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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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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.

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.

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