6)	46.8 (45.6 - 48.0)	47.1 (45.6 - 48.5)
Median (min - max)	46.0 (22.0 - 81.0)	48.0 (28.0 - 64.0)	48.0 (26.0 - 85.0)
Baseline BMI (kg/m)			
Mean (95%CI)	33.1 (32.1 - 34.1)	32.5 (31.5 - 33.6)	31.7 (30.9 - 32.6)
Median (min - max)	32.5 (21.0 - 51.1)	31.4 (20.3 - 54.6)	31.2 (20.5 - 47.9)
Duration of Diabetes at Baseline (years)			
Mean (95%CI)	12.9 (11.7 - 14.2)	14.9 (13.5 - 16.3)	14.3 (13.0 - 15.6)
Median (min - max)	12.5 (0.2 - 41.4)	13.8 (0.1 - 44.2)	14.5 (0.4 - 36.9)

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3.2.4 Results and Conclusions

3.2.4.1 Primary Endpoints

3.2.4.1.1 Active-Control Studies

For the full factorial study P005, the results for the primary endpoint using the sponsor's cLDA demonstrated superiority for both endpoints (E15+S100 vs S100, and E15 + S100 vs E15 - Table 11). For the non-inferiority study P002, the non-inferiority of E15 vs. glimepiride was also achieved for the primary endpoint. A non-inferiority margin of 0.3% was pre-specified.

Table 11: Primary Endpoint Results - Sponsor's Primary Analysis Method – cLDA- ER

Study	Endpoint	Arms	Difference Between Arms	LCL	UCL	P-Value
P005	HbA1c (%)	E15+S100 vs. S100	-0.47	-0.63	-0.30	<.001
P005	HbA1c (%)	E15+S100 vs. E15	-0.44	-0.61	-0.27	<.001
P002	HbA1c (%)	E15 vs. Glim.*	0.10	-0.02	0.22	
P006	HbA1c (%)	E15 vs. Pl.	-0.76	-0.95	-0.58	<.001
P006	HbA1c (%)	E5 vs. Pl.	-0.69	-0.87	-0.50	<.001
P007	HbA1c (%)	E15 vs. Pl.	-0.88	-1.05	-0.71	<.001
P007	HbA1c (%)	E5 vs. Pl.	-0.70	-0.87	-0.53	<.001
P017	HbA1c (%)	E15+S100 v Pl.	-1.24	-1.57	-0.91	<.001
P017	HbA1c (%)	E5 +S100 v Pl.	-1.16	-1.49	-0.84	<.001
P003	HbA1c (%)	E15 vs. Pl.	-1.16	-1.39	-0.93	<.001
P003	HbA1c (%)	E5 vs. Pl.	-0.99	-1.22	-0.76	<.001
P001**	HbA1c (%)	E15 vs. Pl.	-0.15	-0.35	0.06	0.16
P001**	HbA1c (%)	E5 vs. Pl.	-0.03	-0.23	0.18	0.81

Abbreviations: cLDA ER-constrained longitudinal data analysis, excluding rescue;
*E5 vs. Glim. is included as a secondary endpoint for study P002;** P001 not included in label
[Source: Table 14.2.1.1.1.2 from Clinical Study Report]

Using my preferred analysis of RTB (Table 14), superiority was also achieved for the factorial study P005, though the effect sizes were diminished somewhat compared to the sponsor's analysis (Tables 11 and 13). For the non-inferiority study, results using my ANCOVA analysis (Table 12) with a 0.3 % penalty on the experimental arm were consistent with the sponsor's primary analysis results, though effects were also diminished slightly. The results from this ANCOVA analysis were also close to those for the RTB analysis. The upper confidence limit (UCL) for the RTB analysis was 0.23, while the UCL for ANCOVA with 0.3 penalty was 0.24. The sponsor's J2R analysis (not shown), which also included a 0.3 penalty, was also very close to the ANCOVA analysis (UCL of 0.23).

3.2.4.1.2 Placebo Studies

Superiority was demonstrated for the primary endpoint for four of the five placebo studies using the sponsor's analysis. The one exception was Study P001, which was a special population study involving patients with CKD. Some of the subject in Study P001 took a "prohibited" medication, metformin, during the study. This might have reduced the difference in effect between the experimental arm and placebo. However there is nothing prohibiting or restricting use of metformin in this specific study population according to current guidelines. Therefore use of

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metformin can be expected to occur in practice, especially since metformin is considered a first-line therapy. For placebo studies P006, P007, P017, and P003 my preferred method (RTB) also demonstrated superiority, but the effect sizes were diminished.

Table 12: Primary Endpoint Results: ANCOVA J2R– no intermediate measures

Study	Endpoint	Arms	Difference Between Arms	LCL	UCL	P-Value
P005	HbA1c (%)	E15+S100 vs. S100	-0.36	-0.53	-0.19	<.001
P005	HbA1c (%)	E15+S100 vs. E15	-0.39	-0.55	-0.22	<.001
P002*	HbA1c (%)	E15 vs. Glim.	0.12	0.00	0.24*	
P006	HbA1c (%)	E15 vs. Pl.	-0.56	-0.77	-0.35	<.001
P006	HbA1c (%)	E5 vs. Pl.	-0.50	-0.71	-0.30	<.001
P007	HbA1c (%)	E15 vs. Pl.	-0.66	-0.84	-0.47	<.001
P007	HbA1c (%)	E5 vs. Pl.	-0.47	-0.66	-0.28	<.001
P017	HbA1c (%)	E15 +S100 vs. Pl.	-0.89	-1.21	-0.56	<.001
P017	HbA1c (%)	E5 +S100 vs. Pl.	-0.86	-1.18	-0.54	<.001
P003	HbA1c (%)	E15 vs. Pl.	-0.78	-1.03	-0.53	<.001
P003	HbA1c (%)	E5 vs. Pl.	-0.60	-0.84	-0.35	<.001

*Since upper confidence limit (UCL) is less than non-inferiority (NI) margin of 0.3, NI is achieved. Using a penalty of 0.6 instead of 0.3 (for the experimental arms), non-inferiority is still achieved (UCL=0.29); using a return-to-baseline (R2B) penalty for experimental arms, and missing at random (MAR) for the control arm, NI is not achieved (UCL=0.34).Using RTB for all three arms, NI is achieved (UCL=0.22); NI was not achieved for the E5 arm, but this was not pre-specified as a primary endpoint; it is included further down in the multiple testing hierarchy for P002 as a secondary endpoint. Pl. – Placebo; Glim.-glimepiride

[Source: statistical reviewer's analysis]

Secondary Endpoints

Table 13 shows the sponsor's primary analysis results for secondary endpoints. Table 14 shows primary and secondary endpoint results using my preferred RTB analysis. As outlined in Section 3.2.2.1, the sponsor used a hierarchical testing procedure for primary and secondary endpoints for each study. Since the primary endpoints were achieved for active control studies P005 and P002, and for placebo studies P003, P006, P007, and P017, testing of secondary endpoints proceeded according to the order shown in Tabl3 2. (b) (4)

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Table 13: Sponsor Primary Analysis for Secondary Endpoints—cLDA Excluding Rescue

Study	Endpoint	Arms	Difference	LCL	UCL	P-Value
P005	HbA1c (%)	E5+S100 vs. S100	-0.43	-0.60	-0.27	<.001
P005	HbA1c (%)	E5+S100 vs. E5	-0.46	-0.63	-0.30	<.001
P005	FPG mg/dL	E15+S100 vs. S100	-23.1	-28.8	-17.5	<.001
P005	FPG mg/dL	E15+S100 vs. E15	-11.8	-17.4	-6.2	<.001
P005	FPG mg/dL	E5+S100 vs. S100	-18.4	-24.0	-12.8	<.001
P005	FPG mg/dL	E5+S100 vs. E5	-8.2	-13.8	-2.7	<.005
P005	Body Wt. kg	E15+S100 vs. S100	-2.3	-2.9	-1.6	<.001
P005	Body Wt. kg	E5+S100 vs. S100	-1.8	-2.5	-1.2	<.001
P005	SBP mm/Hg	E15+S100 vs. S100	-3.0	-4.9	-1.1	<.005
P005	SBP mm/Hg	E5+S100 vs. S100	-2.8	-4.7	-.8	<.005
			HbA1c<7%			
P005		E5+S100: 52% E15+S100: 49% E5: 26% E15: 32% S100: 33%				
P002	Body Wt. kg	E15 vs. Glim	-4.3	-3.8	-4.8	<.001
P002	Body Wt. kg	E5 vs. Glim	-3.9	-4.4	-3.4	<.001
			HbA1c<7%			
P002		E5: 34% E15: 38% Glim.: 43.5%				
P006	FPG mg/dL	E15 vs. Pl.	-31.3	-38.9	-23.7	<.001
P006	FPG mg/dL	E5 vs. Pl.	-25.2	-32.8	-7.5	<.001
P006	Body Wt. kg	E15 vs. Pl.	-1.7	-2.3	-1.1	<.001
P006	Body Wt. kg	E5 vs. Pl.	-2.0	-2.6	-1.4	<.001
P006	SBP mm/Hg	E15 vs. Pl.	-3.9	-6.4	-1.5	<.025
P006	SBP mm/Hg	E5 vs. Pl.	-2.9	-5.4	-0.5	<.025
			HbA1c<7%			
P006		E5: 32% E15: 40% Placebo 17%				
P007	FPG mg/dL	E15 vs. Pl.	-38.3	-44.5	-32.0	<.001
P007	FPG mg/dL	E5 vs. Pl.	-26.7	-32.9	-20.5	<.001
P007	Body Wt. kg	E15 vs. Pl.	-1.6	-2.2	-1.0	<.001
P007	Body Wt. kg	E5 vs. Pl.	-1.7	-2.2	-1.1	<.001
P007	SBP mm/Hg	E15 vs. Pl.	-4.5	-6.8	-2.2	<.001
P007	SBP mm/Hg	E5 vs. Pl.	-3.7	-6.0	-1.4	<0.025
P007	DBP mm/Hg	E15 vs. Pl.	-2.4	-3.9	-1.0	<.001
P007	DBP mm/Hg	E5 vs. Pl.	-1.8	-3.2	-0.4	<0.025
			HbA1c<7%			
P007		E5: 35% E15: 40% Placebo 16%				
P017	FPG mg/dL	E15 + S100 vs. Pl.	-46.1	-57.1	-35.0	<.001
P017	FPG mg/dL	E5 +S100 vs. Pl.	-38.9	-49.9	-28.0	<.001
P017	PMG mg/l	E15 +S100 vs. Pl.	-69.6	-87.8	-51.5	<.001
P017	PMG mg/l	E5 +S100 vs. Pl.	-62.4	-80.5	-44.4	<.001
P017	Body Wt. kg	E15 +S100 vs. Pl.	-2.1	-3.1	-1.1	<.001
P017	Body Wt. kg	E5 +S100 vs. Pl.	-2.0	-3.0	-1.0	<.001
P017	SBP mm/Hg	E15 +S100 vs. Pl.	-6.4	-9.8	-3.0	<0.001
P017	SBP mm/Hg	E5 +S100 vs. Pl.	-4.4	-7.9	-1.0	<0.025
			HbA1c<7%			
P017		E5+S100: 36% E15+S100: 31% Placebo 8%				
P003	FPG mg/dL	E15 vs. Pl.	-44.0	-52.3	-35.7	<.001
P003	FPG mg/dL	E5 vs. Pl.	-34.5	-42.8	-26.3	<.001
P003	Body Wt. kg	E15 vs. Pl.	-2.2	-3.0	-1.3	<.001
P003	Body Wt. kg	E5 vs. Pl.	-1.8	-2.6	-0.9	<.001
P003	PMG mg/dL	E15 vs. Pl.	-67.3	-81.7	-52.9	<.001
P003	PMG mg/dL	E5 vs. Pl.	-69.0	-83.2	-54.8	<.001
			HbA1c<7%			
P003		E5: 28% E15: 36% Placebo 3%				

Sponsor cLDA (constrained longitudinal data analysis excluding rescue) used for primary analysis for all continuous endpoints; this mixed model repeated measures method constrains baseline value to be equal between treatments. Abbreviations: Glim.- glimepiride; Pl.-placebo
[Source: Table Page 17 (taken from Tables 14.2.2.1.2, 14.2.2.2.1.2, 14.2.2.3.2,…) from Clinical Study Report]

Reference ID: 4144831

Table 14: Primary and Secondary Endpoints for Product Label– RTB Analysis Results

---Study P005---

Endpoint	Arms	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val.
HbA1c (%)	E15+S100 vs. S100	-1.39	-1.02	-0.37	-0.55	-0.19	<.001
HbA1c (%)	E15+S100 vs. E15	-1.39	-1.01	-0.38	-0.56	-0.21	<.001
HbA1c (%)	E5+S100 vs. S100	-1.40	-1.02	-0.37	-0.55	-0.19	<.001
HbA1c (%)	E5+S100 vs. E5	-1.40	-1.04	-0.36	-0.54	-0.18	<.001
FPG mg/dL	E15+S100 vs. S100	-44.3	-24.3	-20.0	-26.4	-13.6	<.001
FPG mg/dL	E15+S100 vs. E15	-44.3	-34.6	-9.8	-16.1	-3.4	<.005
FPG mg/dL	E5+S100 vs. S100	-41.1	-24.3	-16.8	-23.2	-10.4	<.001
FPG mg/dL	E5+S100 vs. E5	-41.1	-34.0	-7.0	-13.3	-0.7	<.025
Body Wt. kg	E15+S100 vs. S100	-2.7	-0.4	-2.3	-3.0	-1.6	<.001
Body Wt. kg	E5+S100 vs. S100	-2.4	-0.4	-1.9	-2.6	-1.3	<.001
SBP mm/Hg	E15+S100 vs. S100	-3.4	-0.5	-2.9	-4.8	-1.0	<.005
SBP mm/Hg	E5+S100 vs. S100	-2.8	-0.5	-2.3	-4.3	-0.4	<.025

HbA1C < 7%

Arm	E5	E15	S100	E5+S100	E15+S100
n(%)	71.6(29.3)	83.2(33.7)	93.1(38.5)	126.3(53.3)	122.6(50.9)

---Study P002---

Endpoint	Arms	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val.
HbA1c (%)	E15 vs. Glim	-0.53	-0.63	0.10	-0.02	0.23	
Body Wt. kg	E15 vs. Glim.	-3.0	0.6	-3.6	-4.1	-3.1	<.001
Body Wt. kg	E5 vs. Glim.	-2.6	0.6	-3.2	-3.7	-2.7	<.001
HbA1c (%)	E5 vs. Glim	-0.46	-0.63	0.17	0.04	0.30	

HbA1c <7%

Arm	E5	E15	Glim.
n(%)	176.6(39.5)	185.6(42.2)	208.3(47.7)

---Study P006---

Endpoint	Arms	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val.
HbA1c (%)	E15 vs. Pl.	-0.79	-0.21	-0.58	-0.76	-0.40	<.001
HbA1c (%)	E5 vs. Pl.	-0.69	-0.21	-0.48	-0.66	-0.30	<.001
FPG mg/dL	E15 vs. Pl.	-32.1	-6.5	-25.6	-33.2	-18.0	<.001
FPG mg/dL	E5 vs. Pl.	-25.7	-6.5	-19.2	-26.8	-11.6	<.001
Body Wt. kg	E15 vs. Pl.	-2.8	-1.0	-1.8	-2.4	-1.2	<.001
Body Wt. kg	E5 vs. Pl.	-3.0	-1.0	-1.9	-2.6	-1.3	<.001
SBP mm/Hg	E15 vs. Pl.	-4.5	-0.2	-4.3	-6.7	-1.9	<.001
SBP mm/Hg	E5 vs. Pl.	-3.8	-0.2	-3.7	-6.1	-1.2	<.005

HbA1c <7%

Arm	E5	E15	Placebo
n(%)	53.6(34.6)	64.3(42.3)	30.6(20.2)

Reference ID: 4144831

Table 14: **Primary and Secondary Endpoints for Product Label– RTB Analysis Results Continued**

---Study P007---

Endpoint	Arms	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val.
HbA1c (%)	E15 vs. Pl.	-0.86	-0.17	-0.69	-0.86	-0.53	<.001
HbA1c (%)	E5 vs. Pl.	-0.72	-0.17	-0.55	-0.71	-0.39	<.001
FPG mg/dL	E15 vs. Pl.	-40.9	-8.7	-32.3	-38.5	-26.0	<.001
FPG mg/dL	E5 vs. Pl.	-30.3	-8.7	-21.7	-27.8	-15.5	<.001
Body Wt. kg	E15 vs. Pl.	-3.0	-1.4	-1.7	-2.2	-1.1	<.001
Body Wt. kg	E5 vs. Pl.	-3.2	-1.4	-1.8	-2.4	-1.2	<.001
SBP mm/Hg	E15 vs. Pl.	-5.7	-1.8	-3.8	-6.1	-1.5	<.001
SBP mm/Hg	E5 vs. Pl.	-5.1	-1.8	-3.3	-5.6	-1.1	<0.005
DBP mm/Hg	E15 vs. Pl.	-1.6	0.3	-1.9	-3.3	-0.4	<0.025
DBP mm/Hg	E5 vs. Pl.	-1.3	0.3	-1.5	-2.9	-0.1	<0.025

HbA1C<7%

Arm	E5	E15	Placebo
n(%)	74.3(36.3)	87.0(43.3)	38.2(18.4)

---Study P017---

Endpoint	Arms	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val.
HbA1c (%)	E15 +S100 vs. Pl.	-1.52	-0.58	-0.94	-1.26	-0.62	<.001
HbA1c (%)	E5 +S100 vs. Pl.	-1.56	-0.58	-0.97	-1.28	-0.66	<.001
FPG mg/dL	E15 +S100 vs. Pl.	-50.8	-11.8	-39.1	-51.4	-26.8	<.001
FPG mg/dL	E5 +S100 vs. Pl.	-47.1	-11.8	-35.4	-47.3	-23.4	<.001
PMG mg/dL	E15 +S100 vs. Pl.	-81.8	-11.5	-70.3	-88.6	-52.1	<.001
PMG mg/dL	E5 +S100 vs. Pl.	-78.0	-11.5	-66.5	-84.9	-48.1	<.001
Body Wt. kg	E15 +S100 vs. Pl.	-2.8	-0.5	-2.3	-3.3	-1.3	<.001
Body Wt. kg	E5 +S100 vs. Pl.	-2.7	-0.5	-2.2	-3.1	-1.2	<.001
SBP mm/Hg	E15 +S100 vs. Pl.	-3.5	1.6	-5.2	-8.4	-1.9	<0.025
SBP mm/Hg	E5 +S100 vs. Pl.	-2.4	1.6	-4.0	-7.2	-0.8	<0.005

HbA1C<7%

Arm	E5+S100	E15+S100	Placebo
n(%)	36.4(37.1)	31.6(32.9)	8.9(9.3)

---Study P003---

Endpoint	Arms	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val.
HbA1c (%)	E15 vs. Pl.	-0.84	-0.17	-0.67	-0.89	-0.44	<.001
HbA1c (%)	E5 vs. Pl.	-0.75	-0.17	-0.58	-0.80	-0.36	<.001
FPG mg/dL	E15 vs. Pl.	-36.4	-11.6	-24.8	-33.2	-16.4	<.001
FPG mg/dL	E5 vs. Pl.	-31.0	-11.6	-19.4	-27.6	-11.2	<.001
Body Wt. kg	E15 vs. Pl.	-3.1	-1.0	-2.1	-2.9	-1.3	<.001
Body Wt. kg	E5 vs. Pl.	-3.0	-1.0	-2.0	-2.8	-1.2	<.001
PMG mg/dL	E15 vs. Pl.	-51.0	2.8	-53.8	-68.8	-38.8	<.001
PMG mg/dL	E5 vs. Pl.	-52.9	2.8	-55.7	-70.9	-40.5	<.001

HbA1c <7%

Arm	E5	E15	Placebo
n(%)	46.7(30.1)	58.6(38.8)	25.9(16.9)

Abbreviations: Exp.-Experimental Arm (LS Mean); Ctrl.-Control Arm (LS Mean); Diff.-Difference Between Arms (LS Means);LCL/UCL-Lower/Upper Confidence Limit for Difference Between Arms; Glim. -glimepiride
[Source: Sponsor's Supplementary Efficacy Analysis - 7/14/2017]

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3.3 Evaluation of Safety

Please see the clinical review of Dr. Frank Pucino for the evaluation of safety. For Cardiovascular Study P004, see both the statistical review of Dr. Elande Baro and the clinical review of Dr. Frank Pucino.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Race, Age, and Geographic Region

To assess the effect of ertugliflozin compared to placebo within sex, race, age, and region subgroups, Studies P003, P005, P006 and P007 were grouped together to increase power. For factorial study P005, only comparisons assessing the added effect of ertugliflozin to background of M + S were included (E5 + S100 + M vs. S100 + M, and E15 + S100 + M vs. S100 + M). Study P017 was excluded because it only assesses the combined effect of ertugliflozin and sitagliptin. Study P002 was also excluded from this pool to avoid potential confounding of subgroup treatment effects due to the comparator arm (glimepiride).

Study and treatment were included as factors in the model, and baseline eGFR and HbA1c (%) were included as covariates. The estimated treatment differences and associated confidence intervals for the subgroups (Table 15) provide no evidence of significant differences between any of the subgroups. The lowest estimated treatment difference for both E15 vs. Placebo and E5 vs. Placebo is found in the Black/African American subgroup: estimated treatment difference of -0.40, with 95% CI of (-0.81, 0.02) for E15 vs. Placebo, and treatment difference of -0.27, with 95% CI of (-0.68, 0.15) for E5 vs. Placebo. Asians had the highest estimated treatment difference for both E15 vs. Placebo (-0.65) and E5 vs. Placebo (-0.54).

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Table 15: Treatment Difference in Change in HbA1c by Subgroup – RTB Imputation

Subgroup	t	Estimate	Lower 95%	Upper 95%
Overall				
15 mg vs. Pl.	-11.50	-0.56	-0.65	-0.46
5 mg vs. Pl.	-9.91	-0.48	-0.57	-0.38
Female				
15 mg vs. Pl.	-8.07	-0.56	-0.69	-0.42
5 mg vs. Pl.	-7.34	-0.50	-0.63	-0.37
Male				
15 mg vs. Pl.	-8.32	-0.57	-0.70	-0.43
5 mg vs. Pl.	-6.97	-0.48	-0.61	-0.34
White				
15 mg vs. Pl.	-9.76	-0.53	-0.65	-0.43
5 mg vs. Pl.	-8.80	-0.48	-0.59	-0.37
Black				
15 mg vs Pl.	-1.86	-0.40	-0.81	0.02
5 mg vs. Pl.	-1.27	-0.27	-0.68	0.15
Asian				
15 mg vs Pl.	-5.01	-0.65	-0.91	-0.40
5 mg vs. Pl.	-4.03	-0.54	-0.80	-0.28
Hispanic/Latino				
15 mg vs. Pl.	-5.01	-0.59	-0.83	-0.36
5 mg vs. Pl.	-4.06	-0.49	-0.73	-0.25
Age ≥ 65				
15 mg vs. Pl.	-5.23	-0.51	-0.70	-0.32
5 mg vs. Pl.	-4.11	-0.39	-0.58	-0.21
Age < 65				
15 mg vs. Pl.	-10.2	-0.57	-0.68	-0.46
5 mg vs. Pl.	-9.00	-0.50	-0.61	-0.39
North America				
15 mg vs. Pl.	-5.47	-0.51	-0.70	-0.33
5 mg vs. Pl.	-5.24	-0.48	-0.67	-0.30
Europe				
15 mg vs. Pl.	-7.96	-0.54	-0.67	-0.41
5 mg vs. Pl.	-6.48	-0.44	-0.57	-0.31

Studies include in subgroup analysis were P003, P006, P007, and P005; for P005, only treatment comparisons involving E+S vs. S were used). Multiple imputation approach – return to baseline; North America subgroup excluded Central America; Europe subgroup included Russia.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

The following statistical issues were identified in this application. Sensitivity analyses used to address these issues did not alter our conclusion that efficacy was demonstrated.

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- Missing data, which ranged from 5% to 23% across the arms in the seven studies, were strongly associated with treatment discontinuation.
- There were very few retrieved dropouts.
- The sponsor's primary analysis treated observations after initiation of rescue therapy as missing.
- Data after treatment discontinuation were completely excluded (i.e. not included in the analysis set) in the sponsor's initially submitted primary and sensitivity analyses.
- The two placebo studies that had a background of diet and exercise only, P017 and P003, had high rescue rates on the placebo arm (31% and 24% respectively).

5.2 Collective Evidence

The primary efficacy endpoint was change from baseline in HbA1c (%) in all the studies reviewed. Three of the five placebo studies demonstrated statistical superiority of the E15 arm and the E5 arm compared to placebo. One placebo study demonstrated superiority of E15/E5 + S100 compared to placebo. A placebo study involving patients with chronic kidney disease (CKD) failed to demonstrate superiority of E5 or E15 compared to placebo. The full factorial study demonstrated superiority of E5/E15 + S100 compared to S100 alone, as well as superiority of E5/E15+S100 compared to E5/E15 alone. For the 52-week non-inferiority study P002, non-inferiority was demonstrated for the primary endpoint for E15 vs. glimepiride. These findings were consistent using the sponsor's primary analysis, and also across our sensitivity analyses which addressed possible shortcomings in the primary analyses.

5.3 Conclusions and Recommendations

In my view, the collective evidence from this review supports the claim of using ertugliflozin to improve glycemic control in adults with T2DM. This NDA is approvable from the statistical point of view.

5.4 Labeling Recommendations

The cLDA primary analysis does not adequately address missing data (b) (4) The retrieved dropout approach is our preferred method, however there were not enough subjects who discontinued treatment and were followed up to perform this analysis. The J2R analysis assumes subjects who discontinue on the experimental arm are represented by subjects who complete treatment on the comparator arm. This assumption is questionable. At the same time it is unclear how much worse the measurements of subjects who discontinue would have been had they been measured. It is my view that the RTB analysis (Table 14) most closely addresses missing data and is (b) (4) the one put in the label.

Table 16: Studies and Section 14 DRAFT Label Claims

Trial ID*	**209803 (E)**	**209805 (E+S)**	**209806 (E + M)**
P005	(b) (4)	Table 6	(b) (4)
P002	Table 6	x	
P006	(b) (4)	Table 7	
P007	Table 5	x	Table 6
P003	Table 4	x	x
P017	x	Table 8	**x**
P001 *	x	x	x

*(In Sect. 8.6 of Renal Impairment)

REFERENCES

The European Medical Agency "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus", dated 2012, (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf)

Carpenter et al. Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation, 2013.

6 Appendices

Table S1: Study P005 –Factorial Study - Treatment and Discontinuation Status for Week 26 %HbA1c

Treatment Group	E5	E5	E15	E15	S100	S100	E5+S100	E5+S100	E15+S100	E15+S100
N per Group	228	16	228	19	220	22	220	17	221	20
Treatment Duration Group	≥22Weeks	<22Weeks	≥22Weeks	<22Weeks	≥22Weeks	<22Weeks	≥22Weeks	<22Weeks	≥22Weeks	<22Weeks
Change from BL- HbA1c										
N	225	1	221	0	211	3	216	1	215	0
Mean (95%CI)	-1.1 (-1.2 - -1.0)	-2.0	-1.1 (-1.3 - -1.0)	. (. - .)	-1.1 (-1.3 - -1.0)	-0.0 (-0.2 - 0.1)	-1.5 (-1.7 - -1.4)	-1.5 (. - .)	-1.6 (-1.7 - -1.4)	. (. - .)
Median (min - max)	-1.0 (-4.1 - 2.5)	-2.0	-1.1 (-3.7 - 1.6)	. (. - .)	-1.1 (-4.2 - 1.6)	0.0 (-0.4 - 0.3)	-1.6 (-4.6 - 2.1)	-1.5 (-1.5 - -1.5)	-1.5 (-4.7 - 2.3)	. (. - .)
Missing	3	15	7	19	9	19	4	16	6	20
HbA1c (%)										
N	225	1	221	0	211	3	216	1	215	0
Mean (95%CI)	7.4 (7.3 - 7.6)	6.4 (. - .)	7.4 (7.3 - 7.6)	. (. - .)	7.3 (7.2 - 7.5)	9.6 (8.9 - 10.2)	7.0 (6.9 - 7.2)	6.8 (. - .)	7.0 (6.9 - 7.1)	. (. - .)
Median (min - max)	7.4 (5.1 - 11.4)	6.4 (6.4 - 6.4)	7.3 (5.4 - 12.1)	. (. - .)	7.1 (5.1 - 10.9)	8.7 (8.6 - 11.4)	6.8 (5.0 - 11.8)	6.8 (6.8 - 6.8)	6.8 (5.2 - 10.6)	. (. - .)
Missing	3	15	7	19	9	19	4	16	6	20
Baseline Estimated GFR (mL/min/1.73m|)										
Mean (95%CI)	92 (90 - 95)	86 (75 - 98)	93 (90 - 95)	92 (82 - 102)	92 (90 - 95)	96 (88 - 104)	92 (89 - 95)	90 (79 - 100)	93 (90 - 95)	90 (79 - 100)
Median (min - max)	89 (35 - 170)	86 (43 - 127)	90 (57 - 196)	89 (52 - 142)	91 (53 - 150)	97 (67 - 134)	88 (53 - 174)	88 (57 - 131)	90 (57 - 155)	91 (54 - 137)
Baseline A1C (%)										
Mean (95%CI)	8.6 (8.4 - 8.7)	8.8 (8.3 - 9.3)	8.6 (8.4 - 8.7)	8.8 (8.3 - 9.2)	8.5 (8.3 - 8.6)	8.8 (8.2 - 9.3)	8.5 (8.4 - 8.7)	8.7 (8.3 - 9.1)	8.6 (8.4 - 8.7)	8.7 (8.2 - 9.1)
Median (min - max)	8.4 (5.4 - 12.3)	8 7 (7 4 - 11 1)	8.4 (5.8 - 11.6)	8 8 (7 4 - 10 6)	8.2 (5.1 - 11.5)	8.7 (5.5 - 11.4)	8.4 (5.6 - 11.9)	8.5 (7.2 - 10.3)	8.4 (6.5 - 11.7)	8.4 (7.3 - 10.7)

Abbreviations: Bl-Baseline; There were no record of subjects with bariatric surgery, or bone mineral density rescue therapy

Table S2: Study P002 Treatment and Discontinuation Status for Week 52 %HbA1c

Treatment Group	**Ert. 5mg**	**Ert. 5mg**	**Ert. 15 mg**	**Ert. 15 mg**	**Glim.**	**Glim.**
N per Group	371	76	376	64	377	60
Treatment Duration Group	≥44 Weeks	<44 Weeks	≥44 Weeks	<44 Weeks	≥44 Weeks	<44 Weeks
Change from BL- HbA1c (%)						
N	357	2	366	3	366	5
Mean (95%CI)	-0.6 (-0.7 - -0.5)	-0.9 (-1.3 - -0.4)	-0.7 (-0.8 - -0.6)	-0.4 (-0.5 - -0.3)	-0.8 (-0.9 - -0.7)	-0.3 (-0.6 - 0.0)
Median (min - max)	-0.6 (-3.8 - 4.7)	-0.9 (-2.3 - 0.6)	-0.7 (-3.2 - 3.7)	-0.3 (-1.0 - 0.1)	-0.8 (-3.5 - 5.9)	-0.1 (-1.6 - 1.3)
Missing	14	74	10	61	11	55
HbA1c (%)						
Mean (95%CI)	7.2 (7.1 - 7.2)	7.4 (7.1 - 7.7)	7.1 (7.0 - 7.2)	7.4 (7.2 - 7.7)	7.0 (6.9 - 7.1)	7.3 (7.0 - 7.6)
Median (min - max)	7.0 (4.7 - 13.2)	7.4 (6.3 - 8.5)	7.0 (5.3 - 11.3)	7.1 (6.6 - 8.6)	6.9 (4.6 - 13.5)	7.3 (6.0 - 8.8)
Missing	14	74	10	61	11	55
Baseline Estimated GFR (mL/min/1.73m])						
Mean (95%CI)	88 (87 - 90)	88 (83 - 92)	88 (86 - 89)	81 (77 - 86)	87 (85 - 88)	86 (81 - 92)
Median (min - max)	86 (49 - 156)	86 (46 - 162)	87 (42 - 158)	78 (41 - 141)	85 (44 - 149)	86 (28 - 133)
Baseline HbA1c (%)						
Mean (95%CI)	7.8 (7.7 - 7.8)	8.0 (7.8 - 8.1)	7.8 (7.7 - 7.9)	7.8 (7.7 - 8.0)	7.8 (7.7 - 7.8)	7.7 (7.5 - 7.8)
Median (min - max)	7.7 (5.9 - 10.5)	7.9 (6.6 - 9.4)	7.7 (6.6 - 9.7)	7.8 (6.9 - 9.3)	7.7 (5.8 - 10.9)	7.6 (6.5 - 9.4)
Treatment Duration*						
Mean (95%CI)	469 (460 - 477)	146 (124 - 167)	470 (461 - 478)	124 (101 - 147)	464 (456 - 473)	148 (123 - 172)
Median (min - max)	455 (312 - 729)	168 (1 - 301)	456 (308 - 735)	102 (1 - 294)	455 (310 - 731)	132 (1 - 303)

* Treatment Duration for a patient is always greater than Start Day of Rescue Medication (when the value for rescue is non-missing) –ie trtedy-rescuedy for a subject is always greater than or equal to 0. Therefore treatment duration can include time on "rescue" therapy; Abbreviations: Ert. - ertugliflozin; Glim. – glimepiride; - there is no record of subjects with bariatric surgery, or bone mineral density rescue therapy

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Table S3: Study P006 - Treatment and Discontinuation Status for Week 26 %HbA1c

Treatment Group	Placebo	Placebo	Ert 5mg	Ert 5mg	Ert 15mg	Ert 15mg
N per Group	141	11	143	12	142	10
Treatment Duration ≥22 Weeks	≥22 Weeks	< 22Weeks	≥22 Weeks	< 22Weeks	≥22 Weeks	< 22Weeks
Ch. from BL- HbA1c (%)						
N	137	1	138	1	140	1
Mean (95%CI)	-0.3 (-0.4 - -0.1)	0.1 (. - .)	-0.8 (-0.9 - -0.7)	-0.9 (. - .)	-0.8 (-1.0 - -0.7)	-1.8 (. - .)
Median (min - max)	-0.2 (-3.2 - 3.1)	0.1 (0.1 - 0.1)	-0.8 (-3.2 - 1.2)	-0.9 (-0.9 - -0.9)	-0.8 (-2.8 - 2.0)	-1.8 (-1.8 - -1.8)
Missing	4	10	5	11	2	9
HbA1c (%)						
N	137	1	138	1	140	1
Mean (95%CI)	7.7 (7.6 - 7.9)	7.8 (. - .)	7.3 (7.1 - 7.4)	6.4 (. - .)	7.2 (7.0 - 7.3)	7.1 (. - .)
Median (min - max)	7.6 (5.4 - 11.9)	7.8 (7.8 - 7.8)	7.2 (5.3 - 9.4)	6.4 (6.4 - 6.4)	7.1 (5.2 - 10.8)	7.1 (7.1 - 7.1)
Missing	4	10	5	11	2	9
Baseline eGFR (mL/min/1.73m)						
Mean (95%CI)	89 (87 - 92)	93 (87 - 98)	87 (84 - 90)	89 (82 - 95)	87 (85 - 89)	87 (74 - 101)
Median (min - max)	87 (54 - 145)	91 (82 - 117)	84 (51 - 144)	88 (69 - 111)	86 (56 - 137)	98 (54 - 108)
Baseline HbA1c (%)						
Mean (95%CI)	8.0 (7.9 - 8.2)	8.1 (7.7 - 8.6)	8.0 (7.9 - 8.2)	8.2 (7.5 - 8.8)	8.0 (7.9 - 8.2)	7.8 (7.4 - 8.2)
Median (min - max)	7.9 (6.3 - 11.1)	8.0 (7.2 - 9.7)	7.9 (5.7 - 10.7)	7.9 (6.7 - 10.3)	7.8 (5.8 - 10.6)	7.9 (6.9 - 8.9)

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Table S4: Study P007 - Treatment and Discontinuation Status for Week 26 %HbA1c

Treatment Group	Placebo	Placebo	Ert 5mg	Ert 5mg	Ert 15mg	Ert 15mg
N per Group	190	17	199	6	187	14
Treatment Duration ≥22 Weeks	≥22 Weeks	< 22Weeks	≥22 Weeks	< 22Weeks	≥22 Weeks	< 22Weeks
Ch. from BL- HbA1c (%)						
N	182	2	192	2	186	1
Mean (95%CI)	-0.2 (-0.4 - -0.1)	0.8 (-0.1 - 1.7)	-0.7 (-0.9 - -0.6)	-0.8 (-1.1 - -0.5)	-1.0 (-1.1 - -0.8)	-0.1 (. - .)
Median (min - max)	-0.2 (-3.5 - 4.3)	0.8 (-0.6 - 2.2)	-0.7 (-4.4 - 1.9)	-0.8 (-1.1 - -0.5)	-0.9 (-3.2 - 1.1)	-0.1 (-0.1 - -0.1)
Missing	8	15	7	4	1	13
HbA1c (%)						
N	182	2	192	2	186	1
Mean (95%CI)	7.9 (7.8 - 8.1)	9.2 (8.6 - 9.7)	7.3 (7.2 - 7.4)	7.9 (7.7 - 8.1)	7.2 (7.1 - 7.3)	6.8 (. - .)
Median (min - max)	7.8 (5.9 - 11.5)	9.2 (8.3 - 10.0)	7.1 (5.5 - 10.1)	7.9 (7.7 - 8.1)	7.1 (5.0 - 9.3)	6.8 (6.8 - 6.8)
Missing	8	15	7	4	1	13
Baseline eGFR (mL/min/1.73m)						
Mean (95%CI)	91 (89 - 94)	88 (77 - 99)	89 (86 - 91)	100 (85 - 116)	91 (88 - 94)	97 (86 - 108)
Median (min - max)	92 (47 - 151)	80 (52 - 125)	87 (55 - 144)	98 (75 - 127)	90 (42 - 178)	93 (70 - 147)
Baseline HbA1c (%)						
Mean (95%CI)	8.2 (8.1 - 8.3)	7.9 (7.6 - 8.3)	8.0 (7.9 - 8.2)	8.4 (7.9 - 8.9)	8.2 (8.0 - 8.3)	7.5 (7.1 - 7.9)
Median (min - max)	8.1 (5.8 - 11.0)	7.8 (6.8 - 8.9)	7.9 (6.2 - 11.3)	8.7 (7.5 - 9.0)	8.0 (6.7 - 10.6)	7.4 (5.7 - 9.2)

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Table S5: Study P003 - Treatment and Discontinuation Status for Week 26 %HbA1c

Treatment Group	Placebo	Placebo	Ert 5mg	Ert 5mg	Ert 15mg	Ert 15mg
N per Group	121	32	137	18	132	19
Treatment Duration ≥22 Weeks	≥22 Weeks	< 22Weeks	≥22 Weeks	< 22Weeks	≥22 Weeks	< 22Weeks
Ch. from BL- HbA1c (%)						
N	116	2	137	2	127	0
Mean (95%CI)	-0.1 (-0.3 - 0.1)	-0.6 (-1.1 - -0.1)	-0.8 (-0.9 - -0.7)	-0.7 (-1.1 - -0.3)	-1.1 (-1.2 - -0.9)	. (. - .)
Median (min - max)	-0.1 (-4.1 - 4.0)	-0.6 (-1.6 - 0.4)	-0.7 (-4.2 - 1.4)	-0.7 (-1.3 - -0.1)	-0.9 (-4.3 - 2.7)	. (. - .)
Missing	5	30	0	16	5	19
HbA1c (%)						
N	116	2	137	2	127	0
Mean (95%CI)	7.9 (7.7 - 8.1)	9.2 (8.8 - 9.5)	7.3 (7.2 - 7.5)	6.7 (6.1 - 7.3)	7.3 (7.1 - 7.5)	. (. - .)
Median (min - max)	7.7 (5.7 - 12.6)	9.2 (8.5 - 9.8)	7.2 (5.1 - 9.9)	6.7 (5.8 - 7.6)	7.1 (5.5 - 11.5)	. (. - .)
Missing	5	30	0	16	5	19
Baseline eGFR (mL/min/1.73m)						
Mean (95%CI)	86 (82 - 89)	88 (81 - 95)	89 (86 - 92)	84 (76 - 92)	88 (85 - 91)	91 (83 - 99)
Median (min - max)	83 (52 - 181)	84 (54 - 149)	87 (47 - 157)	88 (58 - 111)	87 (56 - 143)	91 (64 - 118)
Baseline HbA1c (%)						
Mean (95%CI)	8.0 (7.9 - 8.2)	8.4 (8.0 - 8.7)	8.1 (8.0 - 8.3)	8.4 (8.0 - 8.8)	8.4 (8.2 - 8.5)	8.4 (7.8 - 8.9)
Median (min - max)	7.9 (6.5 - 11.2)	8.3 (6.8 - 10.4)	8.0 (6.6 - 10.6)	8.3 (7.1 - 10.4)	8.1 (6.6 - 11.1)	8.0 (7.1 - 11.0)

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Table S6: Study P017- Treatment and Discontinuation Status for Week 26 %HbA1c

Treatment Group	Placebo	Placebo	E5 + S100	E5 + S100	E15 + S100	E15 + S100
N per Group	75	21	91	7	88	8
Treatment Duration ≥22 Weeks	Yes	No	Yes	No	Yes	No
Ch. from BL- HbA1c (%)						
N	75	1	91	0	86	0
Mean (95%CI)	-0.7 (-1.0 - -0.5)	-1.0 (. - .)	-1.6 (-1.8 - -1.4)	. (. - .)	-1.7 (-1.9 - -1.5)	. (. - .)
Median (min - max)	-0.7 (-3.3 - 1.6)	-1.0 (-1.0 - -1.0)	-1.8 (-3.6 - 2.1)	. (. - .)	-1.7 (-4.8 - 0.6)	. (. - .)
Missing	0	20	0	7	2	8
HbA1c (%)						
N	75	1	91	0	86	0
Mean (95%CI)	8.3 (8.0 - 8.5)	7.2 (. - .)	7.3 (7.0 - 7.5)	. (. - .)	7.3 (7.1 - 7.5)	. (. - .)
Median (min - max)	8.3 (5.7 - 10.8)	7.2 (7.2 - 7.2)	7.1 (5.3 - 11.8)	. (. - .)	7.2 (5.2 - 10.6)	. (. - .)
Missing	0	20	0	7	2	8
Baseline eGFR (mL/min/1.73m)						
Mean (95%CI)	92 (87 - 97)	94 (85 - 102)	90 (87 - 94)	85 (80 - 90)	89 (86 - 93)	92 (79 - 104)
Median (min - max)	87 (57 - 171)	89 (61 - 125)	89 (55 - 137)	88 (74 - 92)	87 (58 - 142)	85 (75 - 130)
Baseline HbA1c (%)						
Mean (95%CI)	9.0 (8.8 - 9.2)	8.9 (8.6 - 9.2)	8.9 (8.7 - 9.1)	8.9 (8.3 - 9.6)	9.0 (8.8 - 9.2)	9.0 (8.4 - 9.5)
Median (min - max)	9.0 (7.0 - 10.8)	8.9 (8.0 - 10.2)	9.0 (6.2 - 10.7)	9.0 (7.8 - 10.1)	8.9 (6.2 - 10.9)	8.8 (7.9 - 10.4)

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Table S7: Study P001 - Treatment and Discontinuation Status for Week 26 %HbA1c

Treatment Group	Placebo	Placebo	Ert 5mg	Ert 5mg	Ert 15mg	Ert 15mg
N per Group	138	14	138	16	137	14
Treatment Duration ≥22 Weeks	Yes	No	Yes	No	Yes	No
Ch. from BL- HbA1c (%)						
N	124	1	132	1	126	0
Mean (95%CI)	-0.3 (-0.4 - -0.1)	-0.6 (. - .)	-0.3 (-0.5 - -0.2)	-2.7 (. - .)	-0.4 (-0.5 - -0.2)	. (. - .)
Median (min - max)	-0.1 (-3.0 - 2.5)	-0.6 (-0.6 - -0.6)	-0.3 (-2.6 - 2.2)	-2.7 (-2.7 - -2.7)	-0.4 (-2.9 - 3.4)	. (. - .)
Missing	14	13	6	15	11	14
HbA1c (%)						
N	124	1	132	1	126	0
Mean (95%CI)	7.9 (7.7 - 8.0)	6.8 (. - .)	7.8 (7.6 - 8.0)	7.0 (. - .)	7.7 (7.6 - 7.9)	. (. - .)
Median (min - max)	7.8 (5.5 - 11.3)	6.8 (6.8 - 6.8)	7.8 (5.1 - 12.3)	7.0 (7.0 - 7.0)	7.6 (6.1 - 10.6)	. (. - .)
Missing	14	13	6	15	11	14
Baseline eGFR (mL/min/1.73m)						
Mean (95%CI)	46 (44 - 47)	52 (46 - 58)	47 (46 - 49)	43 (40 - 46)	47 (46 - 48)	48 (41 - 56)
Median (min - max)	46 (22 - 66)	51 (36 - 81)	48 (28 - 64)	44 (31 - 51)	48 (26 - 72)	48 (28 - 85)
Baseline HbA1c (%)						
Mean (95%CI)	8.1 (7.9 - 8.2)	8.1 (7.5 - 8.7)	8.2 (8.0 - 8.3)	8.6 (8.0 - 9.1)	8.1 (8.0 - 8.3)	8.6 (8.0 - 9.1)
Median (min - max)	8.0 (6.0 - 10.4)	7.8 (6.8 - 9.9)	7.9 (6.4 - 11.9)	8.5 (6.7 - 10.3)	8.0 (6.4 - 10.6)	8.4 (7.2 - 10.6)

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/s/

ALEXANDER CAMBON
08/25/2017

YUN WANG
08/25/2017

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	209803
Drug Name:	Ertugliflozin tablets
Indication:	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant:	Merck Sharp & Dohme Corp.
Dates:	Receipt date: 12/19/2016. PDUFA Goal date: 12/19/2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Primary Reviewer:	Elande Baro, Ph.D.
Concurring Reviewers:	Eugenio Andraca-Carrera, Ph.D., Team Lead Mark Levenson, Ph.D., Division Director
Medical Division:	Division of Metabolism and Endocrinology Products(DMEP)
Clinical Team:	Medical Officer: Frank Pucino, MD Medical Team Leader: William Chong, MD
Project Manager:	Liz Godwin (DMEP)

Keywords: Type 2 diabetes mellitus, cardiovascular safety, meta-analysis

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1 Executive Summary

The proposed indication of ertugliflozin is as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM). The proposed therapeutic dosage is 5 mg or 15 mg, orally, once daily. Per the request of the Division of Metabolism and Endocrinology Products, this statistical review evaluates the cardiovascular (CV) safety of ertugliflozin in 9 Phase 2 and Phase 3 randomized clinical trials (trials P016/ B1521006, P002/ B1521013, P003/ B1521022, P005/ B1521019, P006/ B1521015, P007/ B1521017, P017/ B1521047, P001/ B1521016, and a cardiovascular outcome trial P004/ B1521021 also referred to as CVOT). This review focuses on the pre-marketing evaluation of cardiovascular safety of ertugliflozin. A separate statistical review addressing the efficacy and glycemic control of ertugliflozin is being conducted by Dr. Alexander Cambon.

Merck Sharp & Dohme Corp. (the sponsor) evaluated the cardiovascular safety of ertugliflozin through a meta-analysis of 9 randomized, controlled Phase 2 and Phase 3 trials, including an interim analysis of a cardiovascular outcomes trial (P004/ B1521021) designed to evaluate the cardiovascular safety of ertugliflozin relative to placebo. The background therapy and inclusion criteria were not consistent across the 9 trials: trial P016/ B1521006 enrolled subjects with renal impairment, while the CVOT enrolled subjects with cardiovascular risk factors. An overview of the design of these trials is provided in Section 2.2.

The cardiovascular meta-analysis (CVMA) was conducted in a population consisting of all subjects who were randomized into one of the 9 clinical trials for ertugliflozin and who received at least one dose of blinded study medication. The CVMA compared the ertugliflozin group to a combined comparators group. The ertugliflozin group included subjects on ertugliflozin 1 mg (n=54), ertugliflozin 5 mg (n=3110), ertugliflozin 10 mg (n=55), ertugliflozin 15 mg (n=3034), or ertugliflozin 25 mg (n=55), while the comparator group included subjects on placebo (n=2160), glimepiride (n=437), or sitagliptin 100 mg (n=302). The pre-specified primary safety endpoint for the CVMA was major adverse cardiovascular events plus (MACE-plus), a composite endpoint of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke and hospitalizations due to unstable angina. An independent Clinical Adjudication Committee reviewed and adjudicated all potential cardiovascular events in the 9 trials.

There were (b) (4) MACE-plus observed among 6308 subjects in the ertugliflozin treatment group and (b) (4) MACE-plus observed among 2899 subjects in the comparator group in the 9 trials utilized in the meta-analysis. The CVOT contributed (b) (4) MACE-plus among 2680 subjects in the ertugliflozin treatment group and (b) (4) MACE-plus among 1340 subjects in the placebo group. The primary analysis for the CVMA, which is based on a Cox proportional hazards model with three strata (the CVOT, the combined Phase 2/3 placebo-controlled non-CV studies, and the combined Phase 3 active controlled non-CV studies), yielded an estimated hazard ratio (HR) of ertugliflozin vs. all comparators of (b) (4) and the 95% confidence interval (CI) was ((b) (4)). The upper bound of this 95% confidence interval is below the risk margin of 1.8 necessary to show adequate cardiovascular safety of new antidiabetic products prior to approval in accordance with the FDA Diabetes Guidance for assessing cardiovascular safety (2008)[1]. A sensitivity

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analysis stratified by trial was conducted by the reviewer and obtained similar results. Conclusions based on the CVOT alone (HR = (b) (4), 95% CI = [(b) (4)]) were also similar.

(b) (4)

- In the CVMA, the proportion of subjects who experienced death from all-causes was (b) (4)% and (b) (4)% in the ertugliflozin group and comparator group respectively, and the HR estimate was (b) (4) (95% CI (b) (4)).
- In the CVOT, the proportion of subjects who experienced death from all-causes was (b) (4)% and (b) (4)% in the ertugliflozin group and comparator group respectively, and the HR estimate was (b) (4).

(b) (4)

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- In the CVMA, the proportion of subjects who experienced CV death was (b) (4)% and (b) (4)% in the ertugliflozin group and comparator group respectively, and the HR estimate was (b) (4) (95% CI [(b) (4)]).
- In the CVOT, the proportion of subjects who experienced CV death was (b) (4)% and (b) (4)% in the ertugliflozin group and comparator group respectively, and the HR estimate was (b) (4)

(b) (4)

Subgroup analyses were consistent with the primary analysis results of MACE-plus. There was no evidence of an interaction between the use of ertugliflozin and any of the following variables in terms of risk of MACE-plus: gender, race, age, country of randomization, body mass index (BMI), estimated glomerular filtration (eGFR), prior cardiovascular disease, prior coronary artery disease (CAD), prior cerebrovascular disease, and prior peripheral artery disease.

Based on the results of the CVMA and the CVOT, the 1.8 risk margin for MACE-plus has been met. The available data show no evidence of cardiovascular risk associated with ertugliflozin. The pre-specified final analyses of the CVOT will allow a more precise estimation of the hazard ratio of MACE and death associated with ertugliflozin based on additional events and longer follow-up.

2 Introduction

2.1 Product Description and Regulatory Background

Ertugliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor. The proposed indication of ertugliflozin is as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM). The proposed dosage is 5 mg or 15 mg, orally, once daily. On 19 December 2017, Merck Sharp & Dohme Corp. (the sponsor) submitted a meta-analysis of cardiovascular events conducted in nine randomized clinical trials for ertugliflozin as part of their application package for NDA 209803. The meta-analysis included one Phase 2 trial (Study P016/B1521006), seven Phase 3 trials (Studies P002/B1521013, P003/B1521022, P005/B1521019, P006/B1521015, P007/B1521017, P017/B1521047, P001/B1521016) and an interim analysis of a cardiovascular outcome trial (Study P004/B1521021) also referred to as CVOT. The initial protocol for the CVOT was submitted to IND 106447 on September 6, 2013 and the initial SAP for the program-wide CV meta-analysis was submitted on February 7, 2014 to the same IND. At the time of submission of the initial SAP, one trial had completed (P016/B1521006). The start date for all the other trials was after October 18, 2013. The meta-analysis utilizes data cuts of 28-MAR-2016 for non-event data (e.g., demographics) and 18-APR-2016 for cardiovascular event-based data (e.g., investigator determined and adjudicated events) for the other 7 studies. At the time of the meta-analysis, there were 2 completed trials (P016/B1521006, P017/B1521047), 3 trials (P003/B1521022, P005/B1521019, P006/B1521015) that completed Phase A (26 weeks) and are ongoing in the Phase B extension period, 3 trials (P001/B1521016, P002/B1521013, P007/B1521017) ongoing in Phase A (26 or 52 weeks), and the ongoing cardiovascular outcome trial (P004/B1521021). The latest version of the meta-analysis Statistical Analysis Plan was submitted to NDA 209803on November 22, 2016 and was agreed upon by the Agency. A two-stage approach was utilized to demonstrate acceptable levels of cardiovascular (CV) safety at the time of submission of the initial global registration dossiers (including the NDA submission) (Stage 1) as well as post-approval (Stage 2). At stage 1, up to 2 pre-specified interim analyses were to be conducted in the ertugliflozin development program to rule out a cardiovascular risk increase in ertugliflozin of 80% at alpha of 0.025 (1-sided) based on adjudicated and confirmed cardiovascular (CV) events, to meet the filing requirement set forth in the FDA Diabetes Guidance (2008)[1] for evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. The criteria set forth in the Guidance reads: "*For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA): Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8*." At Stage 2, up to two analyses (an interim analysis and a final analysis) are planned to be conducted to rule out a hazard ratio of 1.3 for MACE at overall alpha of 0.025 (1-sided) in the CVOT alone.

[1] Food and Drug Administration (CDER). Guidance for Industry: diabetes mellitus - evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes.

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This review addresses Merck Sharp & Dohme Corp's submission of the Stage 1 meta-analysis of cardiovascular events for NDA 209803 on 19 December 2016.

2.2 Clinical Trial Overview

The sponsor conducted a cardiovascular meta-analysis (CVMA) of 9 randomized trials which consists of Phase II and Phase III studies for ertugliflozin with duration of at least 12 weeks and includes a cardiovascular outcome trial (P004/B1521021). Table 1 summarizes the design, duration, and sample size per treatment group for these trials.

Table 1. List of Trials Included in the Cardiovascular Meta-Analysis

Protocol	Study Design / Duration	Treatments (Sample Size*)	Background Therapy
P016/ B1521006 (Dose-ranging study)	Randomized, double-blind, double-dummy, placebo-controlled, parallel- group study 12-weeks	o Ertugliflozin 1 mg (n=54) o Ertugliflozin 5 mg (n=55) o Ertugliflozin 10 mg (n=55) o Ertugliflozin 25 mg (n=55) o Placebo (n=54) o Sitagliptin 100 mg (n=55)	Metformin
P002/ B1521013	Randomized, double-blind, active-comparator-controlled, parallel group Phase A 52 weeks, Phase B 52 weeks	o Ertugliflozin 5 mg (n=448) o Ertugliflozin 15mg (n=440) o Glimepiride up to 6 or 8 mg according to the local country label (n=437)	Metformin
P003/ B1521022	Randomized, double-blind, placebo-controlled, parallel group Phase A 26-weeks, Phase B 26 weeks	o Placebo (n=153) + metformin in Phase B o Ertugliflozin 15 mg (n=152) o Ertugliflozin 5 mg (n=156)	None

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Protocol	Study Design / Duration	Treatments (Sample Size*)	Background Therapy
P005/ B1521019	Randomized double-blind, parallel-group, factorial study of co-administration of ertugliflozin and sitagliptin and administration of the individual agents Phase A 26-weeks, Phase B 26 weeks	o Sitagliptin 100 mg (n=247) o Ertugliflozin 15 mg (n=248) o Ertugliflozin 5 mg (n=250) o Ertugliflozin 15 mg/sitagliptin 100 mg (n=244) o Ertugliflozin 5 mg/sitagliptin 100 mg (n=243)	Metformin
P006/ B1521015	Randomized, double-blind, placebo-controlled, parallel group Phase A 26 weeks, Phase B 26 weeks	o Placebo (n=153) o Ertugliflozin 15 mg (n=153) o Ertugliflozin 5 mg (n=156)	Metformin and Sitagliptin
P007/ B1521017	Randomized, double-blind, placebo-controlled Phase A 26 weeks, Phase B 78 weeks	o Placebo (n=209) + glimepiride in Phase B o Ertugliflozin 15 mg (n=205) o Ertugliflozin 5 mg (n=207)	Metformin
P017/ B1521047	Randomized, double-blind, placebo-controlled, parallel group Single phase, 26 weeks	o Placebo (n=97) o Ertugliflozin 15 mg/sitagliptin 100 mg (n=96) o Ertugliflozin 5 mg/sitagliptin 100 mg (n=98)	None

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Protocol	Study Design / Duration	Treatments (Sample Size*)	Background Therapy
P001/ B1521016 (Renal Impairment Population)	Randomized, double-blind, placebo-controlled, parallel group Phase A 26 weeks, Phase B 26 weeks	o Placebo (n=154) o Ertugliflozin 15 mg (n=155) o Ertugliflozin 5 mg (n=158)	Standard diabetes therapy with the exception of metformin, rosiglitazone, or an SGLT2-inhibitor
P004/ B1521021 (CVOT with 3 glycemic sub-studies)	Randomized, double-blind, placebo-controlled, parallel group, event driven trial	o Ertugliflozin 5 mg (n=1339) o Ertugliflozin 15mg (n=1341) o Placebo (n=1340)	Standard of care 1. Insulin ± Metformin 2. SU monotherapy 3. Metformin with sulfonylurea

Source: Created by reviewer from Analysis Data Reviewer's Guide and dataset adslcv.xpt
*Sample size is for subjects randomized and treated

Reviewer Comment
Trial P017/B1521047 only includes subjects randomized to ertugliflozin plus sitagliptin or to placebo. Without a comparator arm with sitagliptin 100mg alone, it may be difficult to assess the effect of ertugliflozin in this trial. This review discusses a sensitivity analysis that excludes this trial from the meta-analysis.

The CVOT (P004/B1521021) is a Phase 3 trial composed of a main cardiovascular study and three 18 week add-on glycemic sub-studies in subjects receiving specific background anti-hyperglycemic treatments. Only the main cardiovascular study is described in this review. The primary objective of this trial was to demonstrate the non-inferiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of MACE (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke). The trial included 3 treatment arms: ertugliflozin 5 mg q.d. (n=1339), ertugliflozin 15 mg q.d. (n=1341), and placebo (n=1340). The trial was conducted in subjects aged ≥40 years with T2DM, HbA1c ≥7.0% and ≤10.5%, eGFR ≥30 mL/min/1.73 m^2, and a BMI ≥18.0 kg/m^2, and a history of established vascular disease involving the coronary, cerebrovascular, or peripheral vascular system. This trial is ongoing. According to clinicaltrials.gov, the start date is 04 November 2013 and estimated completion date for this trial is October 31, 2019. For a detailed discussion about of the design of the other trials included in the CVMA, we refer to Appendix A.1.

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2.3 Data Sources

The applicant submitted electronic documents and datasets for 9 trials: P016/ B1521006, P002/ B1521013, P003/ B1521022, P005/ B1521019, P006/ B1521015, P007/ B1521017, P017/ B1521047, P001/ B1521016, and P004/ B1521021. Baseline characteristics and disposition of subjects randomized in these 9 trials were collected in dataset adslcv.xpt. The applicant compiled the data necessary to conduct time to event analyses of cardiovascular endpoints across these 9 trials in dataset adcvtte.xpt. The time to event data for individual components of the composite cardiovascular endpoint were also collected in dataset adcvtte.xpt. Clinical study reports (CSRs) of each individual trial were available.

The following file folders available within the CDER Electronic Document Room (EDR) were used in this review:

- Location of datasets: \\CDSESUB1\evsprod\NDA209803\0001\m5\datasets\cvma\analysis\legacy\datasets
- Location of sponsor's cardiovascular meta-analysis report: \\CDSESUB1\evsprod\NDA209803\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\cvma
- Location of Statistical Analysis Plan: \\CDSESUB1\evsprod\NDA209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04d522
- Location of Clinical Adjudication Committee Charter for Cardiovascular Events: \\CDSESUB1\evsprod\NDA209803\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\04jbqf

The format, content and documentation of the data submitted in support of this application was adequate to conduct a statistical review of the cardiovascular risk associated with ertugliflozin.

3 Statistical Evaluation

This review focuses on the cardiovascular risk in the pre-specified meta-analysis of the 9 trials and the analysis of cardiovascular risk in the CVOT alone. For a complete statistical evaluation of efficacy results, please refer to the review authored by Dr. Alexander Cambon.

3.1 Evaluation of Safety

3.1.1 Endpoints and Adjudication Methods

3.1.1.1 Primary Endpoint

- The primary endpoint of the meta-analysis is the time until first Major Adverse Cardiovascular Event–plus (MACE-plus), defined as any of the following adjudicated and confirmed events: CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or unstable angina requiring hospitalization. The time to event analysis is calculated from the time of a subject's first dose of randomized treatment to the occurrence of the first MACE-plus.

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Subjects without an observed MACE-plus are censored at the earliest of the study cut-off date, last contact date, or CVMA cutoff date.

- The CVOT contributed MACE-plus events and patient exposure to the meta-analysis. The CVOT is designed to continue to assess the cardiovascular safety of ertugliflozin post-approval. The primary endpoint for the CVOT post-approval is the time to first occurrence of MACE, defined as any of the following adjudicated and confirmed events: CV death, non-fatal MI, or non-fatal stroke.

3.1.1.2 Secondary Endpoint

The meta-analysis did not pre-specify any secondary endpoints. The pre-specified secondary CV endpoints for the CVOT are time to first occurrence of:

- MACE-plus
- CV death or hospitalization for heart failure
- CV death
- Fatal or non-fatal myocardial infarction (FNF MI)
- Fatal or non-fatal stroke (FNF stroke)
- Hospitalization for heart failure (HHF)
- Individual components of MACE (CV death, non-fatal MI, non-fatal stroke)
- All-cause mortality
- Renal composite: the composite of renal death, renal dialysis/transplant, or doubling of serum creatinine from baseline

Analyses of secondary endpoints related to cardiovascular safety are discussed in this review based on the data available at the time of the NDA submission. The analysis of the renal composite endpoint was pre-specified to be conducted during future analyses of the CVOT as discussed in Section 3.1.2.1. The current submission did not include any data on the renal composite endpoint and therefore this endpoint is not discussed further in this review.

3.1.1.3 Adjudication Methods

An independent Clinical Adjudication Committee (CAC) was convened to adjudicate potential cardiovascular events from all trials in the ertugliflozin development program. The CAC is composed of eight members (five cardiovascular specialists and three vascular neurology specialists) and includes no Sponsor representatives. The CAC charter was submitted to the FDA as part of the application package for NDA 209803. Members of the CAC charter were blinded to treatment allocation at all times and applied a pre-specified and standardized process for adjudication of all potential cases of cardiovascular events, venous thromboembolic events and deaths. The details of the structure and processes followed by the CAC and the event definitions used are described in the Clinical Adjudication Committee Charter for Cardiovascular Events.

The initial protocols for all trials except for P016/B1521006 pre-specified a list of serious cardiovascular adverse events to be collected and sent for adjudication by the CAC. All deaths in the trials were also sent for adjudication. Potential clinical cardiovascular events were identified

by the site or by the Sponsor and were sent for adjudication regardless of causality. The Sponsor provided a list of specific documents to support adjudication by the CAC including but not limited to: hospital discharge summaries, clinic notes, ECGs, diagnostic cardiac enzymes, autopsy reports and death certificate information. All SAEs, including confirmed adjudicated cardiovascular events, were reviewed and monitored by an external data monitoring committee (DMC) unblinded to treatment as part of the overall assessment of safety for ertugliflozin.

3.1.2 Statistical Methodologies

Section 3.1.2.1discusses the pre-specified statistical analysis plan submitted by the Sponsor to rule out a hazard ratio risk margin of MACE-plus greater than 1.8 associated with ertugliflozin, as well as the plan to rule out a hazard ratio risk margin of MACE greater than 1.3. These margins are set forth in the Diabetes Guidance for assessing cardiovascular risk. Section 3.1.2.2discusses the statistical methodology used in the primary meta-analysis of MACE-plus in the nine Phase 2 and Phase 3 trials. Section 3.1.2.3discusses secondary pre-specified analyses. Section 3.1.2.4discusses additional analyses. Section 3.1.2.5 discusses methods to evaluate trial heterogeneity.

3.1.2.1 Pre-Specified Statistical Analysis Plan to Meet the FDA Diabetes Guidance Requirements

The pre-specified Statistical Analysis Plan (SAP) stated that:

- At stage 1, a single meta-analysis will be conducted to rule out a hazard ratio for MACE-plus greater than 1.8 at alpha of 0.025 (1-sided) if at least 173 MACE-plus are observed in the ertugliflozin development program at the time of the NDA submission. The single meta-analysis will successfully rule out a hazard ratio of 1.8 if the upper bound of a one-sided 97.5% confidence interval for the HR of MACE-plus is less than 1.8. Assuming that ertugliflozin has no effect on the incidence of MACE-plus (true hazard ratio equal to 1), the pre-specified meta-analysis with 173 events will have approximately 95% power to rule out a hazard ratio greater than 1.8. If fewer than 173 total events were observed at the time of the NDA submission, 2 pre-specified interim analyses were planned that controlled for multiplicity.
- At Stage 2, up to two analyses (an interim analysis and a final analysis) will be conducted to rule out a hazard ratio of 1.3 for MACE at overall alpha of 0.025 (1-sided) in the CVOT alone. An O' Brien-Fleming alpha-spending function to preserve the overall one-sided Type I error rate of 2.5% with respect to the non-inferiority margin of 1.3 will be used:
    - The interim analysis will be conducted with a one-sided α=0.01 after approximately 714 adjudicated MACE events are observed in the CVOT.
    - The final analysis will be conducted with a one-sided α=2.2% after approximately 939 adjudicated MACE events have occurred in the CVOT.

  According to the SAP, 714 and 939 events are expected to be observed in the CVOT approximately 5 years and 6.1 years from the start of this study respectively. The Stage 2 analysis will have approximately 90% overall power to rule out a hazard ratio of 1.3.

- [redacted] (b) (4)

Reviewer's Comment:

- *The primary analysis for the CVMA includes 225 subjects with a first event that contributes to the composite of MACE-plus. Thus, a single meta-analysis was conducted in accordance with the pre-specified SAP to attempt to rule out a hazard ratio risk margin of MACE-plus greater than 1.8 associated with ertugliflozin compared to all comparators.*
- *The Sponsor's power calculations for Stage 1 were based on a trial with 1:1 randomization ratio and 173 events. The randomization ratio in the meta-analysis was closer to 2:1 and the number of events observed was 225. Based on these numbers, the a-priori power for the meta-analysis to rule out a hazard ratio of 1.8 was approximately 97% assuming a true hazard ratio of 1.*

3.1.2.2 Primary Analysis

The agreed upon primary meta-analysis compares the hazard ratio of MACE-plus in subjects randomized to ertugliflozin versus subjects randomized to all comparators (non-ertugliflozin comparator or placebo) using a Cox proportional hazards model with three strata: the CVOT study, the combined Phase 2/3 placebo-controlled non-CV studies, and the combined Phase 3 active controlled non-CV studies. Within each stratum, all doses of ertugliflozin were pooled together as one group and likewise for the comparator. The meta-analysis includes the 9 Phase 2/3 clinical trials described earlier. The primary analysis uses an "on-study" approach, which includes all events confirmed by adjudication regardless of the date of last dose.

Kaplan-Meier curves will be provided to compare the survival functions of MACE-plus in both treatment groups graphically.

Reviewer's Comment:
When combining data across trials, it is advisable to stratify by each trial. The pre-specified Cox proportional hazards model for the CVMA contains only three strata. However, the reviewer conducted a sensitivity analysis with a Cox proportional hazards model stratified by each of the nine trials in the meta-analysis (see Appendix A.5) and found the results to be identical to those of the pre-specified model with three strata.

3.1.2.3 Secondary Analyses

The following secondary analyses at Stage 2, for the CVOT, were pre-specified:

- Cox proportional hazards model of MACE
- Cox proportional hazards models of secondary time-to-event endpoints (eg, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart

failure, cardiovascular death, the composite of cardiovascular death or hospitalization for heart failure, the renal composite, and all-cause mortality) using the same model terms as those included for the primary endpoint.

These analyses are pre-specified to be conducted during Stage 2 of the CVOT. This review discusses analyses of these endpoints based on the interim data of the CVOT (Stage 1) submitted in support of the NDA application.

3.1.2.4 Additional Analyses

The following additional analyses for MACE-plus were pre-specified:

- Sensitivity analysis based on the minimum risk method, which is an alternative approach to the stratified Cox model that does not assume proportional hazards
- Sensitivity analysis based on an "on-treatment + 14 days" approach
- Sensitivity analysis with multiple imputation of missing follow-up
- Subgroup analyses by region, gender, age (<65 and ≥65 years), race, and ethnicity

Reviewer Comments

Some sensitivity analyses that were of interest to FDA were not listed in the SAP, including:

- *Analysis by Ertugliflozin dose*
- *Analysis of MACE-plus excluding Study P017/B1521047*
- *Analysis of All-Cause Mortality including Non-Confirmed Deaths*

These analyses were conducted post-hoc by the reviewer and are described in Appendix A.5.

3.1.2.5 Evaluation of Heterogeneity between Trials

The stratified Cox model allows for different baseline hazards across strata, but assumes that the effect of treatment, the hazard ratio, is constant across strata. Testing for a difference in hazard ratios is equivalent to testing for an interaction of treatment by strata in the Cox model. Given that only the CVOT was powered to evaluate cardiovascular safety and that few MACE-plus are expected in the other trials in the meta-analysis, a test for interaction of treatment by trial in the primary Cox model would have limited power to detect differences in the hazard ratios between trials. Consequently, we do not test for the interaction of treatment and strata in this review. Different trials' populations were heterogeneous by design as can be seen from their inclusion criteria. Subjects in the CVOT had higher baseline CV risk on average than subjects in other trials in the meta-analysis. The influence of the CVOT on the meta-analysis is assessed by conducting the primary meta-analysis of all nine trials and secondary analyses of CVOT alone.

3.1.3 Populations

The meta-analysis was conducted on a Full Analysis Set (FAS) population consisting of all subjects who were randomized into one of the 9 clinical trials for ertugliflozin and who received at least one dose of blinded study medication. Subjects without an observed MACE-plus were censored at the earliest of the study cut-off date or last contact date. The FAS population for the

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9 trials includes 6,308 subjects randomized to ertugliflozin and 2,899 subjects randomized to comparators.

3.1.4 Subject Disposition, Demographics and Baseline Characteristics

3.1.4.1 Baseline Demographic Characteristics

Table 2 shows that baseline demographic characteristics in the CVMA were similar between subjects randomized to ertugliflozin and subjects randomized to comparators. There were no noticeable imbalances in these characteristics. Demographic characteristics of subjects in the CVOT were also balanced between both treatment arms. Compared to the CVMA (which includes the CVOT), the CVOT enrolled fewer women (28% versus 38%), slightly older subjects (mean age 64 versus 60 years old), and slightly more whites (85% versus 79%).

Table 2 Baseline Demographic Characteristics in the Meta-Analysis and the CVOT

Treatment	CVMA (n=9207)		CVOT (n=4020)	
	Ertugliflozin (n=6308)	Non-Ertugliflozin (n=2899)	Ertugliflozin (n=2680)	Non-Ertugliflozin (n=1340)
Female (%)	2505 (39.7)	1083 (37.4)	749 (28.0)	381 (28.4)
Age (years)				
Mean ± SD	60.5 ± 9.9	60.7 ± 10.0	64.3 (8.3)	64.5 (8.1)
<45 (%)	413 (6.5)	188 (6.5)	29 (1.1)	11 (0.8)
45-64 (%)	3645 (57.8)	1632 (56.3)	1305 (48.7)	642 (47.9)
≥65 (%)	2250 (35.7)	1079 (37.2)	1346 (50.2)	687 (51.3)
Race				
White (%)	5008 (79.4)	2311 (79.7)	2287 (85.3)	1143 (85.3)
Asian (%)	750 (11.9)	334 (11.5)	208 (7.8)	100 (7.5)
Black (%)	279 (4.4)	129 (4.4)	101 (3.8)	50 (3.7)
Other (%)	271 (4.3)	125 (4.4)	84 (3.1)	47 (3.5)
Region				
North America (excluding Central America)	2039 (32.3)	938 (32.4)	789 (29.4)	395 (29.5)
South America (including Central America)	553 (8.8)	232 (8.0)	196 (7.3)	97 (7.2)
Europe (including Russia)	2679 (42.5)	1236 (42.6)	1281 (47.8)	642 (47.9)
Asia	716 (11.4)	329 (11.3)	235 (8.8)	114 (8.5)
South Africa	246 (3.9)	122 (4.2)	124 (4.6)	62 (4.6)
Australia/New Zealand	75 (1.2)	42 (1.4)	55 (2.1)	30 (2.2)
BMI (kg/m^2)				
Subjects with Data	6307	2899	2679	1339
Mean ± SD	31.8 (5.8)	31.7 (5.9)	32.0 (5.5)	32.0 (5.6)

Source: Created by reviewer. Dataset: adslcv.xpt

3.1.4.2 Baseline Cardiovascular Risk Factors

Table 3 shows baseline cardiovascular risk factors pooled across the 9 trials included in the CVMA. The two treatment groups appear balanced beyond small differences reasonably explained by chance. As expected due to their inclusion criteria, Table 3 shows that subjects enrolled in the CVOT have higher background CV risk than subjects in the pooled population of all trials in the meta-analysis (which includes CVOT). Compared to the other 8 trials, subjects in the CVOT were more likely to have longer diabetes duration (13 versus10 years), lower eGFR (76 vs 81 mL/min/1.73m^2), prior CV disease (99% versus 56%), coronary artery disease (79% versus 43%), cerebrovascular disease (22% versus 11%), and peripheral artery disease (16% versus 9%).

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Table 3 Baseline Cardiovascular Risk Factors in the Meta-Analysis and the CVOT

Treatment	CVMA (n=9207)		CVOT (n=4020)	
	Ertugliflozin (n=6308)	Non-Ertugliflozin (n=2899)	Ertugliflozin (n=2680)	Non-Ertugliflozin (n=1340)
Duration of Type 2 Diabetes Mellitus (years)				
Subjects with Data	6308	2898	2680	1339
Mean ± SD	10.0 (7.6)	10.2 (8.1)	12.8 (8.3)	13.1 (8.9)
Baseline A1C (%)				
Subjects with Data	6261	2879	2667	1331
Mean ± SD	8.2 (1.0)	8.2 (0.9)	8.3 (1.0)	8.2 (0.9)
Baseline eGFR* (mL/min/1.73m^2)				
Subjects with Data	6088	2789	2680	1340
Mean ± SD	81.6 (21.9)	80.4 (22.2)	76.6 (20.6)	75.8 (20.8)
Medical History of CV Disease (%)	3459 (54.8)	1708 (58.9)	2649 (98.8)	1329 (99.2)
History of Coronary Artery Disease (%)	2634 (41.8)	1290 (44.5)	2137 (79.7)	1071 (79.9)
History of Cerebrovascular Disease (%)	666 (10.6)	324 (11.2)	300 (22.4)	608 (22.7)
History of Peripheral Artery Disease (%)	532 (8.4)	265 (9.1)	410 (15.3)	225 (16.8)

Source: Created by reviewer. Dataset: adslcv.xpt

* For P016/B1521006 (dose- ranging study), all 328 subjects did not have data on eGFR.

3.1.4.3 Follow-up Time by Treatment Arm for MACE-plus

At the time of submission, subjects on ertugliflozin had been followed for MACE-plus for an average of 338 days across all trials, and subjects on comparators had been followed for an average of 332 days. Table 4 shows subject average days of follow-up and total patient-years by trial and randomized treatment.

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Table 4 Mean (SD) Days of Follow-up and patient-years for MACE+ by Trial

Trial	Ertugliflozin		Non-Ertugliflozin	
	Mean (SD) Days of Follow-up	Patient-years of Follow-up	Mean (SD) Days of Follow-up for MACE+	Patient-years of Follow-up
P001/B1521016*	324.3 (85.8)	277.9	326.3 (80.5)	137.6
P002/B1521013	412.4 (111.5)	1002.5	411.1 (105.5)	491.8
P003/B1521022	322.7 (86.7)	272.1	308.4 (102.1)	129.2
P004/B1521021** (CVOT)	337.5 (127.7)	2476.2	333.7 (130.2)	1224.4
P005/B1521019	349.5 (68.9)	942.6	344.3 (77.5)	232.8
P006/B1521015	343.8 (60.0)	290.9	336.1 (70.4)	140.8
P007/B1521017	357.5 (117.9)	403.3	350.8 (126.5)	200.7
P016/B1521006	96.3 (22.2)	57.7	95.9 (23.2)	28.6
P017/B1521047	199.2 (20.8)	105.8	194.0 (35.3)	51.5
Overall	**337.5 (121.3)**	**5829.1**	**332.3 (127.0)**	**2637.5**

Source: Created by reviewer. Dataset: adcvtte.xpt

* One subject (subject id 100046) had a death from undetermined cause at day 238 and was censored for all other outcomes; the time to MACE+ was originally 242 days and was modified to be 238 days.

** One subject (subject id 446832) had a death from undetermined cause at day 108 and was censored for all other outcomes; the time to event for MACE-plus was originally 45 days and was modified to be 108 days.

The reasons for trial discontinuation by trial and treatment arm are given in Table 5. There are no consistent imbalances by reason of discontinuation and treatment arm across trials.

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Table 5 Trial Discontinuation Rates by Reason

Trial	Randomized Treatment	Sample Size	Reason for Discontinuation			
			Adverse Event	Lost to Follow-up	Withdrawal by Subject	Other
P001/B1521016	Ertugliflozin	313	15 (4,8%)	3 (1.0%)	19 (6.1%)	11 (3.5%)
	Non-Ertugliflozin	154	5 (3.2%)	0	7 (4.6%)	8 (5.2%)
P002/B1521013	Ertugliflozin	888	20 (2.3%)	24 (2.7%)	42 (4.7%)	99 (11.2%)
	Non-Ertugliflozin	437	12 (2.8%)	12 (2.8%)	21 (4.8%)	47 (10.8%)
P003/B1521022	Ertugliflozin	308	3 (1.0%)	17 (5.5%)	18 (5.8%)	8 (2.6%)
	Non-Ertugliflozin	153	6 (3.9%)	7 (4.6%)	14 (9.2%)	9 (5.9%)
P004/B1521021 (CVOT)	Ertugliflozin	2680	28 (1.0%)	38 (1.4%)	101 (3.8%)	55 (2.1%)
	Non-Ertugliflozin	1340	8 (0.6%)	16 (1.2%)	51 (3.8%)	30 (2.2%)
P005/B1521019	Ertugliflozin	985	12 (1.2%)	25 (2.5%)	36 (3.7%)	25 (2.5%)
	Non-Ertugliflozin	247	1 (0.4%)	10 (4.1%)	12 (4.9%)	8 (3.2%)
P006/B1521015	Ertugliflozin	309	6 (1.9%)	1 (0.3%)	12 (3.9%)	3 (1.0%)
	Non-Ertugliflozin	153	1 (0.7%)	0	8 (5.2%)	5 (3.3%)
P007/B1521017	Ertugliflozin	412	5 (1.2%)	8 (1.9%)	18 (4.4%)	4 (1.0%)
	Non-Ertugliflozin	209	3 (1.4%)	5 (2.4%)	13 (6.2%)	1 (0.5%)
P016/B1521006	Ertugliflozin	219	7 (3.2%)	4 (1.8%)	0	18 (8.2%)
	Non-Ertugliflozin	109	2 (1.8%)	2 (1.8%)	0	9 (8.3%)
P017/B1521047	Ertugliflozin	194	0	3 (1.5%)	0	0
	Non-Ertugliflozin	97	0	3 (3.1%)	0	3 (3.1%)
Overall	Ertugliflozin	6308	96 (1.5%)	123 (1.9%)	246 (3.9%)	223 (3.5%)
	Non-Ertugliflozin	2899	38 (1.3%)	55 (1.9%)	129 (4.4%)	117 (4.0%)

Source: Created by reviewer. Dataset: adslcv.xpt

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5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The SAP stated that, at Stage 1, the CV safety of ertugliflozin would be evaluated through a meta-analysis of Phase 2 and Phase 3 clinical trials for ertugliflozin, including an interim analysis of the CVOT. The CVMA was conducted in a population consisting of all subjects who were randomized into one of the 9 clinical trials for ertugliflozin and who received at least one dose of blinded study medication. The comparator group in the meta-analysis was comprised of all non-ertugliflozin randomized groups. The pre-specified primary safety endpoint for the CVMA was MACE-plus, a composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke and hospitalizations due to unstable angina.

The CVMA was designed to demonstrate that the hazard ratio of MACE-plus associated with ertugliflozin relative to all comparators is smaller than the risk margin of 1.8 set forth in the FDA Diabetes Guidance for assessing cardiovascular safety. The pre-specified primary model was a Cox proportional hazards model with three strata (the CVOT, the combined Phase 2/3 placebo-controlled non-CV studies, and the combined Phase 3 active controlled non-CV studies). There were [(b) (4)] MACE-plus observed among 6308 subjects in the ertugliflozin treatment group and [(b) (4)] MACE-plus observed among 2899 subjects in the comparator group in the 9 trials utilized in the meta-analysis. The CVOT contributed [(b) (4)] MACE-plus among 2680 subjects in the ertugliflozin treatment group and [(b) (4)] MACE-plus among 1340 subjects in the placebo group. The primary Cox proportional hazards model analysis for the CVMA yielded an estimated hazard ratio of ertugliflozin vs. all comparators of [(b) (4)] (95% CI [(b) (4)]). The upper bound of this 95% confidence interval is below the risk margin of 1.8 necessary to show adequate cardiovascular safety of new antidiabetic products. Conclusions based on the CVOT alone (HR = [(b) (4)], 95% CI = [(b) (4)]) were similar.

[(b) (4)] A summary of the findings for secondary endpoints and components of MACE-plus is shown in Table 23.

Table 23 Secondary Endpoints and Components of MACE-plus in All Trials in the CVMA

	Ertugliflozin (N=6308) n (%)	Non-Ertugliflozin (N=2899) n (%)	HR (95% CI)
CV Death	(b) (4)		
Non-Fatal MI			
Non-Fatal Stroke			
Unstable Angina requiring Hospitalization			
All-Cause Mortality			
MACE			
CV Death or Hospitalization for Heart Failure			
Fatal or Non-Fatal MI			
Fatal or Non-Fatal Stroke			
Hospitalization for Heart Failure			

Source: Created by reviewer. Dataset: adcvtte.xpt

(b) (4)

Subgroup analyses were consistent with the primary analysis results of MACE-plus. There was no evidence of an interaction between the use of ertugliflozin and any of the following variables in terms of risk of MACE-plus: gender, race, age, country of randomization, body mass index, estimated glomerular filtration, prior cardiovascular disease, prior coronary artery disease, prior cerebrovascular disease, and prior peripheral artery disease.

5.2 Conclusions and Recommendations

Merck Sharp & Dohme Corp. evaluated the cardiovascular (CV) safety of ertugliflozin at Stage 1 through a meta-analysis of 9 randomized, controlled Phase 2 and Phase 3 trials, including an interim analysis of a cardiovascular outcomes trial (CVOT). The primary analysis of MACE-plus was based on a Cox proportional hazards model with three strata (the CVOT, the combined Phase 2/3 placebo-controlled non-CV studies, and the combined Phase 3 active controlled non-CV studies) including all 9 trials and yielded an estimated hazard ratio of ertugliflozin vs. all comparators of (b) (4) (95% CI (b) (4)). Thus, the available data show no evidence of cardiovascular risk associated with ertugliflozin. The upper bound of the 95% confidence interval for MACE-plus was smaller than 1.8 and therefore met the hazard ratio risk margin set forth in the FDA Guidance to establish cardiovascular safety of new antidiabetic products.

Based on the agreed-upon SAP, the Sponsor plans to conduct future analyses at Stage 2 to rule out a hazard ratio risk margin of 1.3 for MACE at overall alpha of 0.025 (1-sided) based on the CVOT alone. An interim analysis will be conducted after approximately 714 adjudicated MACE events have been observed and a final analysis will be conducted after approximately 939 adjudicated MACE events have been observed. (b) (4)

The pre-specified future analyses of the CVOT will allow a more precise estimation of the hazard ratio of MACE and death associated with ertugliflozin based on additional events and longer follow-up.

6 References

1. Food and Drug Administration. Guidance for industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. December 2008. (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf)

7 Appendix

A.1 Trials Design

P016/B1521006 is a Phase 2 trial titled: "A 12-week, Phase 2, Randomized, Double-Blinded, Placebo Controlled, Dose-Ranging, Parallel Group Study to Evaluate the Safety, Tolerability and Efficacy of Once Daily PF-04971729 and Sitagliptin on Glycemic Control and Body Weight in Adult Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin". The primary objective of this trial was to evaluate the dose-response of ertugliflozin administered once daily over 12-weeks in adults with T2DM on stable doses of metformin on glycemic

control. The trial included six treatment arms: placebo, ertugliflozin 1 mg qd (n=54), ertugliflozin 5 mg qd (n=55), ertugliflozin 10 mg qd (n=55), ertugliflozin 25 mg qd (n=55), and sitagliptin 100 mg qd (n=55). The trial was conducted in subjects with a diagnosis of T2DM on stable doses of metformin, aged 18 to 70, with HbA1c levels ≥7% and ≤11%, creatinine clearance >60 mL/min, and a BMI between 23 and 45 kg/m². This trial started on 02 March 2010 and completed on 20 January 2011.

P002/B1521013 is a Phase 3 trial titled: "A Phase III, Multicenter, Randomized, Double-Blind, Active-Comparator-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Ertugliflozin (MK-8835/PF-04971729) Compared with the Addition of Glimepiride in Subjects with Type 2 Diabetes Mellitus who have Inadequate Glycemic Control on Metformin". The double-blind treatment period was divided into two 52-week phases (Phase A – Weeks 0-52; Phase B – Weeks 52-104). The primary objectives of this trial were to assess the A1C-lowering efficacy of the addition of ertugliflozin 15 mg q.d. compared with the addition of glimepiride after 52 weeks and to assess the safety and tolerability of ertugliflozin, in subjects with T2DM and inadequate glycemic control on metformin. The trial included 3 treatment arms: ertugliflozin 5 mg q.d. (n=448), ertugliflozin 15 mg q.d. (n=440), and glimepiride up to 6 or 8 mg q.d. (n=437) according to the local country label. The trial was conducted in subjects ≥18 years of age with T2DM, HbA1c ≥7.0% and ≤9.0%, eGFR≥55 mL/min/1.73m², a BMI ≥18.0 kg/m², and on ≥1500 mg/day metformin monotherapy for at least 8 weeks. This trial started on 17 December 2013 and is ongoing (Last Subject Last Visit in Phase A is 28 April 2016). According to clinicaltrials.gov, the completion date for this trial was April 11, 2017.

P003/B1521022 is a Phase 3 trial titled: "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26 Week Multicenter Study with a 26-Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin Monotherapy in the Treatment of Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control despite Diet and Exercise". The treatment period was divided into two 26-week phases (Placebo-Controlled Phase A: Weeks 0-26; Active-Controlled Phase B: Weeks 26-52). The primary objectives of this trial were:

- to assess the effect on HbA1C of a) 15 mg ertugliflozin as compared with placebo, b) 5 mg ertugliflozin as compared with placebo, and
- to assess the safety and tolerability of ertugliflozin, in subjects with T2DM on diet and exercise.

The trial included 3 treatment arms: ertugliflozin 5 mg q.d. (n=156), ertugliflozin 15 mg q.d. (n=152), and placebo (n=153) +Metformin in Phase B. The trial was conducted in subjects on diet and exercise aged ≥18 years with T2DM, HbA1c ≥7.0% and ≤10.5%, eGFR≥55 mL/min/1.73m², and a BMI ≥18.0 kg/m². This trial started on 18 October 2013 and is ongoing (Last Subject Last Visit in Phase A is 6 January 2016). According to clinicaltrials.gov, the completion date for this trial was in July 2016.

P005/B1521019 is a Phase 3 trial titled: "A Phase III, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of the Combination of Ertugliflozin (MK-8835/PF-04971729) with Sitagliptin Compared with Ertugliflozin Alone and Sitagliptin Alone, in the

Treatment of Subjects with T2DM with Inadequate Glycemic Control on Metformin Monotherapy". The double-blind treatment period was 52 weeks in duration and divided into two 26-week phases (Phase A - Weeks 0-26; Phase B - Weeks 26-52). The primary objectives of this trial were:

- to assess the A1C-lowering efficacy of a) the addition of ertugliflozin 15 mg q.d. plus sitagliptin 100 mg q.d. compared with the addition of sitagliptin 100 mg q.d. alone, b) the addition of ertugliflozin 15 mg q.d. plus sitagliptin 100 mg q.d. compared with the addition of ertugliflozin 15 mg q.d. alone, c) the addition of ertugliflozin 5 mg q.d. plus sitagliptin 100 mg q.d. compared with the addition of sitagliptin 100 mg q.d. alone, d) the addition of ertugliflozin 5 mg q.d. plus sitagliptin 100 mg q.d. compared with the addition of ertugliflozin 5 mg q.d. alone, and
- to assess the safety and tolerability of the addition of ertugliflozin plus sitagliptin 100 mg q.d., ertugliflozin alone, and sitagliptin 100 mg q.d. alone, in subjects with T2DM and inadequate glycemic control on metformin ≥1500 mg/day, after 26 weeks. The trial included 5 treatment arms: ertugliflozin 5 mg q.d. + sitagliptin 100 mg q.d. (n=243), ertugliflozin 15 mg q.d. + sitagliptin 100 mg q.d. (n=244), ertugliflozin 5 mg q.d. (n=250), ertugliflozin 15 mg q.d. (n=248), and sitagliptin 100 mg q.d. (n=247), in subjects with T2DM and inadequate glycemic control on metformin ≥1500 mg/day.

The trial was conducted in subjects on ≥1500 mg/day of metformin monotherapy for at least 8 weeks who were ≥18 years of age with type 2 diabetes mellitus (T2DM), HbA1c ≥7.5 and ≤11%, eGFR ≥60 mL/min/1.73 m^2, and a BMI ≥18.0 kg/m^2. This trial started on 29 April 2014 and is ongoing (Last Subject Last Visit in Phase A is 11 November 2015). According to clinicaltrials.gov, the completion date for this trial was in May 2016.

P006/B1521015 is a Phase 3 trial titled: "A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Clinical Trial to Evaluate the Safety and Efficacy of Ertugliflozin (MK-8835/PF-04971729) in the Treatment of Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin and Sitagliptin". The double-blind treatment period was 52 weeks in duration and divided into two 26-week phases (Phase A - Weeks 0-26; Phase B - Weeks 26-52). The primary objectives of this trial were:

- to assess the A1C-lowering efficacy of a) the addition of ertugliflozin 15 mg q.d. relative to the addition of placebo after 26 weeks, b) the addition of ertugliflozin 5 mg q.d. relative to the addition of placebo after 26 weeks, and
- to assess the safety and tolerability of the addition of ertugliflozin, in subjects with T2DM and inadequate glycemic control on treatment with metformin ≥1500 mg/day and sitagliptin 100 mg q.d.. The trial included 3 treatment arms: ertugliflozin 5 mg q.d. (n=156), ertugliflozin 15 mg q.d. (n=153), and placebo (n=153).

The trial was conducted in subjects with T2DM aged ≥18 years, on stable treatment with metformin ≥1500 mg/day and sitagliptin 100 mg q.d, HbA1c ≥7.0% and ≤10.5%, eGFR ≥60 mL/min/1.73 m^2, and a BMI ≥18.0 kg/m^2. This trial started on 07 April 2014 and is ongoing (Last Subject Last Visit in Phase A is 18 November 2015). According to clinicaltrials.gov, the completion date for this trial was in June 2016.

P007/B1521017 is a Phase 3 trial titled: "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study with a 78-Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin in Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control on Metformin Monotherapy". The double-blind treatment period was 104 weeks in duration and was divided into two phases (Placebo-Controlled Phase A - Weeks 0-26; Active-Controlled Phase B - Weeks 26-104). The primary objectives of this trial were:

- to assess the effect on HbA1c of a) 15 mg ertugliflozin as compared with placebo, b) 5 mg ertugliflozin as compared with placebo, and
- to assess the safety and tolerability of ertugliflozin, in subjects with T2DM and inadequate glycemic control on metformin.

The trial included 3 treatment arms: ertugliflozin 5 mg q.d. (n=207), ertugliflozin 15 mg q.d. (n=205), and placebo (n=209). The trial was conducted in subjects aged ≥18 years with T2DM, on metformin monotherapy at a dose ≥1500 mg/day, with HbA1c ≥7.0% and ≤10.5%, eGFR ≥55 mL/min/1.73 m^2, and a BMI ≥18.0 kg/m^2 and ≤40.0 kg/m^2.This trial started on 10 January 2014 and is ongoing (Last Subject Last Visit in Phase A is 26 January 2016). According to clinicaltrials.gov, the completion date for this trial was in August 2017.

P017/B1521047 is a Phase 3 trial titled: "A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Clinical Trial to Evaluate the Efficacy and Safety of the Initial Combination of Ertugliflozin (MK-8835/PF-04971729) with Sitagliptin in the Treatment of Subjects with T2DM with Inadequate Glycemic Control on Diet and Exercise". The double-blind treatment period was 26 weeks in duration. The primary objectives of this trial were:

- to assess the A1C-lowering efficacy of a) ertugliflozin 15 mg q.d. plus sitagliptin 100 mg q.d. relative to placebo, b) ertugliflozin 5 mg q.d. plus sitagliptin 100 mg q.d. relative to placebo, and
- to assess the safety and tolerability of ertugliflozin plus sitagliptin 100 mg q.d., in subjects with T2DM and inadequate glycemic control on diet and exercise after 26 weeks.

The trial included 3 treatment arms: ertugliflozin 5 mg q.d. and sitagliptin 100 mg q.d. (n=98), ertugliflozin 15 mg q.d. and sitagliptin 100 mg q.d. (n=96), and placebo (n=97). The trial was conducted in subjects with T2DM aged ≥18 years, on diet and exercise, with HbA1c ≥8.0% and ≤10.5%, eGFR ≥60 mL/min/1.73 m^2, and a BMI≥18.0 kg/m^2. This trial started on 25 September 2014 and completed 23 February 2016.

P001/B1521016 is a Phase 3 trial titled: "A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Ertugliflozin (MK-8835/PF-04971729) in Subjects with Type 2 Diabetes Mellitus with Stage 3 Chronic Kidney Disease who Have Inadequate Glycemic Control on Background Antihyperglycemic Therapy". The double-blind treatment period was divided into two 26-week phases (Phase A - Weeks 0-26; Phase B - Weeks 26-52). The primary objectives of this trial were:

- to assess the A1C-lowering efficacy of a) the addition of ertugliflozin 15 mg q.d. compared to the addition of placebo, b) the addition of ertugliflozin 5 mg q.d. compared to the addition of placebo, and

- to assess the safety and tolerability of ertugliflozin, in subjects with stage 3 chronic kidney disease, T2DM, and inadequate glycemic control on standard diabetes therapy, after 26 weeks.

The trial included 3 treatment arms: ertugliflozin 5 mg q.d. (n=158), ertugliflozin 15 mg q.d. (n=155), and placebo (n=154). The trial was conducted in subjects with T2DM aged ≥25 years, HbA1c ≥7.0% and ≤10.5%, eGFR ≥30 and <60 mL/min/1.73 m^2, and a BMI ≥18.0 kg/m^2. This trial started on 03 December 2013 and is ongoing (Last Subject Last Visit in Phase A is 11 March 2016). According to clinicaltrials.gov, the completion date for this trial is September 28, 2016.

P004/B1521021 is a Phase 3 trial titled: "Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study to Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin (MK-8835/PF-04971729) in Subjects with Type 2 Diabetes Mellitus and Established Vascular Disease, The VERTIS CV Study". This trial is composed of a main cardiovascular study and three 18 week add-on glycemic sub-studies in subjects receiving specific background anti-hyperglycemic treatments. The primary objective of this trial was to demonstrate the non-inferiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of MACE (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke). The trial included 3 treatment arms: ertugliflozin 5 mg q.d. (n=1339), ertugliflozin 15 mg q.d. (n=1341), and placebo (n=1340). The trial was conducted in subjects aged ≥40 years with T2DM, HbA1c ≥7.0% and ≤10.5%, eGFR ≥30 mL/min/1.73 m^2, and a BMI ≥18.0 kg/m^2, and a history of established vascular disease involving the coronary, cerebrovascular, or peripheral vascular system. This trial is ongoing. According to clinicaltrials.gov, the start date is 04 November 2013 and estimated completion date for this trial is October 31, 2019.

A.2 Assessment of Proportional Hazards

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08/15/2017

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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 209803
Drug Name:	Ertugliflozin (MK-8835, PF-04971729)
Indication:	Treatment of type 2 diabetes mellitus
Studies:	104 Week Carcinogenicity Studies in Rats and Mice
Applicant:	Sponsor for Rats: Pfizer Global Research & Development Eastern Point Road Groton, Connecticut 06340 U.S.A. Testing Facility for Rats: (b) (4) Sponsor for Mice: Merck Research Laboratories, West Point, Pennsylvania, U.S.A. Testing Facility for Mice: Safety Assessment and Laboratory Animal Resources Merck Research Laboratories, West Point, Pennsylvania, U.S.A.
Documents Reviewed:	Electronic submission: Submitted on December 19, 2016 Electronic data: Submitted on December 19, 2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products
Reviewing Pharmacologist:	Jessica Hawes, Ph.D.
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to evaluate the carcinogenic potential of the test article, ertugliflozin (also known as MK-8835, L-004921514, and PF-04971729), a sodium glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes, when administered daily via oral gavage to rats and mice approximately for two years.

For the rat study, all surviving female rats were euthanized during Week 93 (No explanation for the reason of this early termination can be located in the sponsor's report), while all male rats were euthanized during Week 105. For the mouse study, due to the decreasing survival in male mice from the control and the test article-treated dose groups, scheduled termination of all remaining male mice from all dose groups was performed in Week 97. Due to decreasing survival and worsening physical signs upon clinical observation in female mice from the control and the test article-treated dose groups, scheduled termination of all remaining female mice from all dose groups was performed in Week 102.

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

2. Rat Study

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups and one vehicle control group. The dose levels for treated groups were 1.5, 5, and 15 mg/kg/day for both male and female rats. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. Two hundred sixty Crl:CD(SD) rats of each sex were assigned randomly in size of 60 rats per group to the low and mid dose groups, and in size of 70 rats per group to the vehicle control and the high dose groups. The rats in the vehicle control group were administrated with the vehicle [0.5% (w/v) methylcellulose (4000 cps) with 10% (v/v) polyethylene glycol 400 prepared in reverse osmosis water], and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	70	70	Vehicle control	0	0
2	60	60	PF-04971729 Low	1.5	1.5
3	60	60	PF-04971729 Mid	5	5
4	70	70	PF-04971729 High	15	15

Animals were checked twice daily (a.m. and p.m.) for mortality, abnormalities, and signs of pain or distress. Detailed observations were conducted for each carcinogenicity animal once during the predose phase, prior to dosing on Day 1, and weekly (based on Day 1) throughout the dosing phase. Detailed observations were also collected on the days of scheduled euthanasia (all surviving animals). Mass observations were recorded for each carcinogenicity animal once prior to dosing on Day 1, and weekly (based on Day 1 of the dosing phase) throughout the dosing phase. Time of onset, location, size, appearance, and progression information on each

macroscopically visible or palpable mass was recorded. On Day 645 (Week 93) of the dosing phase, all surviving females, having been fasted overnight, were anesthetized with sodium pentobarbital, exsanguinated, and necropsied. On Day 730 (Week 105) of the dosing phase, all surviving males, having been fasted overnight, were anesthetized with sodium pentobarbital, exsanguinated, and necropsied. A macroscopic examination of the external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues was performed. At necropsy, macroscopic examinations were conducted. Protocol-specified tissues (when present) from each animal were preserved in the appropriate fixative, embedded, sectioned, and stained, and slides were examined.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor conducted tests to compare survival with a 2-sided risk for increasing and decreasing mortality with dose, for dose response and for each dosed group against control using Kaplan-Meier product-limit estimates, along with log-rank and Wilcoxon tests. These were conducted using the LIFETEST procedure in SAS. Dosed groups were included as the strata. Animals with an accidental death or a scheduled euthanasia (interim or terminal) status were censored in the analysis.

Sponsor’s findings:

The sponsor’s analysis showed that the numbers of rats surviving to their terminal necropsy were 22 (31%), 15 (25%), 24 (40%), and 27 (39%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 18 (26%), 24 (40%), 26 (43%), and 34 (49%) for female rats respectively. The sponsor reported that no significant findings were noted for male rats. For female rats, the high-dose group (15 mg/kg/day) had lower mortality than control (36 of 70 in high-dose versus 52 of 70 in control), with p=0.0103 and p=0.0194 for the Log-Rank and Wilcoxon tests, respectively. The dose-response test was also significant, with p=0.0273 and p=0.0379 for the Log-Rank and Wilcoxon tests, respectively.

2.1.2. Tumor data analysis

In the sponsor’s report, tests to compare tumor incidence were performed with a one-sided risk for increasing incidence with dose. Tests were performed for dose response and for each treated group against vehicle control.

For tumors occurring in animals dying spontaneously or sacrificed in extremis during the study, the pathologist classified the context of observation as one of the following:
(1) Fatal: the tumor was a factor in the demise of the animal.
(2) Non-fatal: the tumor was not a factor in the demise of the animal.
(3) Uncertain

Occult or non-palpable tumors were analyzed by the IARC asymptotic fixed interval based prevalence test (Peto et al., 1980). For males, the cut off points for the intervalbased test were Weeks 0 to 52, 53 to 78, 79 to 92, 93 to before terminal euthanasia, and the terminal euthanasia (Week 105). For females, the cut off points for the interval-based test were Weeks 0 to 52, 53 to 78, 79 to 92, and the terminal euthanasia (Week 93). Fatal and non-fatal tumors were analyzed together, with separate strata for each. No tumors of uncertain context were noted. The test was

implemented using PROC MULTTEST in the SAS system. In the case of sparse tables (<10 total in the strata), the exact form of the test was used for that strata. Otherwise, the asymptotic version of the test was used. Animals were assigned to the terminal euthanasia strata based on the death or euthanasia status recorded in the data, and were not assigned based on their week of necropsy.

Observable or palpable (superficial as in mammary or skin) tumors were analyzed using the methods previously described for analyzing survival, using the time to death or time of detection of the tumor (in weeks) as a surrogate for the tumor onset time. These tests were conducted with a 1-sided risk for increasing the incidence with dose. Unadjusted P-values were reported for tumors.

The Study Pathologist determined which tumor combinations were statistically analyzed, using the criteria for combination in Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenicity Studies (McConnell et al., 1986) as a guide. Incidences of multiple-organ and combined neoplastic findings, such as hemangioma, fibrosarcoma, and endometrial stromal polyp, were counted by animal, not tissue type. Due to individual values being rounded for inclusion in the report, calculation of summary statistics from these reported values may, in some cases, yield minor differences.

Adjustment for multiple testing:

In the sponsor's report, indication of a possible dosing effect was assessed on the basis of a rare or common tumor type, in line with the current Food and Drug Administration (FDA) guidelines (Food and Drug Administration, 2001). For the dose response tests, the results were interpreted at 0.025 and 0.005 for rare and common tumors respectively. For the pairwise tests, the results were interpreted at 0.05 and 0.01 for rare and common tumors respectively. The incidence rate for defining whether a tumor type was rare or common was determined by the Study Pathologist based on site specific background historical data.

Sponsor's findings:

For male rats, the sponsor reported a statistically significant positive dose response relationship for the incidence of benign pheochromocytoma in adrenal medulla (p-value=0.0010), along with statistically significant increases in the mid and high dose group when compared to the vehicle control group (p-value=0.0087 and 0.0008, respectively). A statistically significant positive dose response relationship was also noted for the incidence of the combined benign and malignant pheochromocytoma in adrenal medulla (p-value=0.0025), along with a statistically significant increase in the high dose group when compared to the vehicle control group (p-value=0.0022). No other statistically significant tumor findings were noted in both male and female rats.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of rats in all four groups (Groups 1, 2, 3, and 4) were estimated using the

Kaplan-Meier product limit method. The dose response relationship was tested across Groups 1, 2, 3, and 4 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all four groups in male and female rats, respectively. The intercurrent mortality data of all four groups, and the results of the tests for dose response relationship and homogeneity of survivals for Groups 1, 2, 3, and 4 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 22 (31%), 15 (25%), 24 (40%), and 27 (39%) in the vehicle control group, low, mid, and high dose groups for male rats, respectively, and 18 (26%), 24 (40%), 26 (43%), and 34 (49%) for female rats respectively. No statistically significant findings in mortality were noted in male rats. For female rats, a statistically significant positive dose-response relationship in mortality was noted (p-value=0.0258), along with a statistically significant increase in the high dose group when compared to the vehicle control group (p-value=0.0114).

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across Groups 1, 2, 3, and 4, and pairwise comparisons of each of the three treated groups (Groups 2, 3, and 4) against the vehicle control group (Group 1), using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the *i*-th treatment group R^* i is defined as $R^*_i = \sum W_{ij}$ where w_{ij} is the weight for the *j*-th animal in the *i*-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / tsacr)^3$ to animals dying without the tumor,

where t_{ij} is the time of death of the *j*-th animal in the *i*-th treatment group, and tsacr is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned w_{ij} =1 since t_{ij} = tsacr. Also animals developed the tumor type being tested before the end of the study will be assigned as w_{ij} = 1.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the tsacr should not be affected by the unplanned early terminations. The tsacr should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than tsacr,

regardless their actual terminal sacrifice time, tsacr was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data.

Multiple testing adjustment:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies (2001). For dose response relationship tests, the guidance suggests the use of test levels of α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species where both are two-years studies, in order to keep the false-positive rate at the nominal level of approximately 10%. For multiple pairwise comparisons of treated group with control, the guidance suggests the use of test levels of α=0.01 for common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 2.

Table 2. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - C vs. L	50 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
Adrenal, Medulla	B-Pheochromocytoma	2/70 (46)	6/60 (40)	9/60 (42)	15/69 (51)
		0.0018 $	0.0925	0.0167 @	0.0010 $
	M-Malignant Pheochromocytoma	3/70 (47)	2/60 (39)	1/60 (40)	4/69 (49)
		0.2862	0.4112	0.6285	0.5235
	B-Pheochromocytoma/ M-Malignant Pheochromocytoma	5/70 (47)	8/60 (40)	10/60 (42)	18/69 (52)
		0.0039 $	0.1791	0.0846	0.0042 $

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
$ = Statistically significant in common tumor at 0.005 level for test of dose response relationship and at 0.01 level for test of pairwise comparisons;
@ = Not statistically significant at 0.01 level in common tumor for test of pairwise comparisons;

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed statistically significant positive dose response relationships for the incidence of benign pheochromocytoma, and the combined benign and malignant pheochromocytoma in adrenal medulla (p-value=0.0018, and 0.0039, respectively), along with statistically significant increases in the high dose group when compared to the vehicle control group (p-value=0.0010, and 0.0042, respectively), regardless whether the tumor is considered to be rare or common. No other statistically significant tumor findings were noted in both male and female rats.

3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 3, in each of these two experiments there were three treated groups and three vehicle control groups. Three hundred CRL:CD1(ICR) mice of each sex were assigned to these six groups (Groups 1 to 6) of 50 females and 50 males each. The three treated groups received 5, 15, or 40 mg/kg/day ertugliflozin (L-pyroglutamic acid co-crystal form) in a vehicle of 0.5% (w/v) methylcellulose (MC) and 10% (v/v) polyethylene glycol (PEG) 400 in deionized water. In this review these dose groups were referred to as the low (Group 4), mid (Group 5), and high (Group 6) dose groups, respectively. The three control groups received either 0.5% (w/v) methylcellulose in deionized water (Vehicle Control 1, Group 1) or 0.5% (w/v) methylcellulose and 10% (v/v) polyethylene glycol 400 in deionized water (Vehicle Control 2 and 3, Group 2 and 3), were handled for the same duration and in the same manner as the treated groups.

Due to the decreasing survival (increased unscheduled death incidence) in male mice from the control and the test article-treated dose groups, scheduled termination of all remaining male mice from all dose groups was performed in Week 97. Due to the decreasing survival and worsening physical signs upon clinical observation in female mice from the control and the test article-treated dose groups, scheduled termination of all remaining female mice from all dose groups was performed in Week 102.

Table 3. Experimental Design in Mouse Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	50	50	Vehicle Control 1 (0.5% MC)	0	0
2	50	50	Vehicle Control 2 (0.5% MC/10% PEG 400)	0	0
3	50	50	Vehicle Control 3 (0.5% MC/10% PEG 400)	0	0
4	50	50	MK-8835 Low	5	5
5	50	50	MK-8835 Mid	15	15
6	50	50	MK-8835 High	40	40

Daily observations for mortality were performed. Clinical sign observations were performed once per week from Week 1 through Week 102. Beginning in Week 26, all animals were palpated for masses once every 4 weeks through Week 102. Additionally, unscheduled palpations were performed on individual animals found with masses during non-palpation weeks. Animals were palpated to provide information regarding the onset of possible neoplasms for use in statistical analyses. Unscheduled death occurrence of comparable incidence was observed between individual control and test article-treated groups. The decreased survival was observed in the control and the test article-treated dose groups prior to scheduled Week 105 termination; and therefore, termination of all remaining male and female animals was performed in Week 97 and Week 102, respectively.

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3.1. Sponsor's analyses

Due to the control mice being administered with either 10% PEG 400 in 0.5% MC (vehicle control group 2 and 3) or 0.5% MC (vehicle control group 1) in this study, 2 separate sets of statistical analyses were conducted in the sponsor’s report. One set of statistical analyses

includes the combined vehicle control groups 2+3 and MK-8835 treated groups since MK-8835 was formulated in the vehicle of the control groups 2 and 3. The other set of statistical analyses was to compare the combined vehicle control groups 2+3 with the vehicle control group 1.

3.1.1. Survival analysis

In the sponsor's report, the analysis of unscheduled death was done by a statistical evaluation of survival curves. A log-rank test was used to test for homogeneity and equality of the survival functions across the dose groups. The survival pattern among dose groups was compared by the Product Limit method. This method uses the censored observations as well as the uncensored observations. The significance level is set to 0.05.

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 16 (32%), 21 (42%), 28 (56%), 18 (36%), 17 (34%), and 27 (54%) in Vehicle Control 1, 2, and 3, and the low, mid and high dose groups for male mice, respectively, and 27 (54%), 19 (38%), 26 (52%), 23 (46%), 18 (36%), and 23 (46%) for female mice, respectively. In male mice, the Control 1, Control 2, low, and mid dose groups were observed with decreased survival prior to Week 97 termination. In female mice, the Control 2 and mid dose groups had decreased survival prior to Week 102 termination. For both of two sets of statistical analyses described above, the sponsor reported no statistically significant findings in survival rates for male and female mice.

3.1.2. Tumor data analysis

In the sponsor's report, the Peto method was used to analyze the palpable and nonpalpable tumor data, taking into account the context of observation of the tumor as well as survival differences among dose groups. The strata used in the Peto method for the male mice were, Day 1-364, 365-467, 468-570, and 571-674, with a separate stratum for male mice that survived to Day 675, the start of terminal necropsy. For female mice, the strata were Day 1-364, 365-450, 451-536, and 537-622, and 623-708 with a separate stratum for female mice that survived to Day 709, the start of terminal necropsy. This analysis includes only types for which at least two mice per sex were observed with a tumor. The significance level was set to 0.05.

In the first set of statistical analyses described above, the primary analysis of tumor incidence was by trend test (an increase or decrease in tumor incidence with increasing dose of the test article). Both unadjusted and adjusted (for multiplicity of tests) p-values were calculated. No pairwise comparisons between the treated groups and the vehicle control groups were conducted in the sponsor's report.

Multiple testing adjustment:

In the sponsor's report, an adjustment was made using SAS Proc Multtest for Peto's test, following the recommendations made by Mantal (1980), Heyse and Rom (1988), and Harter (1957). The adjusted p-value is a proper assessment of the probability that a p-value less than or equal to P_i (the smallest observed p-value from among all tumor types analyzed. If, after adjustment for survival differences among groups, all tumor types have an equal probability of occurring in any treatment group, then there is approximately a 5% chance of observing Adj $P \leq 0.05$ for at least one type of tumor, a 'false positive'. However, if there is supportive information, such as a tumor type occurring

in both genders, both species of rodents, or multiple tumors of similar disease-process occurring in the same organ, then unadjusted p-values are more relevant for inference.

Sponsor's findings:

The sponsor's analysis showed that for both male and female mice, there were no statistically significant dose response relationship or the pairwise comparisons for both of two sets of statistical analyses described above.

3.2. Reviewer's analyses

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

Also, due to the control mice being administered with either 10% PEG 400 in 0.5% MC (vehicle control group 2 and 3) or 0.5% MC (vehicle control group 1) in this study, 2 separate sets of statistical analyses were conducted in the sponsor's report. One set of statistical analyses includes the combined vehicle control groups 2+3 and MK-8835 treated groups since MK-8835 was formulated in this vehicle. The other set of statistical analyses was to compare the combined vehicle control groups 2+3 with the vehicle control group 1.

For the analysis of both the survival data and the tumor data, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data, and the results of the tests for dose response relationship and homogeneity of survivals for the combined vehicle control, low, mid, and high dose groups were given in Tables 3A and 3B in the appendix for male and female mice, respectively.

Reviewer's findings:

In the reviewer's analysis, the numbers of mice surviving to their terminal necropsy were 16 (32%), 21 (42%), 28 (56%), 18 (36%), 17 (34%), and 27 (54%) in Vehicle Control groups 1, 2, and 3, and the low, mid and high dose groups for male mice, respectively, and 27 (54%), 19 (38%), 26 (52%), 23 (46%), 18 (36%), and 23 (46%) for female mice, respectively. No statistically significant findings in mortality were noted in both male and female mice.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tested tumor types are given in Tables 4A and Table 4B in the appendix, for male and female mice, respectively.

Reviewer's findings:

The reviewer's analysis showed no statistically significant dose response relationship or pairwise comparisons for both of the two sets of statistical analysis in both male and female mice.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to evaluate the carcinogenic potential of the test article, ertugliflozin (also known as MK-8835, L-004921514, and PF-04971729), a sodium glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes, when administered daily via oral gavage to rats and mice approximately for two years.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of these two experiments there were three treated groups and one vehicle control group. The dose levels for treated groups were 1.5, 5, and 15 mg/kg/day for both male and female rats. Two hundred sixty Crl:CD(SD) rats of each sex were assigned randomly in size of 60 rats per group to the low and mid dose groups, and in size of 70 rats per group to the vehicle control and the high dose groups. All surviving female rats were euthanized during Week 93 (No explanation for the reason of this early termination can be located in the sponsor's report), while all male rats were euthanized during Week 105.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 22 (31%), 15 (25%), 24 (40%), and 27 (39%) in the vehicle control group, low, mid, and high dose groups for male rats, respectively, and 18 (26%), 24 (40%), 26 (43%), and 34 (49%) for female rats respectively. No statistically significant findings in mortality were noted in male rats. For female rats, a statistically significant positive dose-response relationship in mortality was noted (p-value=0.0258), along with a statistically significant increase in the high dose group when compared to the vehicle control group (p-value=0.0114).

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed statistically significant positive dose response relationships for the incidence of benign pheochromocytoma, and the combined benign and malignant pheochromocytoma in adrenal medulla (p-value=0.0018, and 0.0039, respectively), along with statistically significant increases in the high dose group when compared to the vehicle control group (p-value=0.0010, and 0.0042, respectively), regardless whether the tumor is considered to be rare or common. No other statistically significant tumor findings were noted in both male and female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. In each of these two experiments there were three treated groups and three vehicle control groups. Three hundred CRL:CD1(ICR) mice of each sex were assigned to these six groups (Groups 1 to 6) of 50 females and 50 males each. The three treated groups received 5, 15, or 40 mg/kg/day ertugliflozin (L-pyroglutamic acid co-crystal form) in a vehicle of 0.5% (w/v) methylcellulose (MC) and 10% (v/v) polyethylene glycol (PEG) 400 in deionized water. Due to the decreasing survival in male mice from the control and the test article-treated dose groups, scheduled termination of all remaining male mice from all dose groups was performed in Week 97. Due to decreasing survival and worsening physical signs upon clinical observation in female mice from the control and the test article-treated dose groups, scheduled termination of all remaining female mice from all dose groups was performed in Week 102.

In the reviewer's analysis, the numbers of mice surviving to their terminal necropsy were 16 (32%), 21 (42%), 28 (56%), 18 (36%), 17 (34%), and 27 (54%) in Vehicle Control groups 1, 2, and 3, and the low, mid and high dose groups for male mice, respectively, and 27 (54%), 19 (38%), 26 (52%), 23 (46%), 18 (36%), and 23 (46%) for female mice, respectively. No statistically significant findings in mortality were noted in both male and female mice.

The reviewer's analysis showed no statistically significant dose response relationship or pairwise comparisons for both of the two sets of statistical analysis in both male and female mice.

Hepei Chen.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, DBVI

Cc: Archival NDA 209803

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5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	4	5.71	4	6.67	5	8.33	3	4.29
53 - 78	15	27.14	13	28.33	12	28.33	15	25.71
79 - 91	15	48.57	13	50.00	11	46.67	14	45.71
92 - 104	14	20.00	14	23.33	8	13.33	11	15.71
Accidental Death			1	1.67				
Terminal sacrifice	22	31.43	15	25.00	24	40.00	27	38.57
Total	70		60		60		70	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.2264	0.6184	0.4329	0.3783
Homogeneity (Log-Rank)	0.4547	0.6128	0.4285	0.3721

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	6	8.57	4	6.67	4	6.67	1	1.43
53 - 78	25	44.29	20	40.00	17	35.00	22	32.86
79 - 91	15	65.71	11	58.33	13	56.67	13	51.43
92 - 104	5	7.14	1	1.67				
Accidental Death	1	1.43						
Terminal sacrifice	18	25.71	24	40.00	26	43.33	34	48.57
Total	70		60		60		70	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.0258*	0.1823	0.0637	0.0114*
Homogeneity (Log-Rank)	0.0624	0.1776	0.0611	0.0103*

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level;

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - C vs. L	50 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
Adrenal, Cortex	B-Adenoma	2/70 (46)	1/60 (39)	0/60 (40)	2/69 (49)
		0.4388	0.4376	0.7168	0.3328
	M-Carcinoma	1/70 (46)	1/60 (39)	0/60 (40)	1/69 (49)
		0.4711	0.7101	0.4651	0.2634
	B-Adenoma/M-Carcinoma	3/70 (46)	1/60 (39)	0/60 (40)	3/69 (49)
		0.3525	0.6270	0.8517	0.3693
Adrenal, Medulla	B-Pheochromocytoma	2/70 (46)	6/60 (40)	9/60 (42)	15/69 (51)
		0.0018#	0.0925	0.0167	0.0010#
	M-Malignant Pheochromocytoma	3/70 (47)	2/60 (39)	1/60 (40)	4/69 (49)
		0.2862	0.4112	0.6285	0.5235
	B-Pheochromocytoma/ M-Malignant Pheochromocytoma	5/70 (47)	8/60 (40)	10/60 (42)	18/69 (52)
		0.0039#	0.1791	0.0846	0.0042#
	M-Hemangiosarcoma	0/70 (46)	1/60 (39)	0/60 (40)	0/69 (49)
		0.5115	0.4588	NC	NC
Bone, Other	B-Osteoma	1/70 (46)	0/60 (38)	0/60 (40)	0/70 (49)
		0.7341	0.4524	0.4651	0.5158
Brain	B-Astrocytoma	0/70 (46)	0/60 (38)	1/60 (40)	0/70 (49)
		0.2832	NC	0.4651	NC
	M-Malignant Astrocytoma	0/70 (46)	1/60 (38)	0/60 (40)	0/70 (49)
		0.5145	0.4524	NC	NC
	B-Astrocytoma/ M-Malignant Astrocytoma	0/70 (46)	1/60 (38)	1/60 (40)	0/70 (49)
		0.5399	0.4524	0.4651	NC
	B-Oligodendroglioma	0/70 (46)	0/60 (38)	0/60 (40)	1/70 (49)
		0.2832	NC	NC	0.5158
	B-Astrocytoma/ B-Oligodendroglioma	0/70 (46)	0/60 (38)	1/60 (40)	1/70 (49)
		0.2108	NC	0.4651	0.5158
	B-Astrocytoma/ M-Malignant Astrocytoma/ B-Oligodendroglioma	0/70 (46)	1/60 (38)	1/60 (40)	1/70 (49)
		0.3266	0.4524	0.4651	0.5158
	B-Granular Cell Tumor	1/70 (46)	0/60 (38)	0/60 (40)	3/70 (49)
		0.0693	0.4524	0.4651	0.3328
Femur	M-Osteosarcoma	0/70 (46)	0/60 (38)	1/60 (40)	0/70 (49)
		0.2832	NC	0.4651	NC
Foot/Footpad	B-Papilloma, Squamous Cell	0/70 (46)	0/60 (38)	0/60 (40)	1/70 (50)
		0.2874	NC	NC	0.5208

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

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - C vs. L	50 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
Harderian Gland	B-Adenoma	1/70 (46)	0/60 (38)	0/60 (40)	0/70 (49)
		0.7341	0.4524	0.4651	0.5158
	M-Carcinoma	0/70 (46)	0/60 (38)	1/60 (41)	0/70 (49)
		0.2816	NC	0.4713	NC
	B-Adenoma/M-Carcinoma	1/70 (46)	0/60 (38)	1/60 (41)	0/70 (49)
		0.6431	0.4524	0.7233	0.5158
Hemolympho- Reticular System	M-Histiocytic Sarcoma	5/70 (48)	1/60 (39)	2/60 (41)	4/70 (50)
		0.4345	0.8435	0.7125	0.5262
	M-Malignant Lymphoma	0/70 (46)	1/60 (39)	2/60 (42)	0/70 (49)
		0.6396	0.4588	0.2249	NC
Jejunum	M-Carcinoma	0/67 (44)	1/53 (34)	0/55 (39)	0/61 (45)
		0.5185	0.4359	NC	NC
Kidney	B-Adenoma, Tubule Cell	0/70 (46)	1/60 (39)	0/60 (40)	0/70 (49)
		0.5115	0.4588	NC	NC
	B-Adenoma, Tubule Cell, Amp*	0/70 (46)	1/60 (39)	0/60 (40)	0/70 (49)
		0.5115	0.4588	NC	NC
	B-Adenoma, Tubule Cell/ B-Adenoma, Tubule Cell, Amp	0/70 (46)	2/60 (40)	0/60 (40)	0/70 (49)
		0.7599	0.2134	NC	NC
	M-Carcinoma, Tubule Cell	1/70 (46)	2/60 (39)	0/60 (40)	0/70 (49)
		0.8961	0.4376	0.4651	0.5158
	B-Adenoma, Tubule Cell/ B-Adenoma, Tubule Cell, Amp M-Carcinoma, Tubule Cell	1/70 (46)	4/60 (41)	0/60 (40)	0/70 (49)
		0.9678	0.1464	0.4651	0.5158
Liver	B-Adenoma, Hepatocellular	1/70 (46)	1/60 (38)	1/60 (40)	3/70 (49)
		0.1484	0.7031	0.7168	0.3328
	M-Carcinoma, Hepatocellular	0/70 (46)	0/60 (38)	1/60 (40)	1/70 (49)
		0.2108	NC	0.4651	0.5158
	B-Adenoma, Hepatocellular/ M-Carcinoma, Hepatocellular	1/70 (46)	1/60 (38)	2/60 (40)	4/70 (49)
		0.0775	0.7031	0.4471	0.2011
	M-Hemangiosarcoma	0/70 (46)	1/60 (38)	0/60 (40)	0/70 (49)
		0.5145	0.4524	NC	NC
Lung	B-Adenoma, Bronchiolo-Alveo*	0/70 (46)	1/60 (39)	0/60 (40)	0/70 (49)
		0.5115	0.4588	NC	NC
	M-Squamous Cell Carcinoma	0/70 (46)	0/60 (38)	1/60 (41)	0/70 (49)
		0.2816	NC	0.4713	NC

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

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - C vs. L	50 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
Lymph Node, Mesenteric	B-Lymphangioma	0/70 (46)	1/60 (39)	0/60 (40)	0/68 (47)
		0.5058	0.4588	NC	NC
	M-Hemangiosarcoma	3/70 (46)	1/60 (39)	1/60 (40)	1/68 (48)
		0.7784	0.6270	0.6372	0.7076
Mammary Gland, Male	B-Fibroadenoma	2/62 (42)	1/51 (33)	2/52 (35)	0/64 (46)
		0.8842	0.4092	0.6204	0.7751
	M-Carcinoma	1/62 (42)	1/51 (33)	0/52 (35)	0/64 (46)
		0.8141	0.6897	0.4545	0.5227
Muscle, Biceps Femoris	M-Sarcoma	1/69 (46)	0/60 (38)	0/60 (40)	0/70 (49)
		0.7341	0.4524	0.4651	0.5158
Pancreas	B-Adenoma, Acinar Cell	0/70 (46)	1/59 (38)	1/60 (40)	0/70 (49)
		0.5399	0.4524	0.4651	NC
	B-Adenoma, Islet Cell	8/70 (46)	1/59 (38)	1/60 (40)	4/70 (49)
		0.7195	0.9701	0.9749	0.8517
	M-Carcinoma, Islet Cell	0/70 (46)	2/59 (38)	0/60 (40)	0/70 (49)
		0.7657	0.2017	NC	NC
	B-Adenoma, Islet Cell/ M-Carcinoma, Islet Cell	8/70 (46)	3/59 (38)	1/60 (40)	4/70 (49)
		0.8198	0.8307	0.9749	0.8517
Parathyroid	B-Adenoma	2/66 (43)	1/55 (37)	0/58 (39)	1/68 (48)
		0.6783	0.4431	0.7281	0.5416
Pituitary	B-Adenoma	49/70 (60)	38/60 (49)	33/58 (48)	39/69 (59)
		0.9699	0.6166	0.9086	0.9582
	M-Carcinoma	1/70 (46)	0/60 (38)	0/58 (38)	0/69 (48)
		0.7294	0.4524	0.4524	0.5106
	B-Adenoma/M-Carcinoma	50/70 (60)	38/60 (49)	33/58 (48)	39/69 (59)
		0.9786	0.6985	0.9399	0.9751
Preputial Gland	M-Carcinoma, Squamous Cell	1/70 (46)	0/60 (38)	0/59 (40)	0/70 (49)
		0.7341	0.4524	0.4651	0.5158
Prostate	M-Carcinoma	0/70 (46)	0/60 (38)	0/60 (40)	1/70 (50)
		0.2874	NC	NC	0.5208
	M-Fibrosarcoma	0/70 (46)	0/60 (38)	0/60 (40)	1/70 (49)
		0.2832	NC	NC	0.5158

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

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - C vs. L	50 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
Skin/Subcutis	B-Basal Cell Tumor	1/70 (46)	0/59 (38)	2/60 (40)	0/70 (49)
		0.6809	0.4524	0.4471	0.5158
	B-Chondroma	0/70 (46)	0/59 (38)	0/60 (40)	1/70 (49)
		0.2832	NC	NC	0.5158
	B-Fibroma	5/70 (47)	5/59 (39)	2/60 (41)	3/70 (50)
		0.8439	0.5060	0.7226	0.6770
	M-Fibrosarcoma	1/70 (46)	3/59 (39)	1/60 (41)	0/70 (49)
		0.9129	0.2482	0.7233	0.5158
	B-Fibroma/M-Fibrosarcoma	6/70 (47)	7/59 (40)	3/60 (41)	3/70 (50)
		0.9367	0.3747	0.6845	0.7869
	B-Hemangioma	1/70 (46)	0/59 (38)	1/60 (40)	0/70 (49)
		0.6420	0.4524	0.7168	0.5158
	M-Hemangiosarcoma	1/70 (46)	1/59 (38)	0/60 (40)	0/70 (49)
		0.8129	0.7031	0.4651	0.5158
	B-Hemangioma/ M-Hemangiosarcoma	2/70 (46)	1/59 (38)	1/60 (40)	0/70 (49)
		0.8860	0.4279	0.4471	0.7682
	B-Keratoacanthoma	10/70 (48)	3/59 (38)	6/60 (42)	6/70 (50)
		0.7325	0.9151	0.7018	0.8182
	B-Papilloma, Squamous Cell	0/70 (46)	0/59 (38)	3/60 (41)	1/70 (49)
		0.3294	NC	0.1006	0.5158
	M-Carcinoma, Squamous Cell	0/70 (46)	2/59 (38)	1/60 (40)	0/70 (49)
		0.7232	0.2017	0.4651	NC
	B-Keratoacanthoma/ B-Papilloma, Squamous Cell/ M-Carcinoma, Squamous Cell	10/70 (48)	4/59 (39)	8/60 (42)	7/70 (50)
		0.6693	0.8513	0.4776	0.7342
	B-Lipoma	0/70 (46)	0/59 (38)	0/60 (40)	2/70 (49)
		0.0790	NC	NC	0.2634
	B-Neurofibroma	0/70 (46)	1/59 (38)	1/60 (40)	0/70 (49)
		0.5399	0.4524	0.4651	NC
	M-Neurofibrosarcoma	2/70 (46)	1/59 (38)	1/60 (41)	1/70 (50)
		0.6577	0.4279	0.4564	0.5316
	B-Neurofibroma/ M-Neurofibrosarcoma	2/70 (46)	2/59 (38)	2/60 (41)	1/70 (50)
		0.7474	0.6165	0.6471	0.5316
	M-Osteosarcoma	2/70 (47)	1/59 (38)	1/60 (41)	1/70 (50)
		0.6522	0.4199	0.4483	0.5234

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

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - C vs. L	50 mg Mid (M) P - C vs. M	150 mg High (H) P - C vs. H
Spleen	B-Lipoma	0/70 (46)	1/60 (38)	0/60 (40)	0/70 (49)
		0.5145	0.4524	NC	NC
	M-Hemangiosarcoma	0/70 (46)	0/60 (38)	0/60 (40)	1/70 (49)
		0.2832	NC	NC	0.5158
Stomach, Glandular	M-Leiomyosarcoma	1/70 (46)	0/59 (38)	0/60 (40)	0/70 (49)
		0.7341	0.4524	0.4651	0.5158
Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/70 (46)	0/59 (38)	1/60 (40)	0/70 (49)
		0.2832	NC	0.4651	NC
	M-Carcinoma, Squamous Cell	0/70 (46)	1/59 (38)	0/60 (40)	0/70 (49)
		0.5145	0.4524	NC	NC
	B-Papilloma, Squamous Cell/ M-Carcinoma, Squamous Cell	0/70 (46)	1/59 (38)	1/60 (40)	0/70 (49)
		0.5399	0.4524	0.4651	NC
Testis	B-Interstitial Cell Tumor	1/70 (47)	1/60 (38)	3/60 (41)	4/70 (49)
		0.0919	0.6972	0.2583	0.1941
Thymus	B-Thymoma	1/68 (44)	0/58 (38)	0/59 (40)	0/66 (47)
		0.7396	0.4634	0.4762	0.5165
	M-Hemangiosarcoma	0/68 (44)	1/58 (38)	0/59 (40)	0/66 (47)
		0.5148	0.4634	NC	NC
Thyroid	B-Adenoma, C-Cell	13/70 (48)	13/59 (42)	13/60 (42)	9/70 (52)
		0.9357	0.4314	0.4314	0.8257
	M-Carcinoma, C-Cell	2/70 (46)	4/59 (40)	1/60 (41)	1/70 (50)
		0.8784	0.2737	0.4564	0.5316
	B-Adenoma, C-Cell/ M-Carcinoma, C-Cell	15/70 (48)	17/59 (44)	14/60 (43)	10/70 (52)
		0.9724	0.3001	0.5358	0.8761
	B-Adenoma, Follicular Cell	7/70 (47)	2/59 (39)	6/60 (41)	3/70 (49)
		0.8317	0.8690	0.3935	0.8581
	M-Carcinoma, Follicular Cell	3/70 (46)	3/59 (39)	1/60 (40)	3/70 (49)
		0.5295	0.5799	0.6372	0.3693
	B-Adenoma, Follicular Cell/ M-Carcinoma, Follicular	10/70 (48)	5/59 (40)	6/60 (41)	5/70 (49)
		0.8764	0.7722	0.6833	0.8785
Tongue	B-Papilloma, Squamous Cell	0/70 (46)	1/59 (39)	0/60 (40)	0/70 (49)
		0.5115	0.4588	NC	NC
Urinary Bladder	M-Carcinoma, Transitional Cell	0/70 (46)	0/60 (38)	1/60 (41)	0/70 (49)
		0.2816	NC	0.4713	NC

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

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - L vs. C	50 mg Mid (M) P - M vs. C	150 mg High (H) P - H vs. C
Adrenal, Cortex	B-Adenoma	0/70 (32)	2/60 (30)	0/60 (31)	2/70 (39)
		0.2502	0.2300	NC	0.2982
Adrenal, Medulla	B-Pheochromocytoma	2/69 (32)	1/59 (29)	0/55 (28)	3/70 (39)
		0.2682	0.4625	0.7198	0.5945
	M-Malignant Pheochromocytoma	1/69 (32)	0/59 (29)	0/55 (28)	0/70 (38)
		0.7480	0.4754	0.4667	0.5429
	B-Pheochromocytoma / M-Malignant Pheochromocytoma	3/69 (32)	1/59 (29)	0/55 (28)	3/70 (39)
		0.4033	0.6555	0.8551	0.4363
Brain	B-Granular Cell Tumor	0/70 (32)	0/59 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
	M-Malignant Astrocytoma	0/70 (32)	0/59 (29)	1/60 (31)	1/70 (38)
		0.2243	NC	0.4921	0.5429
	M-Meningeal Sarcoma	0/70 (32)	0/59 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
Cecum	M-Mesothelioma	1/68 (32)	0/59 (29)	0/57 (30)	0/70 (38)
		0.7519	0.4754	0.4839	0.5429
Cervix	B-Granular Cell Tumor	0/70 (32)	1/59 (29)	0/60 (31)	0/70 (38)
		0.5308	0.4754	NC	NC
	B-Polyp, Stromal	0/70 (32)	0/59 (29)	1/60 (31)	0/70 (38)
		0.2923	NC	0.4921	NC
	M-Carcinoma	0/70 (32)	1/59 (29)	0/60 (31)	0/70 (38)
		0.5308	0.4754	NC	NC
	M-Leiomyosarcoma	0/70 (32)	0/59 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
	M-Sarcoma, Stromal	2/70 (32)	0/59 (29)	0/60 (31)	0/70 (38)
		0.9408	0.7290	0.7460	0.7946
	B-Polyp, Stromal / M-Sarcoma, Stromal	2/70 (32)	0/59 (29)	1/60 (31)	0/70 (38)
		0.8564	0.729	0.4879	0.7946
Foot/Footpad	B-Fibroma	0/70 (32)	0/59 (29)	1/60 (31)	0/70 (38)
		0.2923	NC	0.4921	NC
Heart	M-Endocardial Schwannoma	0/70 (32)	2/60 (31)	0/60 (31)	0/70 (38)
		0.7741	0.2381	NC	NC
Hemolympho- Reticular System	M-Histiocytic Sarcoma	1/70 (32)	1/60 (30)	0/60 (31)	2/70 (39)
		0.3091	0.7377	0.4921	0.5748
Ileum	M-Carcinoma	0/67 (31)	0/58 (29)	1/58 (31)	0/69 (37)
		0.2891	NC	0.5000	NC

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

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - L vs. C	50 mg Mid (M) P - M vs. C	150 mg High (H) P - H vs. C
Kidney	B-Adenoma, Tubule Cell	1/70 (33)	0/60 (29)	0/60 (31)	0/70 (38)
		0.7481	0.4677	0.4844	0.5352
	M-Carcinoma, Tubule Cell	1/70 (33)	0/60 (29)	0/60 (31)	3/70 (39)
		0.0771	0.4677	0.4844	0.3731
	B-Adenoma, Tubule Cell/ M-Carcinoma, Tubule Cell	1/70 (33)	0/60 (29)	0/60 (31)	3/70 (39)
		0.0771	0.4677	0.4844	0.3731
	B-Lipoma	0/70 (32)	0/60 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
Liver	B-Adenoma, Hepatocellular	0/70 (32)	1/60 (30)	3/60 (32)	0/70 (38)
		0.6882	0.4839	0.1190	NC
	M-Hemangiosarcoma	0/70 (32)	0/60 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
Mammary Gland, Female	B-Adenoma	6/70 (35)	4/60 (32)	3/60 (33)	8/70 (41)
		0.2530	0.5732	0.7311	0.5144
	M-Carcinoma	32/70 (49)	17/60 (38)	15/60 (39)	13/70 (44)
		0.9989	0.9556	0.9893	0.9995
	B-Adenoma/M-Carcinoma	32/70 (49)	18/60 (39)	17/60 (40)	17/70 (46)
		0.9890	0.9436	0.9738	0.9949
	B-Fibroadenoma	25/70 (44)	16/60 (36)	9/60 (34)	18/70 (45)
		0.8797	0.8096	0.9933	0.9156
	M-Carcinoma, Anaplastic	1/70 (32)	0/60 (29)	1/60 (31)	0/70 (38)
		0.6634	0.4754	0.7460	0.5429
Mesentery	M-Mesothelioma	0/70 (32)	0/60 (29)	1/60 (31)	0/70 (38)
		0.2923	NC	0.4921	NC
Ovary	M-Malignant Granulosa/Theca*	0/70 (32)	0/59 (29)	0/60 (31)	1/69 (37)
		0.2868	NC	NC	0.5362
	M-Tubulostromal Carcinoma	0/70 (32)	0/59 (29)	0/60 (31)	1/69 (37)
		0.2868	NC	NC	0.5362
Pancreas	B-Adenoma, Islet Cell	2/70 (32)	1/60 (30)	1/60 (31)	0/70 (38)
		0.8999	0.4754	0.4879	0.7946
	M-Carcinoma, Islet Cell	2/70 (32)	0/60 (29)	0/60 (31)	0/70 (38)
		0.9408	0.7290	0.7460	0.7946
	B-Adenoma, Islet Cell/ M-Carcinoma, Islet Cell	4/70 (33)	1/60 (30)	1/60 (31)	0/70 (38)
		0.9835	0.7916	0.8025	0.9579

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

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - L vs. C	50 mg Mid (M) P - M vs. C	150 mg High (H) P - H vs. C
Parathyroid	B-Adenoma	0/61 (28)	0/53 (26)	1/58 (31)	0/70 (38)
		0.3089	NC	0.5254	NC
Pituitary	B-Adenoma	57/70 (60)	49/59 (54)	43/60 (49)	55/70 (61)
		0.7359	0.6991	0.8453	0.7463
	M-Carcinoma	3/70 (33)	0/59 (29)	3/60 (32)	2/70 (39)
		0.5269	0.8557	0.6489	0.5800
	B-Adenoma/M-Carcinoma	60/70 (61)	49/59 (54)	46/60 (51)	57/70 (62)
		0.7818	0.9223	0.9326	0.8926
Skin/Subcutis	B-Fibroma	0/70 (32)	0/60 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
	M-Fibrosarcoma	0/70 (32)	0/60 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
	B-Fibroma/M-Fibrosarcoma	0/70 (32)	0/60 (29)	0/60 (31)	2/70 (39)
		0.0870	NC	NC	0.2982
	B-Keratoacanthoma	0/70 (32)	1/60 (30)	1/60 (31)	0/70 (38)
		0.5522	0.4839	0.4921	NC
	B-Papilloma, Squamous Cell	1/70 (32)	0/60 (29)	0/60 (31)	1/70 (38)
		0.5008	0.4754	0.4921	0.2911
	M-Carcinoma, Squamous Cell	0/70 (32)	0/60 (29)	1/60 (31)	0/70 (38)
		0.2923	NC	0.4921	NC
	B-Keratoacanthoma/ B-Papilloma, Squamous Cell/ M-Carcinoma, Squamous Cell	1/70 (32)	1/60 (30)	2/60 (32)	1/70 (38)
		0.5166	0.7377	0.5000	0.2911
	B-Lipoma	1/70 (32)	0/60 (29)	2/60 (32)	0/70 (38)
		0.6984	0.4754	0.5000	0.5429
	M-Hemangiosarcoma	0/70 (32)	2/60 (30)	0/60 (31)	0/70 (38)
		0.7779	0.2300	NC	NC
	M-M-Rhabdomyosarcoma	1/70 (32)	0/60 (29)	0/60 (31)	0/70 (38)
		0.7538	0.4754	0.4921	0.5429
	M-Malignant Melanoma	0/70 (32)	0/60 (29)	1/60 (31)	0/70 (38)
		0.2923	NC	0.4921	NC
	M-Neurofibrosarcoma	1/70 (33)	0/60 (29)	0/60 (31)	1/70 (38)
		0.4976	0.4677	0.4844	0.2829
	M-Osteosarcoma	1/70 (32)	0/60 (29)	0/60 (31)	0/70 (38)
		0.7538	0.4754	0.4921	0.5429

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

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - L vs. C	50 mg Mid (M) P - M vs. C	150 mg High (H) P - H vs. C
Spleen	M-Fibrosarcoma	0/70 (32)	0/60 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
	M-Hemangiosarcoma	0/70 (32)	0/60 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
	M-Mesothelioma	0/70 (32)	1/60 (30)	1/60 (31)	0/70 (38)
		0.5522	0.4839	0.4921	NC
Thymus	B-Thymoma	1/68 (32)	0/59 (29)	1/60 (31)	1/68 (37)
		0.4470	0.4754	0.7460	0.2839
	M-Malignant Thymoma	0/68 (32)	0/59 (29)	0/60 (31)	1/68 (37)
		0.2868	NC	NC	0.5362
	B-Thymoma/ M-Malignant Thymoma	1/68 (32)	0/59 (29)	1/60 (31)	2/68 (38)
		0.2206	0.4754	0.7460	0.5651
Thyroid	B-Adenoma, C-Cell	8/70 (36)	2/59 (30)	10/60 (35)	12/70 (42)
		0.0823	0.9230	0.3663	0.3533
	M-Carcinoma, C-Cell	2/70 (32)	0/59 (29)	1/60 (31)	1/70 (38)
		0.5822	0.7290	0.4879	0.5651
	B-Adenoma, C-Cell/ M-Carcinoma, C-Cell	9/70 (36)	2/59 (30)	10/60 (35)	13/70 (42)
		0.0724	0.9542	0.4712	0.3719
	B-Adenoma, Follicular Cell	1/70 (33)	0/59 (29)	0/60 (31)	1/70 (38)
		0.4976	0.4677	0.4844	0.2829
Ureter	B-Leiomyoma	1/68 (32)	0/58 (29)	0/60 (31)	0/67 (36)
		0.7500	0.4754	0.4921	0.5294
Urinary Bladder	B-Hemangioma	1/70 (33)	0/60 (29)	0/59 (30)	0/70 (38)
		0.7462	0.4677	0.4762	0.5352
Uterus	B-Polyp, Endometrial Stromal	1/70 (33)	2/59 (30)	1/60 (32)	2/70 (39)
		0.4334	0.4637	0.7462	0.5632
	M-Sarcoma, Endometrial Stro*	0/70 (32)	1/59 (29)	0/60 (31)	1/70 (38)
		0.3558	0.4754	NC	0.5429
	B-Polyp, Endometrial Stromal/ M-Sarcoma, Endometria	1/70 (33)	3/59 (30)	1/60 (32)	3/70 (39)
		0.3388	0.2709	0.7462	0.3731
	M-Carcinoma	0/70 (32)	0/59 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429
	M-Hemangiosarcoma	0/70 (32)	0/59 (29)	1/60 (31)	0/70 (38)
		0.2923	NC	0.4921	NC

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

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	15 mg Low (L) P - L vs. C	50 mg Mid (M) P - M vs. C	150 mg High (H) P - H vs. C
Vagina	B-Granular Cell Tumor	0/70 (32)	0/59 (29)	1/60 (31)	0/70 (38)
		0.2923	NC	0.4921	NC
	M-Carcinoma, Squamous Cell	0/70 (32)	0/59 (29)	0/60 (31)	1/70 (38)
		0.2923	NC	NC	0.5429

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

Table 3A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control 1		Vehicle Control 2		Vehicle Control 3		5 mg/kg/day Low		15 mg/kg/day Mid		40 mg/kg/day High RUN	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	7	14.00	4	8.00	6	12.00	4	8.00	8	16.00	7	14.00
53 - 78	10	34.00	14	36.00	6	24.00	13	34.00	15	46.00	8	30.00
79 - 91	12	58.00	9	54.00	9	42.00	10	54.00	8	62.00	6	42.00
92 - 104	5	10.00	2	4.00	1	2.00	5	10.00	2	4.00	2	4.00
Terminal sacrifice	16	32.00	21	42.00	28	56.00	18	36.00	17	34.00	27	54.00
Total	50		50		50		50		50		50	

Test	Trend: Control 2+3, Low, Mid, High	Low vs Control 2+3	Mid vs Control 2+3	High vs Control 2+3	Control 1 vs Control 2+3
Dose-Response (Likelihood Ratio)	0.5416	0.2342	0.0611	0.6091	0.1167
Homogeneity (Log-Rank)	0.1002	0.2246	0.0526	0.6097	0.1076

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 3B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control 1		Vehicle Control 2		Vehicle Control 3		5 mg/kg/day Low		15 mg/kg/day Mid		40 mg/kg/day High RUN	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	3	6.00	3	6.00	2	4.00	7	14.00	5	10.00	7	14.00
53 - 78	11	28.00	10	26.00	9	22.00	6	26.00	8	26.00	8	30.00
79 - 91	6	40.00	7	40.00	9	40.00	6	38.00	12	50.00	9	48.00
92 - 104	3	6.00	11	22.00	4	8.00	8	16.00	7	14.00	3	6.00
Terminal sacrifice	27	54.00	19	38.00	26	52.00	23	46.00	18	36.00	23	46.00
Total	50		50		50		50		50		50	

Test	Trend: Control 2+3, Low, Mid, High	Low vs Control 2+3	Mid vs Control 2+3	High vs Control 2+3	Control 1 vs Control 2+3
Dose-Response (Likelihood Ratio)	0.7146	0.9965	0.3168	0.7978	0.4692
Homogeneity (Log-Rank)	0.7666	0.9964	0.3062	0.7959	0.4712

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Vehicle 2 0 mg	Vehicle 3 0 mg	Vehicle 2+3 (C) 0 mg (2+3) P-Trend	Low (L) 5 mg P-L vs. C	Mid (M) 15 mg P-M vs. C	High (H) 40 mg P-H vs. C	Vehicle 1 (C1) P-C1 vs. C
Adrenal	Pheochromocytoma	0/(50)	0/(50)	0/100 (58) NC	0/50 (28) NC	0/50 (24) NC	0/50 (30) NC	1/50 (27) 0.3176
	Spindle Cell Tumor	1/(50)	4/(50)	5/100 (59) 0.7116	1/50 (28) 0.6332	3/50 (25) 0.4434	1/50 (30) 0.6640	1/50 (27) 0.6167
Bone	Osteosarcoma	0/(50)	0/(50)	0/100 (58) 0.3857	1/50 (28) 0.3256	0/50 (24) NC	0/50 (30) NC	0/50 (27) NC
Bone, Skull	Osteoma	0/(50)	0/(50)	0/100 (58) 0.3857	1/50 (28) 0.3256	0/50 (24) NC	0/50 (30) NC	0/50 (27) NC
Harderian Glands	Adenocarcinoma	0/(50)	1/(50)	1/100 (58) 0.5857	0/50 (28) 0.3256	0/50 (24) 0.2927	0/50 (30) 0.3409	0/50 (27) 0.3176
	Adenoma	5/(50)	6/(50)	11/100 (61) 0.2805	1/50 (28) 0.9433	5/50 (26) 0.5570	6/50 (31) 0.5435	11/50 (30) 0.0473*
	Adenocarcinoma/Adenoma	5/(50)	7/(50)	12/100 (61) 0.3439	1/50 (28) 0.9606	5/50 (26) 0.3935	6/50 (31) 0.3979	11/50 (30) 0.0688
Heart	Hemangiosarcoma	0/(50)	0/(50)	0/100 (58) 0.2143	0/50 (28) NC	0/50 (24) NC	1/50 (30) 0.3409	0/50 (27) NC
Kidney	Adenoma, Tubular Cell	0/(50)	0/(50)	0/100 (58) 0.1187	0/50 (28) NC	1/50 (24) 0.2927	1/50 (30) 0.3409	0/50 (27) NC
Liver	Adenoma, Hepatocellular	4/(50)	6/(50)	10/100 (61) 0.2557	2/50 (28) 0.7997	5/50 (25) 0.4538	6/50 (31) 0.4665	4/50 (28) 0.4653
	Carcinoma, Hepatocellular	1/(50)	3/(50)	4/100 (59) 0.9042	2/50 (28) 0.6332	2/50 (25) 0.5812	0/50 (30) 0.8136	2/50 (27) 0.6167
	Hemangioma	0/(50)	0/(50)	0/100 (58) 0.3901	0/50 (28) NC	1/50 (25) 0.3012	0/50 (30) NC	0/50 (27) NC
	Hemangiosarcoma	1/(50)	0/(50)	1/100 (58) 0.7393	3/50 (29) 0.1059	2/50 (25) 0.2144	0/50 (30) 0.3409	2/50 (28) 0.2462
	Hemangioma/ Hemangiosarcoma	1/(50)	0/(50)	1/100 (58) 0.6851	3/50 (29) 0.1059	3/50 (25) 0.0795	0/50 (30) 0.3409	2/50 (28) 0.2462
Lung	Adenoma	4/(50)	9/(50)	13/100 (62) 0.3274	3/50 (29) 0.8267	5/50 (26) 0.4488	7/50 (31) 0.5285	5/50 (28) 0.5138
	Carcinoma	7/(50)	5/(50)	12/100 (62) 0.7693	6/50 (30) 0.5741	4/50 (26) 0.5438	4/50 (30) 0.6554	4/50 (29) 0.6297
	Adenoma/Carcinoma	11/(50)	14/(50)	25/100 (65) 0.5667	9/50 (32) 0.7803	9/50 (27) 0.5863	11/50 (32) 0.5641	9/50 (30) 0.7133

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

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

Organ name	Tumor name	Vehicle 2 0 mg	Vehicle 3 0 mg	Vehicle 2+3 (C) 0 mg (2+3) P-Trend	Low (L) 5 mg P-L vs. C	Mid (M) 15 mg P-M vs. C	High (H) 40 mg P-H vs. C	Vehicle 1 (C1) P-C1 vs. C
Lymph Node	Hemangioma	0/(50)	0/(50)	0/100 (58) 0.3857	1/50 (28) 0.3256	0/50 (24) NC	0/50 (30) NC	0/50 (27) NC
Mammary Gland	Adenocarcinoma	0/(50)	0/(50)	0/100 (58) NC	0/50 (28) NC	0/50 (24) NC	0/50 (30) NC	1/50 (27) 0.3176
Pancreas	Adenoma, Islet Cell	0/(50)	1/(50)	1/100 (58) 0.5857	0/50 (28) 0.3256	0/50 (24) 0.2927	0/50 (30) 0.3409	0/50 (27) 0.3176
Pituitary	Adenoma	1/(50)	0/(50)	1/100 (58) 0.5857	0/50 (28) 0.3256	0/50 (24) 0.2927	0/49 (30) 0.3409	1/50 (27) 0.5370
Primary Site Undetermined	Leukemia	1/(50)	0/(50)	1/100 (58) 0.4750	2/50 (29) 0.2566	0/50 (24) 0.2927	1/50 (30) 0.5682	2/50 (28) 0.2462
	Lymphoma	3/(50)	6/(50)	9/100 (62) 0.4965	3/50 (29) 0.5731	6/50 (28) 0.2991	4/50 (32) 0.4714	2/50 (28) 0.7311
	Sarcoma, Histiocytic	0/(50)	0/(50)	0/100 (58) 0.2199	0/50 (28) NC	0/50 (24) NC	1/50 (31) 0.3483	1/50 (27) 0.3176
Seminal Vesicle	Adenoma	0/(50)	1/(50)	1/100 (58) 0.5857	0/50 (28) 0.3256	0/50 (24) 0.2927	0/50 (30) 0.3409	0/50 (27) 0.3176
Skin	Fibrosarcoma	5/(50)	2/(50)	7/100 (62) 0.8316	1/50 (28) 0.7787	3/50 (26) 0.6159	1/50 (30) 0.8052	7/50 (30) 0.1169
	Hemangiosarcoma	0/(50)	1/(50)	1/100 (58) 0.6621	1/50 (29) 0.5581	0/50 (24) 0.2927	0/50 (30) 0.3409	0/50 (27) 0.3176
	Osteosarcoma	0/(50)	0/(50)	0/100 (58) 0.3830	1/50 (29) 0.3333	0/50 (24) NC	0/50 (30) NC	0/50 (27) NC
	Papilloma	0/(50)	0/(50)	0/100 (58) 0.2143	0/50 (28) NC	0/50 (24) NC	1/50 (30) 0.3409	0/50 (27) NC
	Sarcoma	0/(50)	0/(50)	0/100 (58) 0.3857	1/50 (28) 0.3256	0/50 (24) NC	0/50 (30) NC	0/50 (27) NC
Small Intestine	Adenocarcinoma	0/(50)	0/(50)	0/100 (58) 0.3857	1/50 (28) 0.3256	0/50 (24) NC	0/50 (30) NC	0/50 (27) NC
Stomach	Papilloma	0/(50)	1/(50)	1/100 (58) 0.4109	1/50 (29) 0.5581	0/50 (24) 0.2927	1/50 (30) 0.5682	0/50 (27) 0.3176

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

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

Organ name	Tumor name	Vehicle 2 0 mg	Vehicle 3 0 mg	Vehicle 2+3 (C) 0 mg (2+3) P-Trend	Low (L) 5 mg P-L vs. C	Mid (M) 15 mg P-M vs. C	High (H) 40 mg P-H vs. C	Vehicle 1 (C1) P-C1 vs. C
Testis	Carcinoma, Rete Testis	0/(50)	1/(50)	1/100 (58)	0/50 (28)	0/50 (24)	0/50 (30)	0/50 (27)
				0.5857	0.3256	0.2927	0.3409	0.3176
	Hemangioma	2/(50)	0/(50)	2/100 (59)	0/50 (28)	0/50 (24)	0/50 (30)	0/50 (27)
				0.8266	0.5426	0.4972	0.5631	0.5319
	Leydig Cell Tumor	1/(50)	0/(50)	1/100 (58)	1/50 (28)	0/50 (24)	1/50 (30)	1/50 (27)
				0.4115	0.5477	0.2927	0.5682	0.5370
Thyroid	Adenoma, Follicular Cell	0/(50)	1/(50)	1/100 (58)	0/50 (28)	0/50 (24)	0/50 (30)	1/50 (27)
				0.5857	0.3256	0.2927	0.3409	0.5370
Tongue	Papilloma	0/(50)	0/(50)	0/100 (58)	1/50 (28)	0/50 (24)	0/50 (30)	0/50 (27)
				0.3857	0.3256	NC	NC	NC
Urinary Bladder	Mesenchymal Tumor	0/(50)	1/(50)	1/100 (59)	0/50 (28)	0/50 (24)	1/50 (30)	0/50 (27)
				0.3815	0.3218	0.2892	0.5631	0.3140
	Papilloma	0/(50)	1/(50)	1/100 (59)	0/50 (28)	0/50 (24)	0/50 (30)	0/50 (27)
				0.5816	0.3218	0.2892	0.3371	0.3140
Whole Body	Hemangioma	2/(50)	0/(50)	2/100 (59)	1/50 (28)	1/50 (25)	0/50 (30)	0/50 (27)
				0.7391	0.6933	0.6588	0.5631	0.5319
	Hemangiosarcoma	1/(50)	1/(50)	2/100 (59)	4/50 (30)	2/50 (25)	1/50 (30)	2/50 (28)
				0.6153	0.0962	0.3429	0.2617	0.3866
	Hemangioma/ Hemangiosarcoma	3/(50)	1/(50)	4/100 (59)	5/50 (30)	3/50 (25)	1/50 (30)	2/50 (28)
				0.7860	0.1385	0.3444	0.5504	0.6332

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

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	Vehicle 2 0 mg	Vehicle 3 0 mg	Vehicle 2+3 (C) 0 mg (2+3) P-Trend	Low (L) 5 mg P-L vs. C	Mid (M) 15 mg P-M vs. C	High (H) 40 mg P-H vs. C	Vehicle 1 (C1) P-C1 vs. C
Adrenal	Pheochromocytoma	1/(50)	1/(50)	2/100 (69)	1/50 (34)	0/50 (32)	0/50 (32)	0/50 (34)
				0.8266	0.7037	0.5354	0.5354	0.5534
	Spindle Cell Tumor	1/(50)	0/(50)	1/100 (69)	1/50 (34)	0/50 (32)	1/50 (32)	0/50 (34)
				0.3820	0.5534	0.3168	0.5354	0.3301
Brain	Meningioma	0/(50)	0/(50)	0/100 (69)	0/50 (34)	1/50 (33)	0/50 (32)	0/50 (34)
				0.3869	NC	0.3235	NC	NC
Cervix	Hemangioma	0/(50)	0/(50)	0/100 (69)	0/50 (34)	0/50 (32)	1/50 (32)	0/50 (34)
				0.1916	NC	NC	0.3168	NC
	Hemangiosarcoma	0/(50)	0/(50)	0/100 (69)	1/50 (34)	1/50 (33)	0/50 (32)	0/50 (34)
				0.3832	0.3301	0.3235	NC	NC
	Hemangioma/ Hemangiosarcoma	0/(50)	0/(50)	0/100 (69)	1/50 (34)	1/50 (33)	1/50 (32)	0/50 (34)
				0.1613	0.3301	0.3235	0.3168	NC
	Leiomyoma	1/(50)	0/(50)	1/100 (70)	0/50 (34)	0/50 (32)	0/50 (32)	0/50 (34)
				0.5833	0.3269	0.3137	0.3137	0.3269
	Stromal Sarcoma	1/(50)	0/(50)	1/100 (69)	1/50 (34)	1/50 (33)	2/50 (32)	1/50 (35)
				0.1230	0.5534	0.5446	0.2351	0.5620
	Stromal Tumor	1/(50)	0/(50)	1/100 (69)	0/50 (34)	0/50 (32)	0/50 (32)	0/50 (34)
				0.5868	0.3301	0.3168	0.3168	0.3301
Clitoral Glands	Carcinoma, Squamous Cell	1/(50)	0/(50)	1/100 (70)	0/50 (34)	0/50 (32)	0/50 (32)	0/50 (34)
				0.5833	0.3269	0.3137	0.3137	0.3269
Harderian Glands	Adenoma	2/(50)	3/(50)	5/100 (71)	2/50 (35)	1/50 (32)	1/50 (32)	1/50 (35)
				0.7761	0.4219	0.6084	0.6084	0.6489
Heart	Hemangiosarcoma	0/(50)	0/(50)	0/100 (69)	0/50 (34)	0/50 (32)	0/50 (32)	1/50 (35)
				NC	NC	NC	NC	0.3365
Large Intestine	Adenocarcinoma	0/(50)	0/(50)	0/100 (69)	1/50 (34)	0/50 (32)	0/50 (32)	0/50 (34)
				0.3832	0.3301	NC	NC	NC
	Leiomyoma	0/(50)	1/(50)	1/100 (69)	0/50 (34)	0/50 (32)	0/50 (32)	0/50 (34)
				0.5868	0.3301	0.3168	0.3168	0.3301

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

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle 2 0 mg	Vehicle 3 0 mg	Vehicle 2+3 (C) 0 mg (2+3) P-Trend	Low (L) 5 mg P-L vs. C	Mid (M) 15 mg P-M vs. C	High (H) 40 mg P-H vs. C	Vehicle 1 (C1) P-C1 vs. C
Liver	Adenoma, Hepatocellular	1/(50)	0/(50)	1/100 (69) 0.0765	0/50 (34) 0.3301	2/50 (33) 0.2440	2/50 (32) 0.2351	2/50 (35) 0.2614
	Hemangioma	0/(50)	0/(50)	0/100 (69) 0.1916	0/50 (34) NC	0/50 (32) NC	1/50 (32) 0.3168	1/50 (35) 0.3365
	Hemangiosarcoma	0/(50)	0/(50)	0/100 (69) 0.1878	1/50 (34) 0.3301	2/50 (33) 0.1025	1/50 (32) 0.3168	1/50 (35) 0.3365
	Hemangioma/ Hemangiosarcoma	0/(50)	0/(50)	0/100 (69) 0.0593	1/50 (34) 0.3301	2/50 (33) 0.1025	2/50 (32) 0.0982	2/50 (35) 0.1111
Lung	Adenoma	3/(50)	4/(50)	7/100 (70) 0.2340	5/50 (34) 0.3441	6/50 (34) 0.2120	5/50 (32) 0.3052	5/50 (36) 0.3825
	Carcinoma	2/(50)	4/(50)	6/100 (71) 0.2296	2/50 (34) 0.5115	4/50 (34) 0.4135	4/50 (33) 0.3949	1/50 (35) 0.7397
	Adenoma/Carcinoma	5/(50)	8/(50)	13/100 (72) 0.1348	7/50 (34) 0.4740	10/50 (35) 0.1606	9/50 (33) 0.2047	6/50 (36) 0.4567
	Mesothelioma	0/(50)	0/(50)	0/100 (69) 0.3869	0/50 (34) NC	1/50 (33) 0.3235	0/50 (32) NC	0/50 (34) NC
Mammary Gland	Adenoacanthoma	0/(50)	0/(50)	0/100 (69) 0.3832	1/50 (34) 0.3301	0/50 (32) NC	0/50 (32) NC	0/50 (34) NC
	Adenoma	1/(50)	0/(50)	1/100 (69) 0.5868	0/50 (34) 0.3301	0/50 (32) 0.3168	0/50 (32) 0.3168	0/50 (34) 0.3301
	Adenocarcinoma	2/(50)	3/(50)	5/100 (70) 0.7050	1/50 (34) 0.6424	2/50 (33) 0.3986	1/50 (32) 0.6150	2/50 (36) 0.4442
	Adenocarcinoma/Adenoma	3/(50)	3/(50)	6/100 (70) 0.7837	1/50 (34) 0.7337	2/50 (33) 0.5027	1/50 (32) 0.7079	2/50 (36) 0.5517
	Sarcoma	0/(50)	0/(50)	0/100 (69) 0.3832	1/50 (34) 0.3301	0/50 (32) NC	0/50 (32) NC	0/50 (34) NC
Mesentery/Peritoneum	Hemangiosarcoma	0/(50)	0/(50)	0/100 (69) 0.1097	0/50 (34) NC	1/50 (32) 0.3168	1/50 (32) 0.3168	0/50 (34) NC

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

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle 2 0 mg	Vehicle 3 0 mg	Vehicle 2+3 (C) 0 mg (2+3) P-Trend	Low (L) 5 mg P-L vs. C	Mid (M) 15 mg P-M vs. C	High (H) 40 mg P-H vs. C	Vehicle 1 (C1) P-C1 vs. C
Ovary	Adenocarcinoma	0/(50)	0/(50)	0/100 (69)	1/50 (34)	0/50 (32)	0/50 (32)	0/50 (34)
				0.3832	0.3301	NC	NC	NC
	Adenoma	0/(50)	0/(50)	0/100 (69)	0/50 (34)	0/50 (32)	0/50 (32)	1/50 (35)
				NC	NC	NC	NC	0.3365
	Adenocarcinoma/Adenoma	0/(50)	0/(50)	0/100 (69)	1/50 (34)	0/50 (32)	0/50 (32)	1/50 (35)
				0.3832	0.3301	NC	NC	0.3365
	Cystadenoma	0/(50)	0/(50)	0/100 (69)	0/50 (34)	1/50 (32)	0/50 (32)	2/50 (35)
				0.3832	NC	0.3168	NC	0.1111
	Granulosa Cell Tumor	0/(50)	2/(50)	2/100 (69)	0/50 (34)	1/50 (32)	1/50 (32)	0/50 (34)
				0.4029	0.5534	0.6856	0.6856	0.5534
	Luteoma	1/(50)	3/(50)	4/100 (70)	6/50 (35)	0/50 (32)	2/50 (33)	2/50 (35)
				0.6890	0.0665	0.7842	0.6290	NC
	Sertoli Cell Tumor	0/(50)	1/(50)	1/100 (69)	0/50 (34)	1/50 (33)	0/50 (32)	1/50 (35)
				0.4632	0.3301	0.5446	0.3168	0.5620
Pituitary	Adenoma	0/(50)	4/(50)	4/100 (69)	2/50 (34)	1/50 (32)	0/50 (32)	3/50 (35)
				0.9189	0.6489	0.5089	0.7883	0.4369
Primary Site Undetermined	Leukemia	0/(50)	0/(50)	0/100 (69)	1/50 (34)	1/50 (33)	0/50 (32)	0/50 (34)
				0.3832	0.3301	0.3235	NC	NC
	Lymphoma	14/(50)	10/(50)	24/100 (80)	12/50 (39)	6/50 (34)	6/50 (34)	7/50 (38)
				0.9441	0.5465	0.8735	0.8735	0.8676
	Sarcoma, Histiocytic	0/(50)	3/(50)	3/100 (71)	1/50 (34)	1/50 (33)	2/50 (33)	3/50 (35)
				0.3295	0.3902	0.3785	0.5098	0.3100

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

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle 2 0 mg	Vehicle 3 0 mg	Vehicle 2+3 (C) 0 mg (2+3) P-Trend	Low (L) 5 mg P-L vs. C	Mid (M) 15 mg P-M vs. C	High (H) 40 mg P-H vs. C	Vehicle 1 (C1) P-C1 vs. C
Skin	Carcinoma, Squamous Cell	0/(50)	0/(50)	0/100 (69) 0.3832	0/50 (34) NC	1/50 (32) 0.3168	0/50 (32) NC	0/50 (34) NC
	Fibrosarcoma	1/(50)	1/(50)	2/100 (70) 0.8237	1/50 (34) 0.6994	0/50 (32) 0.5312	0/50 (32) 0.5312	1/50 (35) NC
	Hemangioma	1/(50)	0/(50)	1/100 (69) 0.5868	0/50 (34) 0.3301	0/50 (32) 0.3168	0/50 (32) 0.3168	0/50 (34) 0.3301
	Hemangiosarcoma	1/(50)	0/(50)	1/100 (70) 0.5833	0/50 (34) 0.3269	0/50 (32) 0.3137	0/50 (32) 0.3137	0/50 (34) 0.3269
	Hemangioma/ Hemangiosarcoma	2/(50)	0/(50)	2/100 (70) 0.8278	0/50 (34) 0.5491	0/50 (32) 0.5312	0/50 (32) 0.5312	0/50 (34) 0.5491
	Papilloma	0/(50)	0/(50)	0/100 (69) 0.3832	1/50 (34) 0.3301	0/50 (32) NC	0/50 (32) NC	0/50 (34) NC
	Sarcoma	0/(50)	0/(50)	0/100 (69) 0.1916	0/50 (34) NC	0/50 (32) NC	1/50 (32) 0.3168	2/50 (35) 0.1111
	Schwannoma	0/(50)	0/(50)	0/100 (69) 0.3832	1/50 (34) 0.3301	0/50 (32) NC	0/50 (32) NC	1/50 (35) 0.3365
Small Intestine	Adenocarcinoma	0/(50)	0/(50)	0/100 (69) NC	0/50 (34) NC	0/50 (32) NC	0/50 (32) NC	1/50 (35) 0.3365
Spleen	Hemangiosarcoma	0/(50)	1/(50)	1/100 (69) 0.7759	2/50 (34) 0.2527	0/50 (32) 0.3168	0/50 (32) 0.3168	0/50 (34) 0.3301
Stomach	Papilloma	0/(50)	1/(50)	1/100 (69) 0.4632	0/50 (34) 0.3301	1/50 (33) 0.5446	0/50 (32) 0.3168	1/50 (35) 0.5620
Thyroid	Adenoma, Follicular Cell	0/(50)	0/(50)	0/100 (69) 0.3832	1/50 (34) 0.3301	0/50 (32) NC	0/50 (32) NC	0/50 (34) NC
Urinary Bladder	Mesenchymal Tumor	0/(50)	0/(50)	0/100 (69) 0.1106	0/50 (34) NC	1/50 (33) 0.3235	1/50 (32) 0.3168	0/50 (34) NC

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

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle 2 0 mg	Vehicle 3 0 mg	Vehicle 2+3 (C) 0 mg (2+3) P-Trend	Low (L) 5 mg P-L vs. C	Mid (M) 15 mg P-M vs. C	High (H) 40 mg P-H vs. C	Vehicle 1 (C1) P-C1 vs. C
Uterus	Granular Cell Tumor	0/(50)	0/(50)	0/100 (69)	1/50 (34)	0/50 (32)	0/50 (32)	0/50 (34)
				0.3832	0.3301	NC	NC	NC
	Hemangioma	0/(50)	1/(50)	1/100 (69)	1/50 (34)	0/50 (32)	0/50 (32)	0/50 (34)
				0.6615	0.5534	0.3168	0.3168	0.3301
	Hemangiosarcoma	0/(50)	0/(50)	0/100 (69)	1/50 (34)	0/50 (32)	0/50 (32)	1/50 (35)
				0.3832	0.3301	NC	NC	0.3365
	Hemangioma/ Hemangiosarcoma	0/(50)	1/(50)	1/100 (69)	2/50 (34)	0/50 (32)	0/50 (32)	1/50 (35)
				0.7759	0.2527	0.3168	0.3168	0.5620
	Leiomyoma	1/(50)	0/(50)	1/100 (70)	1/50 (34)	1/50 (32)	0/50 (32)	0/50 (34)
				0.5677	0.5491	0.5312	0.3137	0.3269
	Leiomyosarcoma	0/(50)	0/(50)	0/100 (69)	0/50 (34)	0/50 (32)	1/50 (32)	0/50 (34)
				0.1916	NC	NC	0.3168	NC
	Leiomyoma/ Leiomyosarcoma	1/(50)	0/(50)	1/100 (70)	1/50 (34)	1/50 (32)	1/50 (32)	0/50 (34)
				0.3161	0.5491	0.5312	0.5312	0.3269
	Polyp, Endometrial Stromal	3/(50)	3/(50)	6/100 (69)	1/50 (34)	0/50 (32)	3/50 (32)	2/50 (35)
				0.4181	0.7398	0.9054	0.5885	0.5440
	Stromal Sarcoma, Endometrial	0/(50)	1/(50)	1/100 (69)	1/50 (34)	0/50 (32)	1/50 (32)	0/50 (34)
				0.3820	0.5534	0.3168	0.5354	0.3301
	Polyp, Endometrial Stromal/ Stromal Sarcoma, Endometrial	3/(50)	4/(50)	7/100 (70)	2/50 (34)	0/50 (32)	4/50 (33)	2/50 (35)
				0.3655	0.6147	0.9351	0.4931	0.6310
Vagina	Papilloma	0/(50)	0/(50)	0/100 (69)	0/50 (34)	1/50 (33)	0/50 (32)	0/50 (34)
				0.3869	NC	0.3235	NC	NC
Whole Body	Hemangioma	1/(50)	1/(50)	2/100 (69)	1/50 (34)	0/50 (32)	2/50 (32)	1/50 (35)
				0.2359	0.7037	0.5354	0.3776	0.2614
	Hemangiosarcoma	1/(50)	1/(50)	2/100 (70)	5/50 (34)	4/50 (33)	2/50 (32)	3/50 (36)
				0.3858	0.0363	0.0815	0.3720	0.2146
	Hemangioma/ Hemangiosarcoma	2/(50)	2/(50)	4/100 (70)	6/50 (34)	4/50 (33)	4/50 (32)	4/50 (36)
				0.2451	0.0604	0.2250	0.2117	0.2652

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

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

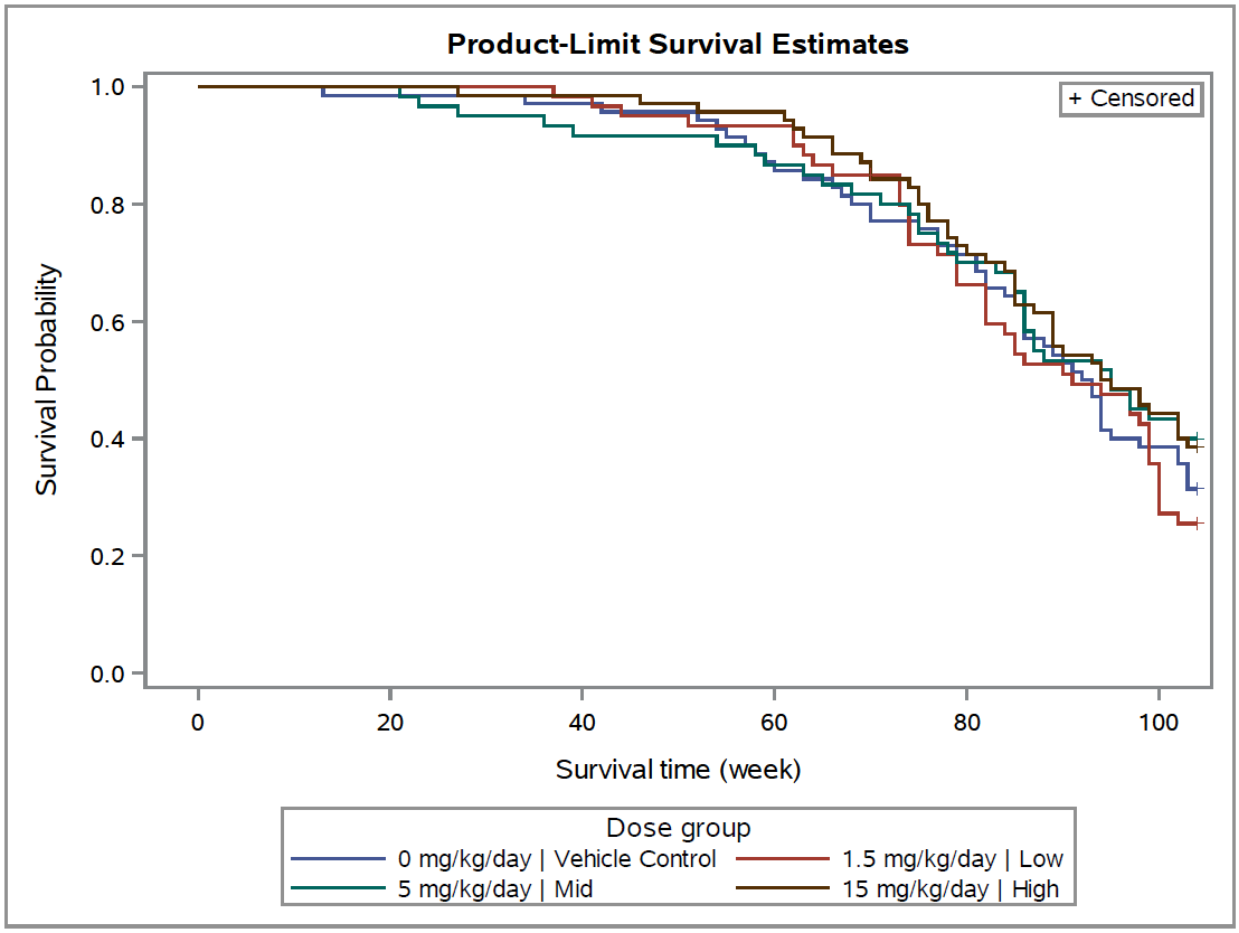


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

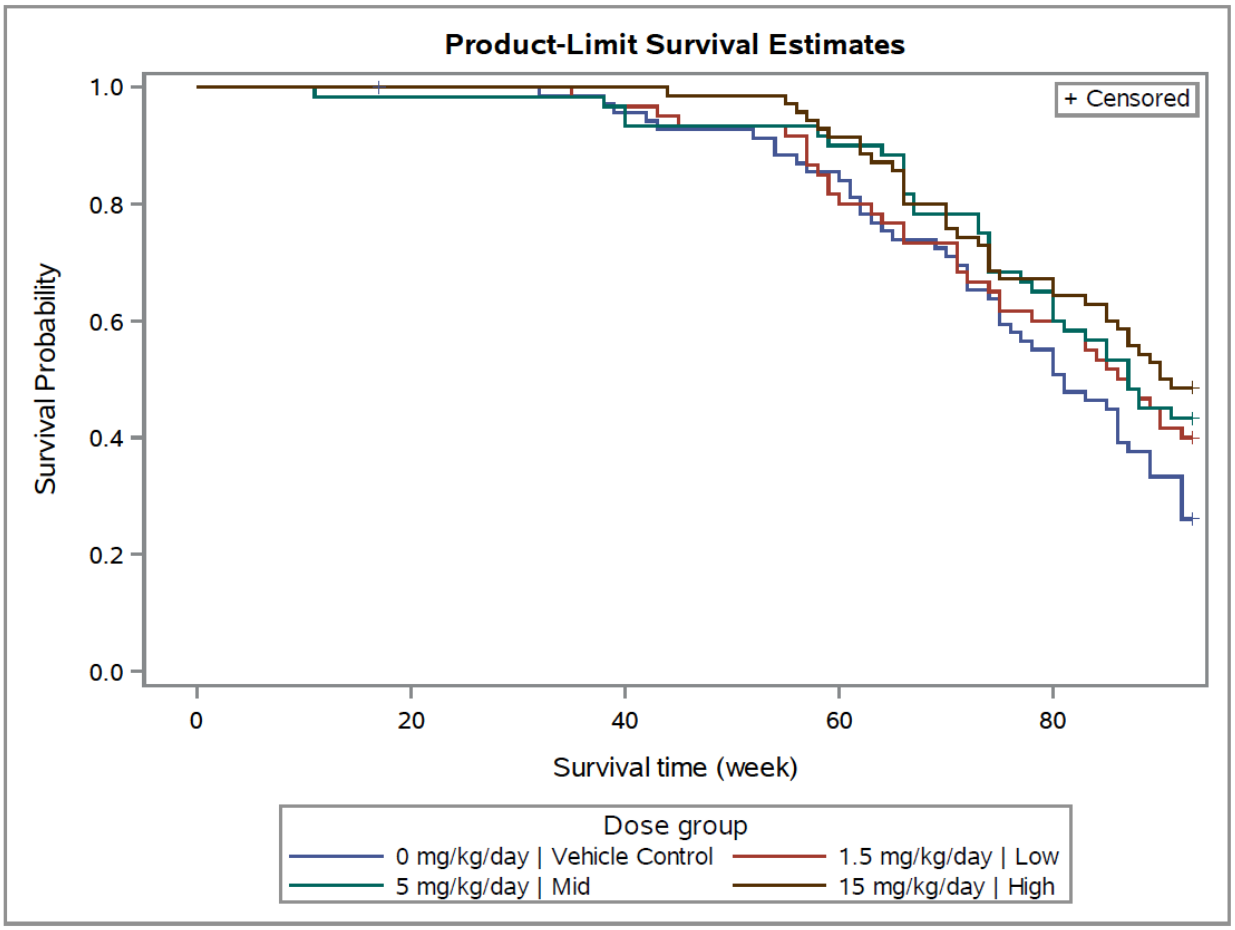


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

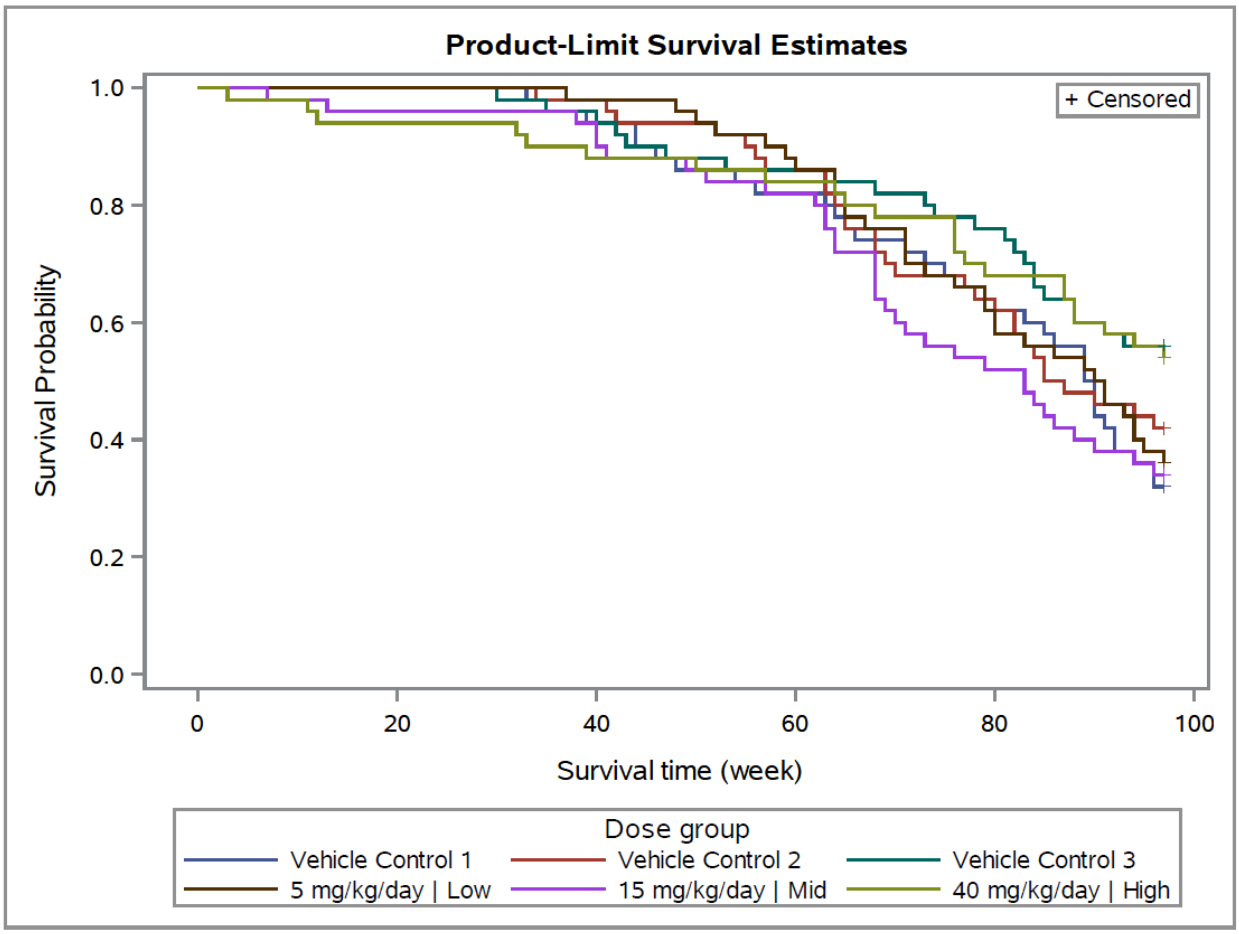
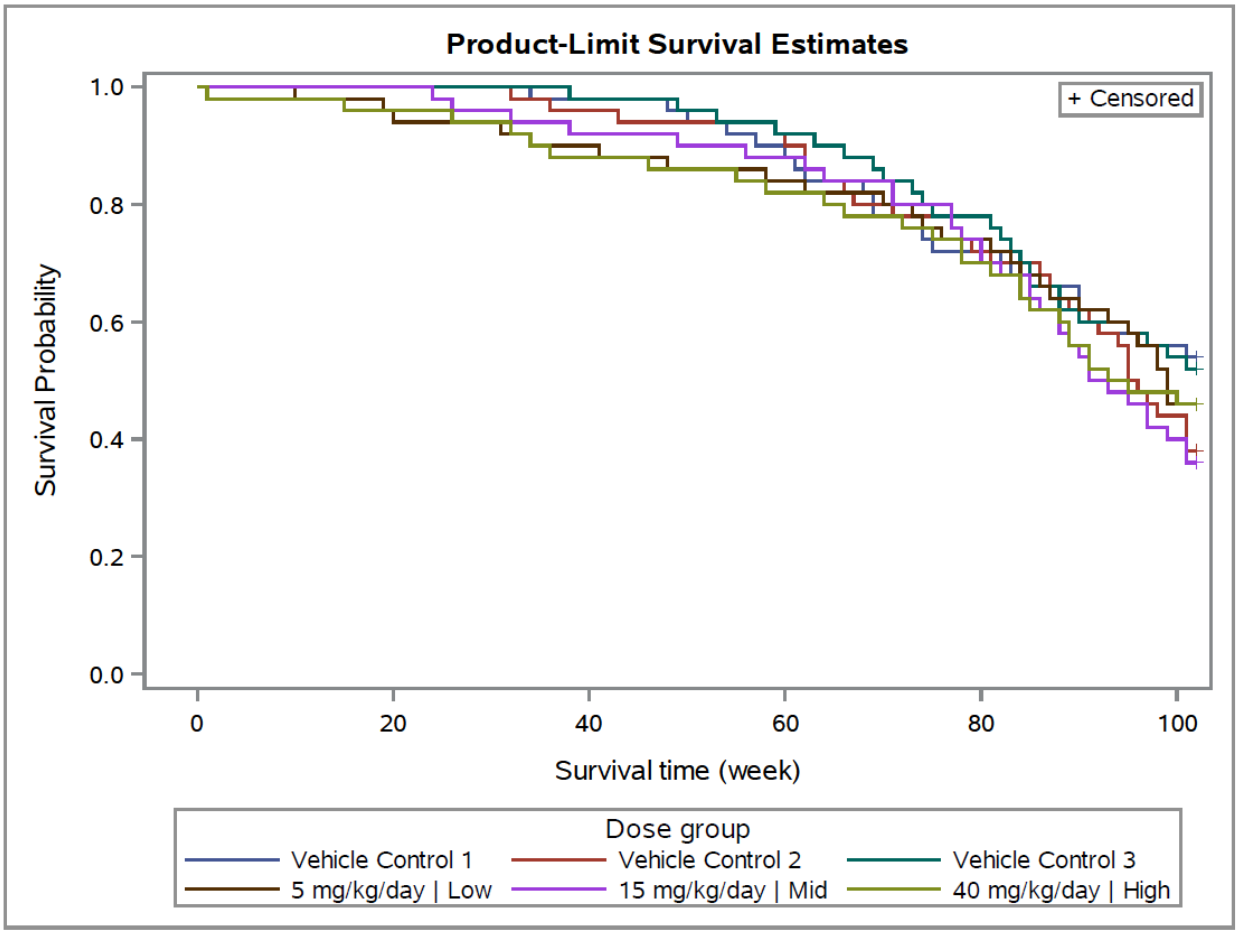


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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/s/

HEPEI CHEN
06/29/2017

KARL K LIN
06/29/2017
Concur with review

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 209806
Related IND #:	IND 122329
Product Name:	Ertugliflozin and Metformin Hydrochoride
Indication(s):	Ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride tablet, a biguanide, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, (b) (4) . The proposed doses are 2.5/500, 2.5/1000, 7.5/500, 7.5/1000 mg/mg.
Applicant:	Merck Sharp & Dohme Corporation
Dates:	Submission Date: December 19, 2016. PDUFA Date: December 19, 2017
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Alexander Cambon
Concurring Reviewers:	Yun Wang, Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Frank Pucino/Lisa Yanoff
Project Manager:	Elizabeth Godwin

Reference ID: 4058439

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

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

Trial ID*	Design**	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
P006/B1521015 (b) (4) (Add-on Study of Ert. In Combination with Metf. and Sit.)	Refer to filing review for NDA 209803	--	--	--
P007/B1521017 (Table 6) with a 78-Week Extension Ertugliflozin –T2DM-Inadequate Glycemic Control on Metformin Monotherapy.	Refer to filing review for NDA 209803	--	--	--
P002/B1521013 (b) (4) Ert. Vs. Glim. As Add-on therapy in patients inadequately controlled on Metf.	Refer to filing review for NDA 209803	--	--	--
P005- Factorial Study (b) (4) Sit. and Ert. as add-on comb. therapy with Metf. compared to individual components alone.	Refer to filing review for NDA 209803	--	--	--

* Ert.: Ertugliflozin; Sit. - Sitagliptin; Metf.-Metformin; Glim.-Glimepride; comb. – combination; all table numbers are the table numbers in the label for NDA 209806** MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled, MN:Multinational;

Reference ID: 4058439

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**NA**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	NA
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	See Filing review for NDA 209803

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	Section 5.3.5.1 / "Data Analysis Data" / " Analysis Dataset Legacy"
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	Yes
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	Adeff.xpt
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation?	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	

Reference ID: 4058439

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	x			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	x			Refer to Statistical Filing Review for NDA 209803
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	x			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	x			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None

5.2. Information Requests/Review Issues

See statistical filing review for NDA 209803

Reference ID: 4058439

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/s/

ALEXANDER CAMBON
02/17/2017

YUN WANG
02/22/2017

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 209805
Related IND #:	IND 122330
Product Name:	Ertugliflozin and Sitagliptin
Indication(s):	Ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and sitagliptin tablet, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, when treatment with both ertugliflozin and sitagliptin is appropriate. The proposed doses are (b) (4) 5/100; 15/100 mg/mg.
Applicant:	Merck Sharp & Dohme Corporation
Dates:	Submission Date: December 19, 2016. PDUFA Date: December 19, 2017
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Alexander Cambon
Concurring Reviewers:	Yun Wang, Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Frank Pucino/Lisa Yanoff
Project Manager:	Elizabeth Godwin

Reference ID: 4058415

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

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

Trial ID*	Design**	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
P006/B1521015 (Table 7) (Add-on Study of Ert. In Combination with Metf. and Sit.)	Refer to filing review for NDA 209803	--	--	--
P005- Factorial Study (b) (4) ; Sitag. and Ert. as add-on comb. therapy with Metf. compared to individual components alone.	Refer to filing review for NDA 209803	--	--	--
P017 (b) (4) Study of Initial Comb. Of Ert. and Sit.	MC, R,DB, PG, PC	Ert5+Sit/98 Ert 15+Sit/96 Placebo/96	Primary:HbA1c, 26 Wk Key Secondary: HbA1c<7% FPG Body Weight Syst. BP	(b) (4)
For studies P007, P002, and P003: see filing review for NDA 209803 – these studies are not included in label for 209805, but they are included in the ISE for 209805	--	--	--	--

* Ert.: Ertugliflozin; Sit. - Sitagliptin; Metf.-Metformin; comb. – combination; All table numbers are the numbers found in Section 14 of the label for NDA 209803**MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled, MN: Multinational; Wk-Week; FPG-Fasting Plasma Glucose; BP-Blood Pressure

Reference ID: 4058415

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	NA
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	NA
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Refer to filing review for NDA 209803

Reference ID: 4058415

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	Section 5.3.5.1 / "Data Analysis Data" / " Analysis Dataset Legacy"
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	Both
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	Adeff.xpt
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation?	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	

Reference ID: 4058415

4. Filing Issues

[*Note to Reviewer: This information is needed or essential to be able to review the application.*]

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	x			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	x			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	x			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	x			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None

5.2. Information Requests/Review Issues

See Filing Review for NDA 209803

Reference ID: 4058415

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/s/

ALEXANDER CAMBON
02/17/2017

YUN WANG
02/17/2017

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 209803
Related IND #:	IND 106447
Product Name:	Ertugliflozin
Indication(s):	Ertugliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended starting dose of ertugliflozin is 5 mg once daily, taken in the morning, with or without food. Dose may be increased to ertugliflozin 15 mg once daily in those tolerating ertugliflozin and needing additional glycemic control.
Applicant:	Merck Sharp & Dohme Corporation
Dates:	Submission Date: December 19, 2016. PDUFA Date: December 19, 2017
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Alexander Cambon
Concurring Reviewers:	Yun Wang, Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Frank Pucino/Lisa Yanoff
Project Manager:	Elizabeth Godwin

Reference ID: 4058297

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

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

Trial ID*	Design**	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
P003/B1521022 (Table 4) Ert. Monotherapy Phase A 26 Week	R, DB, PG, PC	Ert. 5mg/156 Ert. 15mg/152 Placebo/153	Primary:HbA1c, 26 Wk Key Secondary: HbA1c<7% FPG Body Weight	Per label: All endpoints p<0.001 (comparison of 5 mg vs placebo and 15 mg vs placebo –sponsor analysis)
P006/B1521015 (b) (4) (Add-on Study of Ert. In Combination with Metf. and Sit.)	MC, R, DB, PG, PC	Ert. 5mg/156 Ert. 15mg/153 Placebo/153	Primary:HbA1c, 26 Wk Key Secondary: HbA1c<7% FPG Body Weight Syst. BP	All endpoints for Ert. 5mg/15mg vs. Placebo p<.001
P007/B1521017 (Table 5) with a 78-Week Extension Ertugliflozin –T2DM-Inadequate Glycemic Control on Metformin Monotherapy.	MC,R,DB, PG, PC	Ert. 5mg/207 Ert. 15mg/205 Placebo/209	Primary:HbA1c, 26 Wk Key Secondary: HbA1c<7% FPG Body Weight Syst. BP Diast BP	Per label: First four endpoints p<.001 for both 5 mg / 15 mg vs placebo
P002/B1521013 (Table 6) Ert. Vs. Glim. As Add-on therapy (to Metformin) in patients inadequately controlled on Metf.	MC, R, DB,PG, AC, MN trial (52 wks –phase A)	+Ert. 5 mg/ 448 +Ert. 15 mg/ 440 +Glim./ 437	Primary:HbA1c 52 Wk Key Secondary: HbA1c<7% Body Weight	Per label: Non Inferiority for HbA1C (both 5mg and 15 mg), (b) (4) NI margin for primary endpoint was pre-specified (0.3%) in 9/2013 protocol
P005/B1521019- Factorial Study (b) (4); Sit. and Ert. as add-on comb. therapy with Metf. compared to individual components alone.	MC, R, DB, PG, AC	Ert. 5 mg/ 250 Ert. 15 mg/248 Sit. 100 mg/247 Ert. 5 mg+Sit 100 mg/ 243/ Ert 15mg +Sit 100 mg / 245 All Add-on Comb therapy with Metf.	Primary:HbA1c, 26 Wk Key Secondary: HbA1c<7% FPG Body Weight Syst. BP	For all endpoints, the combination of Ert. And Sit. (both Ert. 5 mg and 15 mg +Sit. 100mg), superiority was demonstrated (p>.001) vs individual components. Including rescue analysis was also significant for primary analysis (p<.001), though effect size was lower
P001 (**In Section 8.6 of Label – Renal Impairment**) with Stage 3 Chronic Kidney Disease Who Have Inadequate Glycemic Control on Background Antihyperglyc. Therapy.	MC, R, DB, PG, PC	Ert. 5 mg/158 Ert 15mg /155 Placebo/154	Primary:HbA1c, 26 Wk Key Secondary: HbA1c<7% FPG Body Weight Syst. BP	No efficacy claims were made in Section 14. In Section 8.6, it states: (b) (4)
P004 – CV Study	--	--	--	--
P017- Evaluate the Efficacy and Safety of Comb. of Ert. with Sit. in the Treatment of Subjects with T2DM with Inadequate Glycemic Control on Diet and Exercise	See Filing Review for NDA 209805	--	--	--

* Ert.: Ertugliflozin; Sit. - Sitagliptin; Metf.-Metformin; Glim.-Glimepride; comb. – combination; All table numbers are the numbers found in Section 14 of the label for NDA 209803**MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled, MN: Multinational; Wk-Week; FPG-Fasting Plasma Glucose; BP-Blood Pressure

Reference ID: 4058297

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes – all parallel group
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	NA
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	NA
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	This will be evaluated during the review. Example from protocol P005 (which is not a filing issue) : their "include rescue" sensitivity analysis approach includes data after glycemic or bariatric rescue. Hoewever for other data that are missing, the MAR* assumption of the cLDA may not be adequate.

*MAR- Missing at Random; cLDA – constrained Longitudinal Data Analysis

Reference ID: 4058297

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	Section 5.3.5.1 / "Data Analysis Data" / " Analysis Dataset Legacy"
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM are both included
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	Adeff.xpt
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation?	I was able to run sponsor's code for "including rescue" analysis for the factorial study and some of the other studies. The other studies (for example P002) have similar data sets (adeff), code and variables. More explanation was given during the walk through.
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	

Reference ID: 4058297

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	x			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	x			Table 111 in ISE (Placebo-controlled studies) has subgroup analysis including rescue. I am requesting the sponsor to send code.
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	x			I have not detected any meaningful data errors
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements				None that I have detected.

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes.

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None

5.2. Information Requests/Review Issues

I requested a walk through to make sure I understand their data files and analyses. This took place Thursday February 16, 2017 and is documented separately.

Reference ID: 4058297

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/s/

ALEXANDER CAMBON
02/17/2017

YUN WANG
02/17/2017

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 209803
Supplement #:	0001
Product Name:	Ertugliflozin tablets
Indication(s):	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant:	Merck Sharp & Dohme Corp.
Dates:	Cardiovascular Meta-Analysis Safety report submitted 12/19/2016. NDA submitted 12/20/2016
Review Priority:	Standard
Biometrics Division:	Biometrics 7
Statistical Reviewer:	Elande Baro
Statistical Team Leader:	Eugenio Andraca-Carrera
Concurring Reviewers:	Mark Levenson
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Frank Pucino (DMEP), Lisa Yanoff (DMEP)
Project Manager:	Liz Godwin (DMEP)

Reference ID: 4051770

1. Brief Summary of Controlled Clinical Trials

A cardiovascular meta-analysis (CVMA) of 9 trials was conducted to meet the FDA filing requirement to exclude an 80% increase in cardiovascular risk in ertugliflozin. These trials, which consist of Phase II and Phase III studies including a cardiovascular outcome trial, are summarized in **Error! Reference source not found.**. The CVMA includes data through study completion for 2 studies (P017/1047 and P016/1006) and utilizes data cuts of 28-MAR-2016 for non-event data (e.g., demographics) and 18-APR-2016 for cardiovascular event-based data (e.g., investigator determined and adjudicated events) for the other 7 studies.

Table 1. List of Trials Included in the Cardiovascular Meta-Analysis

Protocol / Goal	Study Design	Treatments (Sample Size for subjects randomized and treated)
P001/1016 Evaluate the Efficacy and Safety of Ertugliflozin for T2DM with Renal Impairment	Randomized, double-blind, placebo-controlled, parallel group Phase A 26 weeks, Phase B 26 weeks	○ Placebo (n=154) ○ Ertugliflozin 15 mg (n=155) ○ Ertugliflozin 5 mg (n=158) Background Therapy: Standard diabetes therapy with the exception of metformin, rosiglitazone, or an SGLT2- inhibitor
P002/1013 Evaluate the Safety and Efficacy of the Addition of Ertugliflozin Compared With the Addition of Glimepiride for T2DM	Randomized, double-blind, active-comparator- controlled, parallel group Phase A 52 weeks, Phase B 52 weeks	○ Ertugliflozin 5 mg (n=448) ○ Ertugliflozin 15mg (n=440) ○ Glimepiride up to 6 or 8 mg according to the local country label (n=437) Background Therapy: Metformin
P003/1022 Evaluate the Efficacy and Safety of Ertugliflozin monotherapy	Randomized, double-blind, placebo-controlled, parallel group Phase A 26-weeks, Phase B 26 weeks	○ Placebo (n=153) + metformin in Phase B ○ Ertugliflozin 15 mg (n=152) ○ Ertugliflozin 5 mg (n=156) Background Therapy: None
P005/1019 Evaluate the Efficacy and Safety of the Combination of Ertugliflozin with Sitagliptin Compared with Ertugliflozin Alone and Sitagliptin Alone, in the Treatment of Subjects with T2DM	Randomized double-blind, parallel-group, factorial study of co-administration of ertugliflozin and sitagliptin and administration of the individual agents Phase A 26-weeks, Phase B 26 weeks	○ Sitagliptin 100 mg (n=247) ○ Ertugliflozin 15 mg (n=248) ○ Ertugliflozin 5 mg (n=250) ○ Ertugliflozin 15 mg/sitagliptin 100 mg (n=244) ○ Ertugliflozin 5 mg/sitagliptin 100 mg (n=243) Background Therapy: Metformin
P006/1015 Evaluate the Safety and Efficacy of Ertugliflozin on top of Metformin + Sitagliptin	Randomized, double-blind, placebo-controlled, parallel group Phase A 26 weeks, Phase B 26 weeks	○ Placebo (n=153) ○ Ertugliflozin 15 mg (n=153) ○ Ertugliflozin 5 mg (n=156) Background Therapy: Metformin and Sitagliptin

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Protocol / Goal	Study Design	Treatments (Sample Size for subjects randomized and treated)
P007/1017 Evaluate the Efficacy and Safety of Ertugliflozin on top of Metformin	Randomized, double-blind, placebo-controlled Phase A 26 weeks, Phase B 78 weeks	○ Placebo (n=209) + glimepiride in Phase B ○ Ertugliflozin 15 mg (n=205) ○ Ertugliflozin 5 mg (n=207) Background Therapy: Metformin
P017/1047 Evaluate the Efficacy and Safety of the Initial Combination of Ertugliflozin with Sitagliptin for T2DM	Randomized, double-blind, placebo-controlled, parallel group Single phase, 26 weeks	○ Placebo (n=97) ○ Ertugliflozin 15 mg/sitagliptin 100 mg (n=96) ○ Ertugliflozin 5 mg/sitagliptin 100 mg (n=98) Background Therapy: None
P016/1006 Dose- ranging study to evaluate safety and efficacy in subjects with inadequate glycemic control on background therapy with metformin	Randomized, double-blind, double-dummy, placebo-controlled, parallel-group study 12-week duration	○ Ertugliflozin 1 mg (n=54) ○ Ertugliflozin 5 mg (n=55) ○ Ertugliflozin 10 mg (n=55) ○ Ertugliflozin 25 mg (n=55) ○ Placebo (n=54) ○ Sitagliptin 100 mg (n=55) Background Therapy: Metformin
P004/1021 Evaluate Cardiovascular Outcomes with Ertugliflozin Compared with Non-Ertugliflozin in subjects with T2DM	Randomized, double-blind, placebo-controlled, parallel group, event driven trial	○ Ertugliflozin 5 mg (n=1339) ○ Ertugliflozin 15mg (n=1341) ○ Placebo (n=1340) Background Therapy: Overall trial: standard of care 1) Insulin ± Metformin (substudy) 2) SU monotherapy (substudy) 3) Metformin with sulfonylurea (substudy)

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2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and Study Report(s)

Content Parameter	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			The strength of the conclusions will be discussed in the review.
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			The SAP states that the sponsor will account for the interim using a two-sided adjusted CI for the HR calculated using an O'Brien-Fleming spending function to preserve the overall Type I error rate of 2.5% with respect to the non-inferiority margin of 1.8. Adequacy of the method will be assessed during review.
Appropriate references for novel statistical methodology (if present) are included.			X	
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	X			This will be assessed in the statistical review.

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA209803\0001\m5\datasets\cvma\analysis\legacy\datasets
Dataset structure (e.g., SDTM or ADaM)	SDTM v1.1/SDTM IG v3.1.1
List the dataset(s) that contains the primary endpoint(s)	ADCV.xpt, ADCVTTE.xpt
Are the define files sufficiently detailed?	Yes
Based on the *analysis datasets*, can results of the primary endpoint(s) be reproduced?	Yes
Are there any concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

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4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
Data sets in EDR are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Any other deficiency that on their face render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements		X		

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Information Requests

None

5.2. Information Requests/Review Issues

None at this time

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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/

ELANDE N BARO
02/06/2017

EUGENIO ANDRACA-CARRERA
02/06/2017