

CENTER FOR DRUG EVALUATION AND RESEARCH

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NDA 21-574

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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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
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TABLE OF CONTENTS

1 Summary and conclusions	3
2 Introduction	4
3 Design	4
4 Baseline and demographic variables	6
5 Disposition	6
6 Statistical methods	8
7 Results	8
7.1 Dosing of test drug	8
7.2 Efficacy	9
7.2.1 HbA1c	9
7.2.2 Fasting plasma glucose	16
7.3 Comedications	17
7.4 Compliance	18
7.5 Assay sensitivity	18
8 Suggestions for labeling	18

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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 Glucophage 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)

Table 2 shows study visits and corresponding weeks on study.

Table 2. Study visit schedule

Period	Screening		Titration			Treatment				
Visit	1	2	3 ¹	4	5	6	7	8	9	10
Week	-2	-1	0	3	6	9	13	17	21	26

¹ Patients were randomized at Visit 3 (Week 0)

Patients entered the trial on Glucophage and were randomized at Visit 3 to XT or Glucophage. The dose of study drug (1000, 1500, 200 or 2500 mg/day) was determined from the prior Glucophage dose and Visit 2 fasting plasma glucose (FPG) level. During the first 6 weeks, the dose of XT or Glucophage was titrated up or down in 500 mg increments based on FPG. Patients remained on a fixed dose of study drug for the last 20 weeks of the study.

There were 4 types of study medication dose categories. Baseline, starting and final doses were 1000, 1500, 2000 or 2500 mg:

- Prior dose – Glucophage dose prior to entering the trial
- Baseline dose – Dose assigned at randomization based on prior Glucophage dose
- Starting dose – Actual dose taken by the patient at randomization and based on Visit 2 FPG level. Equal to the baseline dose, baseline dose + 500mg, or baseline dose – 500mg depending on FPG.
- Final dose – Dose at the end of titration

The primary objective of the trial was to evaluate the efficacy of XT in comparison to Glucophage over a 6-month treatment period.

The primary efficacy variable was change from baseline in HbA1c at endpoint.

Secondary efficacy variables were (1) changes from baseline (mean of Weeks -2 and 0) in HbA1c at Weeks 9, 13, 17 and 21; (2) changes from baseline (mean of Weeks -1 and 0) in fasting plasma glucose at Weeks 9, 13, 17, 21, 26 and endpoint; (3) changes from baseline (Week 0) in fructosamine and insulin at Weeks 9, 17, 26 and endpoint; and (4) change in dose from baseline dose to final dose.

For all efficacy variables, endpoint was defined as the last fasting value up to 3 days after the last dose.

The sponsor calculated that 240 patients per group would give 90% power assuming the true difference in HbA1c change from baseline was zero, non-inferiority margin = 0.4, SD = 1.3% and alpha (1-sided) = 2.5%. Randomization was increased to 600 total patients to account for an estimated 15-20% dropout rate. The sample size was later amended to 700 patients (see protocol amendments below for more details).

Protocol amendments

The protocol was amended twice.

Amendment 1 (dated December 18, 2000, approximately midway through the trial) increased the number of randomized patients from 600 to 700 "in order to achieve a sufficient number of evaluable patients". The actual number of desired evaluable patients (240 / group) did not change in the amendment. The sponsor did not state a rationale for the amendment, or what type of patient was considered as evaluable. In the statistical analysis, the sponsor designated 542 patients as per-protocol.

Amendment 2 (dated August 24, 2001) clarified the definitions of baseline and endpoint for all efficacy variables. The primary endpoint definition was changed from the Week 26 value to the last observation on treatment. Baseline HbA1c was defined as the mean of Visits 1 and 3 in the protocol and as the mean of Visits 1 and 2 in the statistical analysis section. The definition was clarified as the mean of Visits 1 and 3 and extended in the event that one or more of the Visit 1 or 3 data were missing.

4 Baseline and demographic variables

Race, age, weight, height and BMI patient characteristics were similar between groups for all randomized patients. The mean age was 57 years. The mean weight was 94 kg and mean BMI was 31 kg/m². 75% of patients were Caucasian, 14% Hispanic. There was a nominal imbalance (p=.029) in gender (XT, 63% males; Glucophage, 55% males) which did not translate into between-treatment differences in weight, height or BMI.

5 Disposition

Table 3 shows the number of patients on study at various time points during the study. On-study time is defined by the time of the last HbA1c measurement. 82% of patients completed the trial. About 50% more patients discontinued in the XT group (n=76) compared to the Glucophage group (n=49).

Table 3. Number of patients by weeks on study ¹

Last week on study	Metformin XT	Glucophage	Total
Week 0	339 (100%)	341 (100%)	680 (100%)
Week 3	327 (96%)	332 (97%)	659 (97%)
Week 6	320 (94%)	328 (96%)	648 (95%)
Week 9	311 (92%)	321 (94%)	632 (93%)
Week 13	298 (88%)	316 (93%)	614 (90%)
Week 17	288 (85%)	309 (91%)	597 (88%)
Week 21	280 (83%)	305 (89%)	585 (86%)
Week 26	266 (78%)	294 (86%)	560 (82%)
Completers ²	263 (78%)	292 (86%)	555 (82%)
Sponsor's ITT	313 (92%)	322 (94%)	635 (93%)
Reviewer's ITT ³	327 (96%)	332 (97%)	659 (97%)

¹ On-study time is defined by time of last HbA1c measurement.

² Sponsor's designation

³ Same as sponsor's sensitivity population

Table 4 shows numbers of dropouts and reasons for dropout. More XT patients discontinued for lack of efficacy than did Glucophage patients (n=18 vs n=8, p=.047). XT Patients withdrew consent at almost double the rate as Glucophage patients (7% vs 4%). Patients were not asked by the sponsor to state why they withdrew consent.

Withdrawals due to AE's were similar in the groups.

Table 4. Numbers of dropouts and reason for dropout

Reason	Metformin XT (n=339)	Glucophage (n=341)	Total (n=680)
AE	17 (5%)	15 (4%)	32 (5%)
Consent w/d	22 (7%)	13 (4%)	35 (5%)
Lost to F/U	6 (2%)	4 (1%)	10 (2%)
Medication non-compliance	2 (1%)	1 (<1%)	3 (<1%)
Protocol violation	4 (1%)	3 (1%)	7 (1%)
Lack of efficacy	18 (5%)	8 (2%)	26 (4%)
Other	7 (2%)	5 (1%)	12 (2%)
Total	76 (22%)	49 (14%)	125 (18%)

6 Statistical methods

The sponsor compared treatment groups on HbA1c change from baseline using ANCOVA with treatment group and center as main effects and baseline HbA1c as a covariate. Non-inferiority was assessed using a 97.5% one-sided CI (upper bound only) for the difference in least square means (XT change from baseline minus Glucophage change from baseline) and a non-inferiority margin of 0.4.

The sponsor employed 3 analysis populations: intent-to-treat (ITT), per-protocol and sensitivity. The ITT population consisted of patients with on-treatment data and such that the last value was no later than 3 days of the last dose. HbA1c values had to be fasting as well. The sensitivity population consisted of all patients with any on-treatment data, consistent with the commonly applied definition of ITT.

This reviewer constructed 2-sided 95% CI's for the treatment difference for HbA1c to assess non-inferiority. The 2-sided 95% CI yields the same upper bound as the 97.5% one-sided CI and also provides a lower bound ("best case") for the treatment effect. The sensitivity population and completers were examined.

7 Results

7.1 Dosing of test drug

Final mean daily doses were similar for the 2 groups, 2112mg for XT and 2122mg for Glucophage. Table 5 shows cross-classifications for the start and final doses of XT and Glucophage by treatment group. The shaded numbers in the Table are the numbers of patients whose final dose increased from their starting dose. Only a few patients in each group had their dose titrated down.

A slightly greater % of Glucophage patients had dose increases during titration (137/341; 40%) compared to XT patients (120/339; 35%). For patients with dose increases, the mean increase was 688mg for XT and 653mg for Glucophage. Overall, mean dose changes from start to final dose were similar between groups (XT, +256mg; Glucophage, +235mg).

None of the dose differences was statistically significant.

Table 5. Number of patients by starting dose and final dose

Start dose (mg / day)	Final dose (mg/ day)				Total
	1000	1500	2000	2500	
Metformin XT					
1000	43	9	11	3	66
1500	0	14	19	28	61
2000	0	4	49	50	103
2500	0	0	1	108	109
All doses	43	27	80	189	339
Glucophage					
1000	34	16	8	2	60
1500	0	26	22	30	78
2000	1	2	35	59	97
2500	0	0	0	106	106
All doses	35	44	65	197	341

Shaded cells show patients whose final dose was increased over their starting dose

7.2 Efficacy

7.2.1 HbA1c

Table 6 shows the analysis results for this reviewer's ITT analysis at Week 26, equivalent to the sponsor's sensitivity analysis. Mean changes from baseline for XT and Glucophage were 0.40 and 0.14, respectively. The least square mean treatment difference was 0.25 (95% CI = 0.14, 0.37). The upper bound of the 2-sided 95% confidence interval (CI) for the mean was 0.37, smaller than the pre-defined non-inferiority margin of 0.40. XT was therefore non-inferior to Glucophage according to the pre-defined criterion to establish efficacy.

All 3 analysis populations gave roughly similar results on the primary endpoint. For the completers population, the LS mean treatment difference was 0.18 (upper bound of CI = 0.30).

The FDA disqualified the investigator at Center [] unchanged when data from the 9 patients at this site [] removed from the analysis.

[] Results were [] were

**Table 6. HbA1c (%) results
Reviewer's ITT population (LOCF) ¹**

	Metformin XT (n=327)	Glucophage (n=332)
Baseline		
Mean (SD)	7.04 (0.88)	7.07 (0.76)
Range	L	J
Endpoint		
mean (SD)	7.44 (1.09)	7.21 (0.97)
Completers ² mean (SD)	7.29 (0.99)	7.19 (0.98)
Change from baseline		
Mean (SE)	0.40 (0.04)	0.14 (0.04)
Min	L	J
Max	L	J
Adjusted mean ³ (SE)	0.41 (0.05)	0.16 (0.05)
Adj. treatment difference		
Mean (SE)		0.25 (0.06)
95% CI ⁴		(0.14, 0.37)

¹ Same as sponsor's sensitivity analysis

² Sponsor's designation

³ Adjusted for center and baseline HbA1c

⁴ Sponsor calculated one-sided 97.5% CI which gives equivalent upper bound

Because the lower bound of the CI for the mean difference excluded zero, XT was also statistically inferior to Glucophage ($p < .0001$) in addition to being clinically non-inferior. The statistical difference is illustrated graphically in Figure 1 which shows the cumulative distribution functions (CDF) of the primary endpoint for each treatment group. The graph shows a clear separation in the CDF's between groups.

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Figure 1
Cumulative Distribution functions
HbA1c change at Week 26
(Metformin XT n=327; Glucophage n=332)

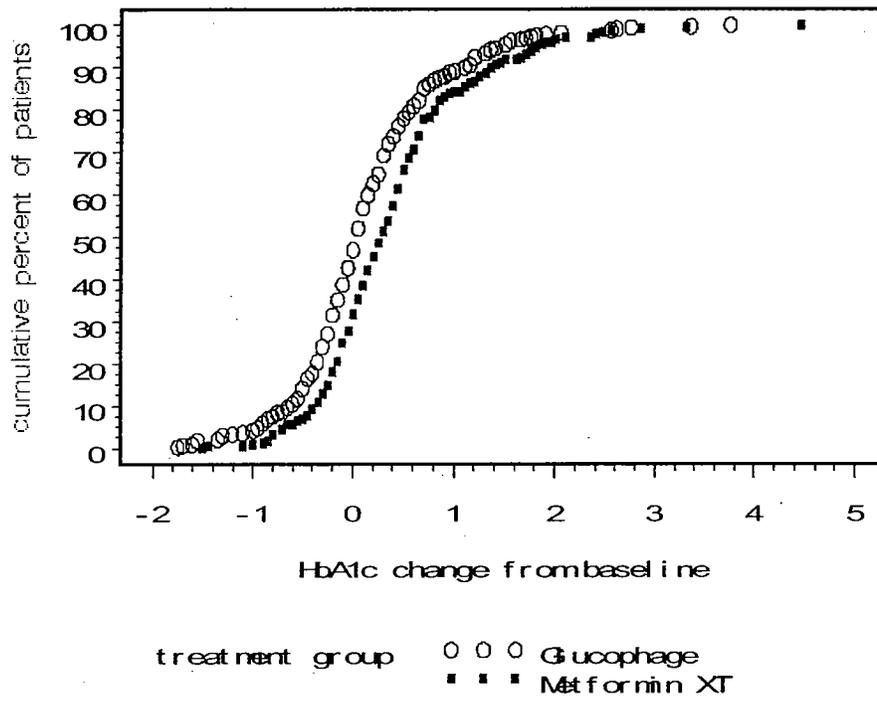


Figure 2 shows individual data for HbA1c change from baseline. Regression lines are drawn for each group.

Figure 2
HbA1c change from baseline by baseline HbA1c
(Metformin XT n=327; Glucophage n=332)

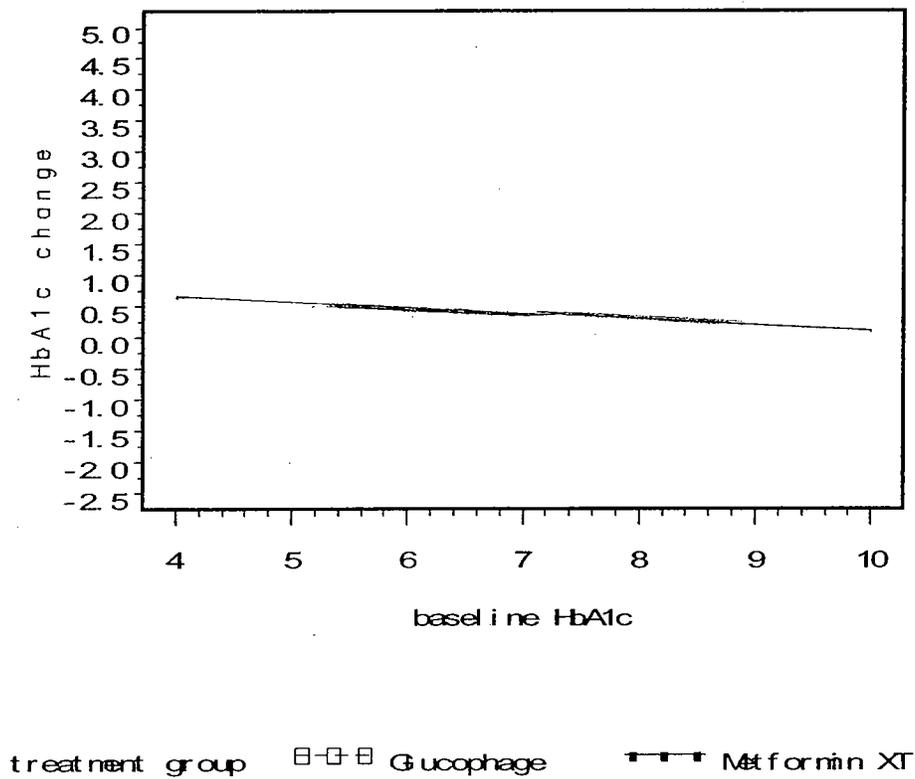
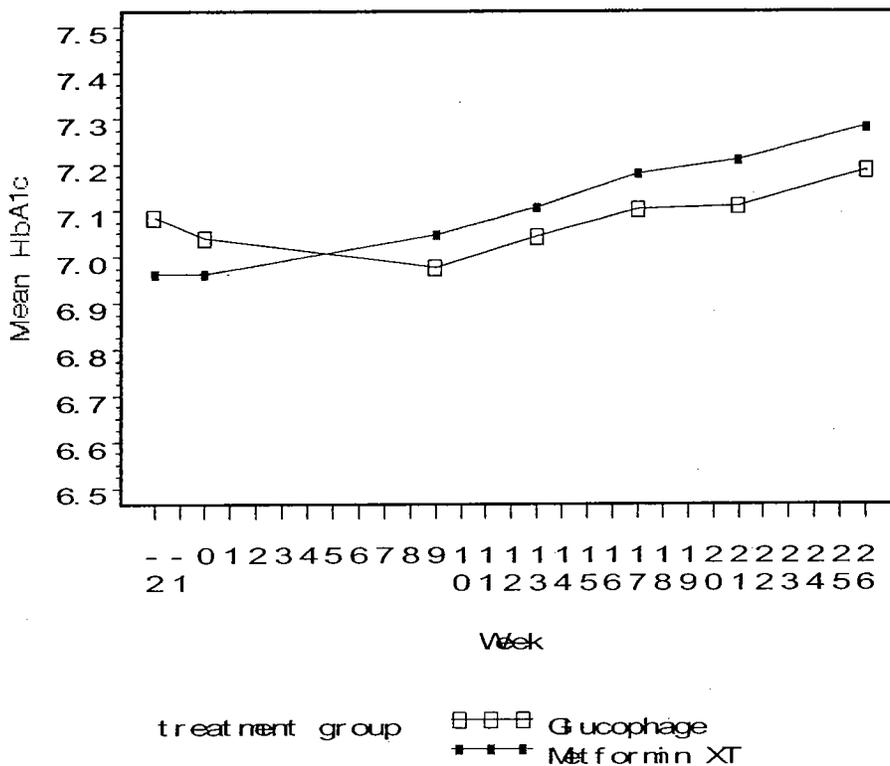


Figure 3 shows mean HbA1c change from baseline over time (weeks) for completers. The time courses in the two groups from Weeks 9-26 are similar. Up to Week 9, however, XT patients experienced an increase in HbA1c whereas Glucophage patients experienced a decrease. This pattern up to Week 9 is not explained by the dosing data showing the 2 groups had comparable titrations.

The graph does not show time-course data for dropouts. Dropouts will be analyzed in more detail in the next section.

Figure 3
 Mean HbA1c for completers
 Metformin XT n=263; Glucophage n=292



Dropouts

Table 7 shows mean the HbA1c change from baseline by dropout cohorts. Dropout cohorts are mutually exclusive groups of patients defined by the time of last HbA1c on study. The combined dropout cohorts on XT experienced a mean 0.73 increase in HbA1c from baseline compared with a 0.19 increase on Glucophage (shaded row in the Table). The mean treatment difference was 0.54.

**Table 7. Mean HbA1c change from baseline by dropout cohort ¹
Reviewer's ITT population**

Dropout cohort	Metformin XT (n=327)	Glucophage (n=332)	Treatment Difference (SE)
Week 3	0.46 (n=7)	0.03 (n=4)	0.44 (0.46)
Week 6	0.21 (n=9)	0.61 (n=7)	-0.41 (0.56)
Week 9	0.60 (n=13)	0.08 (n=5)	0.52 (0.36)
Week 13	0.46 (n=10)	0.04 (n=7)	0.42 (0.45)
Week 17	0.83 (n=8)	0.08 (n=4)	0.76 (0.58)
Week 21	1.44 (n=14)	0.17 (n=11)	1.26 (0.39)
Weeks 3 to 21 combined	0.73 (n=61)	0.19 (n=38)	0.54 (0.19)
Week 26 ²	0.32 (n=266)	0.14 (n=294)	0.18 (0.06)

¹ Dropout cohorts are mutually exclusive groups of patients defined by the time of last HbA1c on study.

² Cohort contains data for all completers plus 5 non-completers with Week 26 data. Two completers in the cohort did not have Week 26 data. Their last data on study was Week 21.

This reviewer compared age, sex, race and baseline HbA1c characteristics between dropouts and completers (Table 7, last 2 rows) to see whether there were factors that might have contributed to the observed difference in responses. Only baseline HbA1c was statistically different between completers (mean 7.01) and dropouts (mean 7.30) ($p=.001$).

Table 8 further explores HbA1c responses for all dropouts. Interestingly, patients who dropped due to AE's had a mean treatment difference of 0.65, higher than the mean for all dropouts (not shown in Table). The poor XT response for

dropouts was therefore not confined to patients that dropped due to a stated lack of efficacy.

Table 8. HbA1c for Dropouts with data – Reviewer’s ITT LOCF

	Metformin XT (n=61)	Glucophage (n=38)	Treatment Difference
Baseline			
Mean (SD)	7.37 (0.94)	7.19 (0.91)	0.18
Median	7.45	7.13	0.32
Endpoint			
Mean (SD)	8.10 (1.28)	7.38 (0.90)	0.72
Median	7.80	7.10	0.70
Change from Baseline			
Mean (SD)	0.73 (0.95)	0.19 (0.91)	0.54
Median	0.50	-0.03	0.53

Longitudinal analysis

To further investigate the impact of dropouts, I conducted a post-hoc analysis of the repeated measures data over time (longitudinal data) using a mixed model with patient as a random effect. The purported strengths of longitudinal models are that they use multiple observations on the same patient, provide a method for handling missing data, and allow the examination of treatment effects over time.

The model was:

$$\text{HbA1c change from baseline} = \text{baseline HbA1c} + \text{group} + \text{week} + \text{center} + \text{group*week} + \text{baseline HbA1c*week}$$

Twenty-seven (27, 4%) patients in the sensitivity population had Week 3 or Week 6 HbA1c data. The data at these early, sparse time points were deleted so that the model could converge. The analysis involved a total of n=2906 observations at Weeks 9, 13, 17, 21 and 26.

The treatment contrast at Week 26 (0.26) was almost identical to the LOCF result (95% CI = 0.14, 0.38). The mean treatment effect did not vary significantly over the time period examined (p=.27).

Response rate

This reviewer performed post-hoc analyses of response rates using a criterion for response suggested by Robert Misbin, the reviewing Medical Officer. A positive response was defined as a change from baseline in HbA1c of less than +0.7, a negative response as a change of +0.7 or greater. The 0.7 figure, while somewhat arbitrary, was chosen because it corresponded to the smallest effect size seen in placebo controlled trials for Type 2 diabetes drugs approved to date by the Medical Division and also represents an approximate 10% increase in HbA1c over baseline for patients in the trial. Table 9 shows response rates for each group.

Table 9. HbA1c response rates at Week 26 (ITT - LOCF) ¹

	Metformin XT	Glucophage
Response rates	246/327 (75%)	276/332 (83%)
p-value (Fisher's exact test)	.013	

¹ A positive response for a patient was defined as a HbA1c Week 26 change from baseline < +0.7

An analysis using a responder cutoff of 0.5 gave similar results.

7.2.2 Fasting plasma glucose

Table 10 shows this reviewer's FPG results for the sponsor's ITT population (all values fasting; last value within 3 days of last dose of study drug). The 95% CI for the difference in least square mean change from baseline was (0.6, 12.3) measured in mg/dL units. These results agreed with the sponsor's results.

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**Table 10. Fasting Plasma glucose (mg/dL) results
Sponsor's ITT population (LOCF) ¹**

	Metformin XT (n=329)	Glucophage (n=333)
Baseline		
Mean (SD)	146.7 (31.8)	145.6 (29.4)
Range	(78, 251.5)	(72, 236)
Endpoint		
mean (SD)	156.8 (48.5)	149.8 (41.2)
Completers ¹ mean (SD)	148.8 (37.7)	148.7 (40.9)
Change from baseline		
Mean (SE)	10.1 (2.2)	4.2 (2.0)
Adjusted mean ² (SE)	11.0 (2.4)	4.5 (2.4)
Adj. treatment difference		
Mean (SE)		6.5 (3.0)
95% CI		(0.6, 12.3)
p-value		0.03

¹ Sponsor's designation

² Adjusted for center and baseline HbA1c

7.3 Comedications

Table 11 shows insulin use during the trial by WHO drug preferred term (specific).

Table 11. Number of patients taking insulins and insulin analogues

	Metformin XT	Glucophage
Insulin and analogues total	26	23
Insulin	7	3
Insulin human	2	3
Insulin human injection, isophane	11	14
Insulin human semisynthetic	0	1
Insulin human zinc suspension	6	11
Insulin injection, biphasic	0	1
Insulin injection, isophane	6	3
Insulin isophane human semisynthetic	0	1
Insulin lispro	1	2
Insulin zinc suspension	0	2

The same approximate numbers of patients in both groups were taking insulin or analogues; however, 16 of 23 (70%) Glucophage patients taking insulins took multiple insulins vs just 6 of 26 (23%) XT patients. Results for the primary

endpoint were essentially unchanged (95% CI for treatment difference = 0.14, 0.38) when patients taking one or more insulins were removed from the analysis.

The analysis above was repeated for patients taking concomitant glibenclamide or glipizide (XT, n=144; Glucophage, n=157), the most frequently prescribed Type 2 oral anti-diabetic medications. Statistical results were similar for patients taking either medication and patients taking neither medication.

7.4 Compliance

Compliance rates were similar in the groups, 96% for XT and 97% for Glucophage. The compliance rate was presumably calculated as

$$\text{Compliance} = 100\% - (\# \text{ tablets returned} / \# \text{ tablets dispensed})$$

7.5 Assay sensitivity

Although Glucophage is an established, standard treatment for Type 2 diabetes, one could ask whether the drug was effective in the trial since patients receiving Glucophage experienced a mean increase in HbA1c over baseline. This result might call the assay sensitivity of the trial into question.

Assay sensitivity can be directly inferred in placebo controlled trials whenever a drug is shown to be superior to placebo. In active control trials, where the goal is to show non-inferiority, evidence of assay sensitivity usually cannot be inferred in the same way since there is typically not a placebo group present. Evidence of assay sensitivity typically comes from historical data outside the trial. In the current trial without a placebo control, however, assay sensitivity can be inferred from the trial itself since one of the treatments (Glucophage) was shown to be statistically superior to the other (XT).

8 Suggestions for labeling

1. Study 302 was a tolerability and safety study and not powered for efficacy. Efficacy data should not be labeled. Safety data can be put in the Adverse Reactions section of the label.
2. Table 5 -- present 2-sided CI's for HbA1c treatment difference
3. Figure 2 -- show results for completers and SE bars instead of SD.

4. The text describing results for LDL-C, HDL-C, TC and TG can be deleted since Tables 6 and 7 have the same information. Table 6 may be unnecessary.
5. Although Study 301 showed XT to be non-inferior to Glucophage on HbA1c, dropouts fared poorly on XT. A significant percentage of these dropouts were due to a stated lack of efficacy. The label should incorporate these data in some appropriate fashion.

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