CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-574

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-574
Name of drug:	Fortamet extended release (metformin XT)
Applicant:	Andrx Labs
Indication:	Type 2 diabetes
Documents and datasets reviewed:	\\Cdsesub1\n21574\N_000\2003-01-17\clinstat \\Cdsesub1\n21574\N_000\2002-12-17\crt\datasets
Dates:	Received 12/19/02; user fee (10 months) 10/19/03
	HFD-510
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Keywords:	NDA review, clinical studies, dropouts

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1 Summary and conclusions

The sponsor submitted data from two Phase 3, controlled trials of Fortamet (metformin XT or "XT"), an extended release oral anti-diabetic medication given once-a-day.

Study 301 was a multi-center, randomized, double-blind (double-dummy), active-controlled clinical trial in 680 patients with type 2 diabetes. The trial compared XT and Glucophage, an immediate-release oral anti-diabetic medication given twice-a-day.

Study 302 was a multi-center, randomized, double-blind (double-dummy), controlled trial in 115 Type 2 patients. The primary objective was to compare the tolerability and safety of 2000 mg and 2500 mg of XT given once a day and the same dose of Glucophage given twice a day. The rationale for the study was to provide sufficient safety data for XT at the 2 highest doses to give 100 patients at each dose for both studies combined. HbA1c data were collected but the protocol stated that "efficacy will not be evaluated" because this was not the stated objective of the trial. Trial 302 was not reviewed for efficacy.

In trial 301, XT was non-inferior to Glucophage on the primary efficacy variable, HbA1c change from baseline, using the pre-defined non-inferiority margin of 0.40. Mean changes from baseline for XT and Glucphage were 0.40 and 0.14, respectively. The least square mean treatment difference was 0.25 (2-sided 95% CI = 0.14, 0.37). XT was also statistically inferior to Glucophage since the lower bound of the CI excluded zero ($p<.0001$).

One hundred twenty-five (125, 18%) randomized patients did not complete the trial. The ratio of these dropouts in the XT : Glucophage groups was 3 to 2. Although XT was shown to be non-inferior to Glucophage for the trial as a whole, dropouts appeared to represent a significant subgroup of patients who were unable to establish diabetic control with XT. The 61 XT dropouts with on-treatment data had a mean HbA1c of 8.10, an increase of 0.73 over baseline. The 38 Glucophage dropouts with on-treatment data had a mean HbA1c of 7.38, an increase of 0.19 over baseline. The treatment difference was 0.54 for dropouts.

Eighteen (18, 5%) XT patients and 8 (2%) Glucophage patients dropped out due to a stated lack of efficacy ($p=.047$). However, the poor XT response for dropouts was not confined to patients that dropped due to lack of efficacy but was also seen for patients who dropped for other reasons as well.

The groups were similar with respect to study drug dosing, concomitant insulin and oral anti-diabetic use, and compliance. Therefore, the statistical difference between the groups on the primary endpoint could not be attributed to any imbalances between the groups in these variables.

2 Introduction

The sponsor submitted data from two Phase 3, active-controlled trials of Fortamet (metformin XT or "XT"), an extended release oral anti-diabetic medication given once-a-day.

Study 301 was a multi-center, randomized, double-blind (double-dummy), controlled trial in 680 patients with Type 2 diabetes. The trial compared XT and Glucophage, an immediate-release oral anti-diabetic medication given twice-a-day. The objective of the trial was to evaluate the non-inferiority of XT compared to Glucophage at therapeutic doses over a 6-month period on the change from baseline in HbA1c. The pre-defined non-inferiority margin was 0.4 (%).

Study 302 was a multi-center, randomized, double-blind (double-dummy), controlled trial in 115 Type 2 patients. The primary objective was to compare the tolerability and safety of 2000 mg and 2500 mg of XT given once a day and the same dose of Glucophage given twice a day. The rationale for the study was to provide sufficient safety data for XT at the 2 highest doses to give 100 patients at each dose for both studies combined. HbA1c data were collected; however, the protocol stated that "efficacy will not be evaluated" because it was not the stated objective of the trial. No power calculations were performed. (This reviewer calculated the power of the study to be approximately 21% to test for non-inferiority, given the number of patients studied and assuming the same parameter estimates from Study 301.) For these reasons, Trial 302 was not reviewed.

3 Design

Table 1 shows major design characteristics of trial 301.

Table 1. Study characteristics

Trial # Centers Dates	Patients	# randomized	Design Primary endpoint	Duration of double blind period
155-301 47 US centers 7/00 - 6/01	M and F ages 30-70 with NIDDM [1] receiving Glucophage. HbA1c ≤9% at Visit 1	Metformin XT QD n=339 Glucophage BID n=341	Randomized active-controlled double-blind Change from baseline in HbA1c	6 weeks titration followed by 20 weeks maintenance

[1] NIDDM = non insulin dependent diabetes mellitus (Type 2 diabetes)

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