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APPLICATION NUMBER:

201281Orig1s000

STATISTICAL REVIEW(S)



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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/BLA Serial Number: NDA 201281 / Sequence 0000

Drug Name: Linagliptin/Metformin Hydrochloride Tablets

Indication(s): To improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Date(s): January 19, 2011

Review Priority: Standard (10-month)

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Keywords: NDA review, clinical studies, factorial design

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1. EXECUTIVE SUMMARY

This statistical review covers one randomized trial of co-administered linagliptin and metformin (Study 46). Other (Lina + Met) combination trials submitted by the sponsor (Studies 17, 18 and 20) were reviewed in NDA 202180, the original submission for linagliptin, therefore were not reviewed as part of the current submission.

Confirmation of efficacy: The results of the pivotal study 1218.46 support the efficacy of linagliptin add-on to metformin hydrochloride at fixed dose as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus after 24 weeks of treatment based HbA1c reduction. Particularly, the combination treatment is statistically superior to the placebo and to each corresponding component treatment after 24 weeks treatment at a 0.05 level (two-sided).

Table 1.1. Glycemic Parameter HbA1c at Week 24 for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes (LOCF)

Study population	Placebo	Lina 5 mg Once Daily	Met 500 mg Twice Daily	Lina 2.5 mg + Met 500 mg Twice Daily	Met 1000 mg Twice Daily	Lina 2.5 mg + Met 1000 mg Twice Daily
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean, SE)	8.7 (0.1)	8.7 (0.1)	8.7 (0.1)	8.7 (0.1)	8.5 (0.1)	8.7 (0.1)
Change from baseline ¹ (SE)	0.1 (0.1)	-0.5 (0.1)	-0.6 (0.1)	-1.2 (0.1)	-1.0 (0.1)	-1.6 (0.1)
Diff from placebo ¹ (95% CI)	--	-0.6 (-0.8, -0.3)	-0.8 (-1.1, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Diff from Met alone ¹ (95% CI)				-0.6 (-0.8, -0.4)		-0.5 (-0.7, -0.3)
Diff from Lina alone ¹ (95% CI)				-0.8 (-1.0, -0.6)		-1.1 (-1.4, -0.9)
achieving A1C <7% (n, %)*	7 (10.8)	14 (10.4)	27 (19.1)	44 (32.1)	43 (31.6)	76 (54.3)
Patients (% , n) receiving rescue medication	29.2 (19)	11.1 (15)	13.5 (19)	7.3 (10)	8.0 (11)	4.3 (6)

(* the numbers were based on LOCF population)

The results from the sensitivity analyses (such as MMRM, completers, and per protocol) and key secondary endpoint, fasting plasma glucose level, support the superior of the combination to the placebo and to each corresponding component treatment on both HbA1c and FPG reductions after 24 weeks treatment at a 0.05 level (two-sided).

Subgroup analyses suggest that females derive greater benefit from adding either Lina or Met to the other drug than do males.

There were no significant differences in adverse event rates between each (Lina+Met) combination and its components. Laboratory assays suggest significant elevations in some immune system reactions in patients treated by the combined (Lina+Met) drugs versus those by the component drugs.

The results from non-LOCF analysis methods (this reviewer's MMRM, completers, and per protocol) showed that linagliptin 5 mg was not statistically superior to placebo at the 0.05 alpha

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