CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-386

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/Serial Number: 22-386 (original 22-232)/000

Drug Name: PrandiMet ™ (repaglinide/metformin fixed dose combination tablets)

Intended Indication(s): Indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual repaglinide and metformin therapy is appropriate.

Applicant: Novo Nordisk Inc.

Submission Date(s): August 15, 2007

Review Priority: Standard

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1. EXECUTIVE SUMMARY

PrandiMetTM tablets (repaglinide/metformin hydrochloride (HCl) fixed dose combination (FDC) tablets) were developed based on marketed products repaglinide tablets and metformin tablets. The non-proprietary names of the two drug substances in the FDC tablets are repaglinide and metformin hydrochloride. The solid dosage form tablets are for oral use and are produced in two strengths:

- Repaglinide 1 mg, metformin HCl 500 mg
- Repaglinide 2 mg, metformin HCl 500 mg

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The sponsor stated, "Clinical trial AGEE-053, originally submitted with the repaglinide NDA 20-741, demonstrates that combination therapy with repaglinide and metformin provides a level of glycemic control significantly greater than that of each individual component alone. Furthermore, the bioequivalence trial NN4440-1753 establishes that fixed dose combination tablets are bioequivalent to concomitantly administered repaglinide and metformin."

Note: New Drug Application is abbreviated by NDA. Tables and Figures presented in this document are referenced by "below" or "above". Those referenced with an extended numbering system are in the NDA Study Report.

1.1 Conclusions and Recommendations

These are open-label studies. I do not know how it has been guaranteed that no bias could occur; e.g., evaluation bias.

Apart from issues of credibility, the data available to me provide the statistical evidence in favor of the superiority of the combination repaglinide/metformin to the pooled group of the two arms metformin alone and gliclazide alone. The data do not provide the statistical evidence in favor of the superiority of the combination repaglinide/metformin to gliclazide alone.

Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6: Study AGEE-3017

	N	LS Mean (SE)	95% CI
Analysis of HbA_{1c} changes, No Adjustment			
Repaglinide/Metformin	148	-2.134 (0.11)	[-2.342, -1.926]
Gliclazide	70	-1.920 (0.15)	[-2.223, -1.617]
Metformin	78	-1.387 (0.15)	[-1.674, -1.100]
Repaglinide/Metformin – Gliclazide		-0.214 (0.19)	[-0.581, 0.154]
Repaglinide/Metformin – Metformin		-0.747 (0.18)	[-1.101, -0.392] *
Analysis of HbA_{1c} changes, Adjusting for Centre			
Repaglinide/Metformin	148	-2.029 (0.12)	[-2.261,-1.796]
Gliclazide	70	-1.819 (0.16)	[-2.135,-1.502]
Metformin	78	-1.275 (0.15)	[-1.570,-0.980]
Repaglinide/Metformin – Gliclazide		-0.210 (0.18)	[-0.565, 0.145]
Repaglinide/Metformin – Metformin		-0.754 (0.17)	[-1.096,-0.412] *

*: Statistically significant, $p < 0.001$.

Changes in HbA1c (%) from Baseline to End-of-Trial: Study AGEE/DCD/053/AUS

	Mean (SEM)	95% CI
ANOVA of HbA_{1c} changes, No Adjustment		
Repaglinide/Metformin	-1.41 (0.23)	[- 1.87, - 0.95] *
Repaglinide	- 0.38 (0.23)	[- 0.84, 0.08]
Metformin	- 0.33 (0.24)	[- 0.80, 0.15]
Repaglinide/Metformin – Repaglinide	- 1.03 (0.32)	[- 1.78, - 0.29] *
Repaglinide/Metformin – Metformin	- 1.08 (0.33)	[- 1.84, - 0.33] *
ANOVA of HbA_{1c} changes Adjusting for Centre		
Repaglinide/Metformin	- 1.40 (0.23)	[- 1.86, - 0.94] *
Repaglinide	- 0.34 (0.23)	[- 0.80, 0.13]
Metformin	- 0.32 (0.25)	[- 0.81, 0.18]
Repaglinide/Metformin – Repaglinide	- 1.06 (0.32)	[- 1.81, -0.32] *
Repaglinide/Metformin – Metformin	- 1.08 (0.33)	[- 1.84, - 0.33] *

*: Statistically significant, $p < 0.05$.

1.2 Brief Overview of Clinical Studies

Trial ID	Study Design	TRX Duration	Regimens	Total No. Subjects	Endpoints
Efficacy and Safety Trial (OAD-Naïve)					
AGEE-3017	Multicentre, randomised, open-label, 3-arm comparison trial. Subjects were randomised in a 2:1:1 ratio to receive repaglinide/ metformin combination therapy, gliclazide monotherapy, or metformin monotherapy. The study consisted of a 4-week run-in period, a 4-week titration period, and a 12-week maintenance period. Enrolled subjects had diabetes for at least 3 months, had no pharmaceutical treatment for the previous 3 months, and had shown inadequate glycemic control using diet and exercise alone (HbA1c ≥ 7.0% and ≤ 12.0%, FPG ≥ 131 mg/dL, 2-hr PPG ≥ 208 mg/dL). There were 15 sites, in China, Malaysia, Philippines, and Thailand.	16 weeks	**Repaglinide/Met** Initial doses = 0.5 mg repaglinide/meal and 500 mg metformin at dinner. Repaglinide could be titrated up to 2 mg/meal based upon 2-hr PPG targets, metformin up to 1500 mg/day based upon FPG targets. **Gliclazide** Initial dose = 80 mg/day (once daily). Gliclazide could be titrated up to 320 mg/day (160 mg BID) based upon FPG targets. **Metformin** Initial dose = 500 mg BID. Metformin could be titrated up to 2500 mg/day based upon FPG targets.	322 subjects with type 2 diabetes randomised	**Primary:** HbA_{1c} **Secondary:** FPG, 2-hr PPG, 7-point glucose profiles (FPG and prandial glucose increase), fasting lipids, treatment satisfaction questionnaires

Cross reference: Module 5.3.5.1, study reports AGEE/DCD/053/AUS and AGEE-3017; Module 5.3.1.2, study report NN4440-1753.

Efficacy and Safety Trial (OAD Monotherapy Failures)					
AGEE/ DCD/ 053/ AUS	Multicentre, randomized, double-blind, double-dummy, 3-arm comparison trial. Patients received metformin for a 4- to 5-week baseline period, followed by a 4- to 8-week repaglinide dose titration period, followed by a 3-month maintenance period. Enrolled patients had inadequate glycaemic control (HbA_{1c} > 7.1%) using prior metformin therapy at clinically appropriate doses. All patients received two products (including placebo as appropriate) during the titration and maintenance periods. There were 9 study sites, all in Australia.	4 to 5 months	**Repaglinide/Met** Initial dose = 0.5 repaglinide/ meal, not to exceed 4 mg/meal, adjusted during titration period. 1 to 3 g metformin daily, constant throughout trial. **Repaglinide** Initial dose = 0.5 repaglinide/ meal, not to exceed 4 mg/meal, adjusted during titration period. **Metformin** 1 to 3 g metformin daily, constant throughout trial.	83 patients with type 2 diabetes randomised	**Primary:** HbA_{1c}, FPG **Secondary:** Fasting insulin, fasting C-peptide, HBGP, lipids

1.3 Statistical Issues and Findings

These are open-label studies. I do not know how it has been guaranteed that no bias could occur; e.g., evaluation bias.

I do not agree with the sponsor's argument for open-label, "This trial was conducted as an open-label trial (see Section 5.1). Blinding was considered unfeasible due to the number of tablet administration necessary to maintain blinding, given the different timing of administration of the different treatments." Placebo tablets can easily be used for all the time-slots, even if the drug does not need to be administered for a particular arm, to maintain the blind.

In Study 3017, the sponsor did not plan to show that the combination is superior to each component. The primary analysis was the comparison between the repaglinide/metformin combination therapy arm and the pooled gliclazide and metformin monotherapy arms.

Apart from issues of credibility, the data available to me provide the statistical evidence in favor of the superiority of the combination repaglinide/metformin to the pooled group of the two arms metformin alone and gliclazide alone. The data does not provide the statistical evidence in favor of the superiority of the combination repaglinide/metformin to gliclazide alone.

2. INTRODUCTION

PrandiMetTM tablets (repaglinide/metformin hydrochloride (HCl) fixed dose combination (FDC) tablets) were developed based on marketed products repaglinide tablets and metformin tablets.

PROPOSED INDICATIONS AND USAGE

• PrandiMet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual repaglinide and metformin therapy is appropriate.

Important limitations for use: Prandi*Met* should not be used in patients with type 1 diabetes, for the treatment of diabetic ketoacidosis or patients with known hypersensitivity to repaglinide, metformin hydrochloride or any inactive ingredients in Prandi*Met*.

2.1 Overview

Repaglinide is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM). Repaglinide, S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues.

Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is an oral blood glucose-lowering drug of the biguanide class. Metformin HCl is not chemically or pharmacologically related to any other classes of oral antihyperglycaemic agents.

PrandiMet combines two anti-hyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes.

Repaglinide Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations. Repaglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at specific sites. This potassium channel blockade depolarizes the ß-cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle. Metformin hydrochloride Metformin HCl is an anti-hyperglycemic agent, which improves glucose tolerance

in patients with type 2 diabetes by lowering both the basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objectives of Study	Study Design and Type of Control	Test Products, Dosage Regimen, Route of Administration	No. of Subjects: TOTAL	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status: Type of Report
Efficacy	AGEE/DCD/053/AUS	Module 5.3.5.1 AGEE/ DCD/053/ AUS CTR	Efficacy and Safety	Multicenter, randomized, double-blind, double-dummy, 3-arm comparison trial. Comparisons between metformin monotherapy, repaglinide monotherapy and metformin/repaglinide combination therapy (1:1:1)	**Repaglinide/Metformin** Initial dose = 0.5 repaglinide/ meal, not to exceed 4 mg/meal, adjusted during titration period. 1 to 3 g metformin daily, constant throughout trial. **Repaglinide** Initial dose = 0.5 repaglinide/ meal, not to exceed 4 mg/meal, adjusted during titration period. **Metformin** 1 to 3 g metformin daily, constant throughout trial.	83	Type 2 Diabetes; Inadequate glycaemic control (HbA_{1c} > 7.1%) using prior metformin therapy.	6 months (4- to -5 week baseline period where all patients were on metformin monotherapy followed by a 4- to -8 week repaglinide titration period and a 3 month maintenance period where patients were assigned to one of the 3 treatments).	Completed; full
Efficacy	AGEE-3017	Module 5.3.5.1 AGEE-3017 CTR + Module 5.3.5.1 AGEE-3017 Suppl. Tables	Efficacy and Safety	Multicenter, randomised, open-label, 3-arm comparison trial. Comparisons between repaglinide/ metformin combination therapy, gliclazide monotherapy, or	**Repaglinide/Metformin Combination Therapy** Initial doses = 0.5 mg repaglinide/meal and 500 mg metformin at dinner. Repaglinide could be titrated up to 2 mg/meal based upon 2-hr PPG targets, metformin up to 1500 mg/day based upon FPG targets.	322	Type 2 diabetes for at least 3 months; OAD naïve with inadequate glycemic control using diet and exercise alone (HbA_{1c} ≥ 7.0% and ≤ 12.0%, FPG ≥ 131 mg/dL, 2-hr PPG ≥ 208	16 weeks (4 weeks titration, 12 weeks maintenance)	Completed; full

The most important difference between the two clinical trials AGEE/DCD/053/ AUS and AGEE-3017 was that AGEE/DCD/053/AUS enrolled subjects who had previously failed oral monotherapy, while study AGEE-3017 enrolled OAD-naïve patients, resulting in a somewhat higher duration of diabetes and somewhat higher incidence of pre-existing complications of diabetes in study AGEE/DCD/053/ AUS as compared to AGEE-3017. The two studies AGEE/DCD/053/AUS and AGEE-3017 showed small differences in the overall incidence of pre-existing neuropathy (15.9% vs. 19.0%) or pre-existing retinopathy (8.5% vs. 2.5%); however the reported overall incidence of pre-existing nephropathy was notably higher in the population of study AGEE/DCD/ 053/AUS (14.6% vs. 1.2%). The age of enrolled subjects was also slightly younger for study AGEE-3017 than AGEE/DCD/053/AUS. Average weight and average BMI values of enrolled subjects were also somewhat lower for study AGEE-3017 than AGEE/DCD/053/AUS, perhaps due to differences of ethnic origin in populations (Australian demographics vs. Asian).

Subject Disposition: Studies AGEE/DCD/053/AUS and AGEE-3017

	AGEE/DCD/053/AUS (OAD Monotherapy Failure Subjects)		
	Repaglinide/Metformin N (%)	**Repaglinide** N (%)	**Metformin** N (%)
Randomised	27 (100)	29 (100)	27 (100)
Completed	27 (100)	26 (90)	21 (78)
Discontinued	0	3 (10)	6 (22)
Adverse events	0	1 (3)	2 (7)
Ineffective therapy	0	0	1 (4)
Non-compliance	0	2 (7)	1 (4)
Other reason	0	0	2 (7)

	AGEE-3017 (OAD-Naïve Subjects)		
	Repaglinide/Metformin N (%)	**Gliclazide** N (%)	**Metformin** N (%)
Randomised	163 (100)	77 (100)	82 (100)
Completed	129 (79)	61 (79)	68 (83)
Discontinued	34 (21)	16 (21)	14 (17)
Adverse events	1 (<1)	0	1 (1)
Ineffective therapy	0	1 (1)	0
Non-compliance	9 (6)	5 (6)	4 (5)
Other reason	24 (15)	10 (13)	9 (11)

Demographic and Baseline Characteristics:

	AGEE/DCD-053/AUS (OAD Monotherapy Failure Subjects)			AGEE-3017 (OAD-Naive Subjects)		
	Repaglinide/Metformin	Repaglinide	Metformin	Repaglinide/Metformin	Gliclazide	Metformin
Total Subjects Randomised				163	77	81
Total Subjects Treated	27	28	27			
Sex, N (%)						
Male	9 (33.3)	13 (46.4)	10 (37.0)	69 (42.3)	32 (41.6)	40 (49.4)
Female	18 (66.7)	15 (53.6)	17 (63.0)	94 (57.7)	45 (58.4)	41 (50.6)
Age, years						
Mean (SD)	57.23 (8.34)	60.33 (7.66)	57.75 (9.49)	50.7 (11.5)	48.6 (12.1)	51.0 (9.1)
Min – Max	43.97 – 74.04	46.32 – 72.01	40.46 – 73.74	21.0 – 79.0	19.0 – 75.0	25.0 – 69.0
Ethnic origin, N (%)						
Caucasian	26 (96.3)	26 (92.9)	23 (85.2)	-	-	-
India	1 (3.7)	0	0	-	-	-
Oriental or Chinese	0	2 (7.1)	2 (7.4)	-	-	-
Other	0	0	2 (7.4)	-	-	-
Weight, kg						
Mean (SD)	92.50 (16.64)	86.49 (18.05)	90.96 (21.32)	67.1 (12.8)	66.7 (13.8)	67.3 (11.8)
Min – Max	62.00 – 122.00	56.00 – 122.00	58.10 – 138.00	39.5 – 115.0	44.5 – 114.2	46.0 – 100.0
BMI, kg/m^2						
Mean (SD)	33.20 (5.60)	31.15 (7.18)	31.78 (5.99)	26.1 (3.9)	25.8 (3.8)	25.9 (3.9)
Min – Max	21.89 – 47.07	20.57 – 54.95	22.98 – 45.25	19.1 – 38.2	19.2 – 39.5	19.1 – 36.9
Duration of Diagnosed Diabetes, years						
Mean (SD)	3.89 (2.45)	3.24 (3.25)	4.14 (3.71)	2.70 (4.1)	2.13 (3.1)	2.81 (3.7)
Min – Max	0.70 – 9.37	0.64 – 15.89	0.59 – 15.92	0.0 – 32.96	0.0 – 13.62	0.0 – 21.35
Total Subjects Randomised				163	77	81
Total Subjects Treated, N	27	28	27			
Retinopathy, N (%)						
No	26 (96.3)	26 (92.9)	23 (85.2)	159 (97.5)	74 (96.1)	80 (98.8)
Yes	1 (3.7)	2 (7.1)	4 (14.8)	4 (2.5)	3 (3.9)	1 (1.2)
Nephropathy, N (%)						
No	22 (81.5)	25 (89.3)	23 (85.2)	162 (99.4)	76 (98.7)	79 (97.5)
Yes	5 (18.5)	3 (10.7)	4 (14.8)	1 (0.6)	1 (1.3)	2 (2.5)
Neuropathy, N (%)						
No	23 (85.2)	25 (89.3)	21 (77.8)	132 (81.0)	61 (79.2)	67 (82.7)
Yes	4 (14.8)	3 (10.7)	6 (22.2)	31 (19.0)	16 (20.8)	14 (17.3)
HbA_{1c}, %						
Mean (SD)	8.32 (0.89)	8.58 (1.29)	8.63 (1.09)	9.22 (1.3)	9.18 (1.4)	9.00 (1.4)
Min – Max	7.20 – 10.30	7.30 – 12.30	7.20 – 10.70	7.00 – 12.00	7.00 – 12.00	7.00 – 11.70

Cross reference: Module 5.3.5.1, study report AGEE/DCD/053/AUS Tables 6-1, 6-2, 6-3; Module 5.3.5.1, AGEE-3017 Supplemental Tables 2 and 3.

2.2 Data Sources

Location of the NDA in EDR (electronic documents room):
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Statistical Amendments:

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STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This Section contains the Subsections **Study Design and Endpoints; Patient Disposition, Demographic and Baseline Characteristics; Statistical Methodologies; Results and Conclusions**.

A list of abbreviation and definition of terms has been provided in the sNDA and is reproduced in this document as Appendix I.

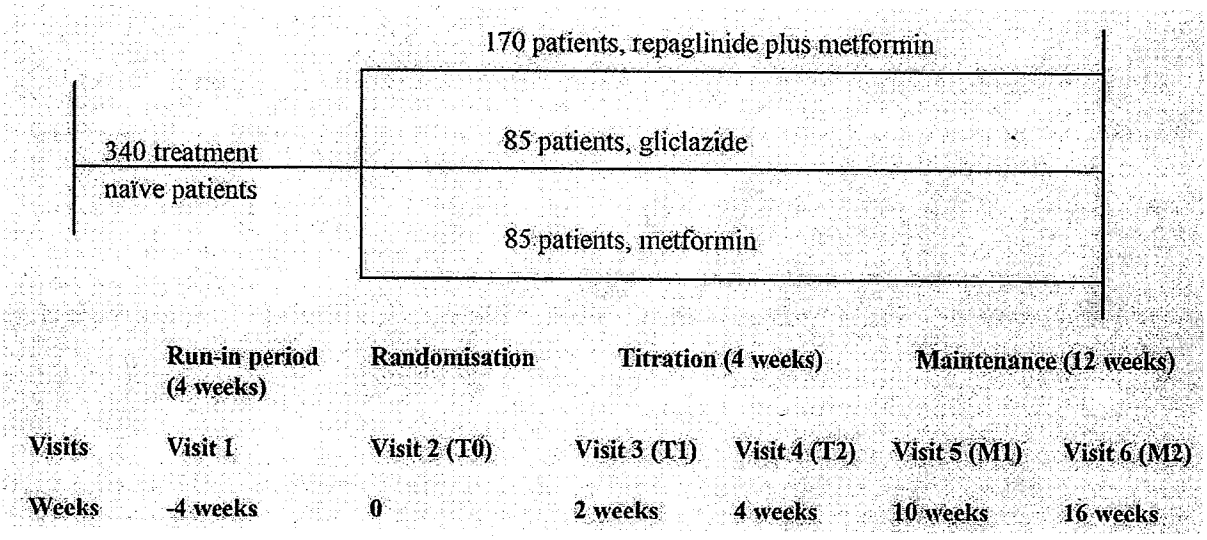
3.1.1 Study AGEE-3017

Study Design and Endpoints

This was a multi-centre, multinational, open-label, randomized, parallel group trial of 16 weeks duration.

The trial included a screening visit to assess subjects' eligibility followed by a 4- week run-in period and randomization to either combination treatment or monotherapy for a 4-week titration period followed by a 12-week maintenance period.

At the end of the trial all subjects continued on commercially available treatment. There was no follow-up period.



Treatment Regimen

Repaglinide and Metformin Combination Therapy

Repaglinide 0.5 mg, 1 mg and 2 mg tablets were supplied. Subjects started with 0.5 mg repaglinide per meal from visit 2. They were instructed to take one dose with each main meal, usually three main meals (breakfast, lunch and dinner) per day, but not less than two and not more than four meals per day. When a meal was omitted, the dose was not taken. Subjects also started with 500 mg metformin in the evening per day from visit 2.

After 2 weeks of titration, if the FPG (4.2–6.2 mmol/L) and 2-hr PPPG (< 10.4 mmol/L) targets were not achieved, the dose of repaglinide was titrated up to a maximum of 2 mg and metformin up to a maximum of 1500 mg. The titration continued until the treatment goals were achieved at the end of the 4-week titration period (visits 2 and 4).

The titration of repaglinide was done based on 2-hr PPPG and metformin based on FPG values recorded in the patient diaries.

Metformin Monotherapy

Metformin 500 mg tablets were supplied. Treatment was initiated as 500 mg twice daily and titrated up to a maximum of 2500 mg based on FPG. Starting dose and dose adjustments were performed at the investigators' discretion and manufacturer's local product information.

Gliclazide Monotherapy

Gliclazide 80 mg tablets were supplied. Treatment was initiated as 80 mg once daily and titrated up to a maximum of 320 mg (divided over 160 mg) based on FPG. Starting dose and dose adjustments were performed at the investigator's discretion and manufacturer's local product information.

Trial Population

A total of 340 subjects were planned to be enrolled in the trial. The inclusion and exclusion criteria reflected the intent of enrolling a wide range of subjects, while excluding those who exhibited poor compliance and those with poor function of organ systems involved in drug/glucose metabolism.

Variables for Evaluation

The purpose of the trial was to determine whether there was a difference between combination therapy of repaglinide and metformin and conventional treatment with a sulphonylurea or metformin in monotherapy for the following variables:

· The primary endpoint of the efficacy assessment of glycaemic control was the change in HbA1c from visit 2 to visit 6.

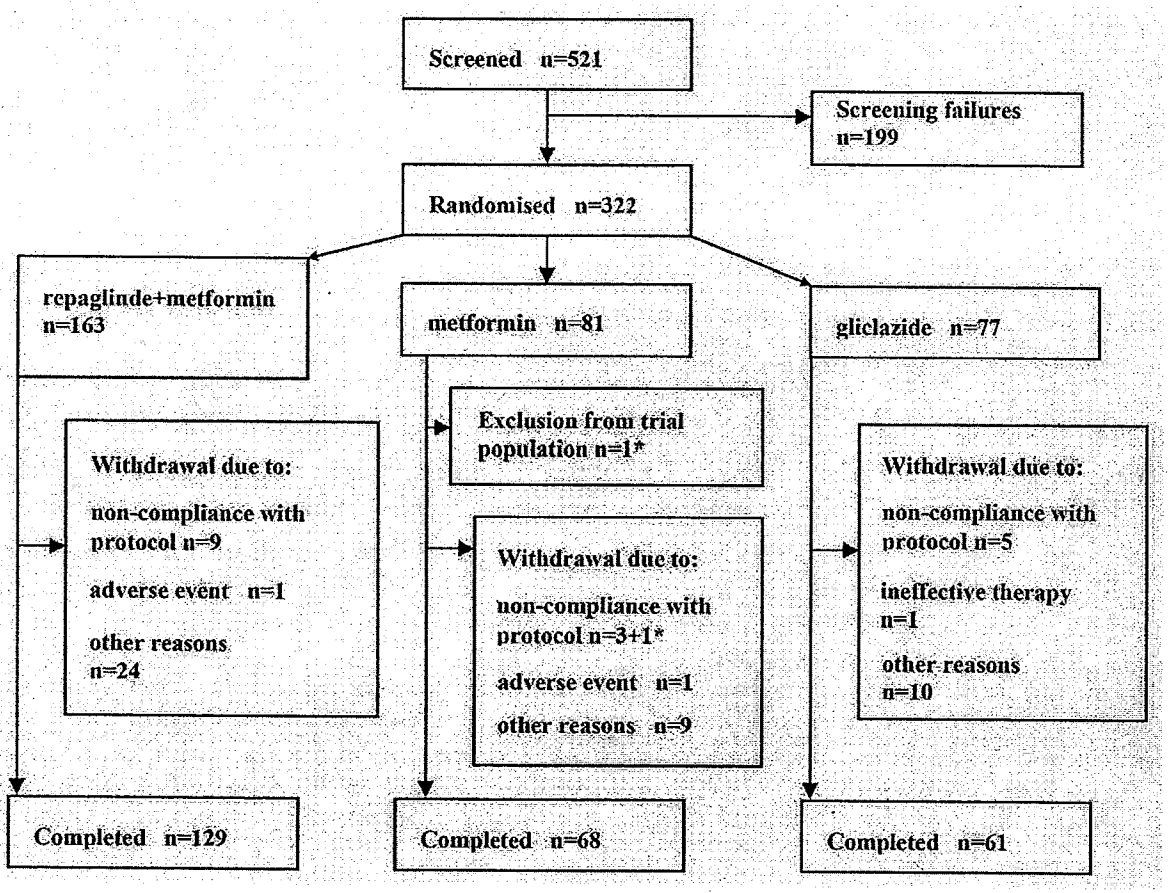
The secondary efficacy endpoints included the changes from visit 2 to visit 6 in FPG, 2-hr PPPG, 7-pt PG profile (change from pre-visit 3 to visit 6 in FPG and visit 6 mean delta PG), fasting lipids, QoL assessment and treatment satisfaction.

· Safety – adverse events (AEs), hypoglycaemic events, physical examination, vital signs and electrocardiogram (ECG), haematology and biochemistry.

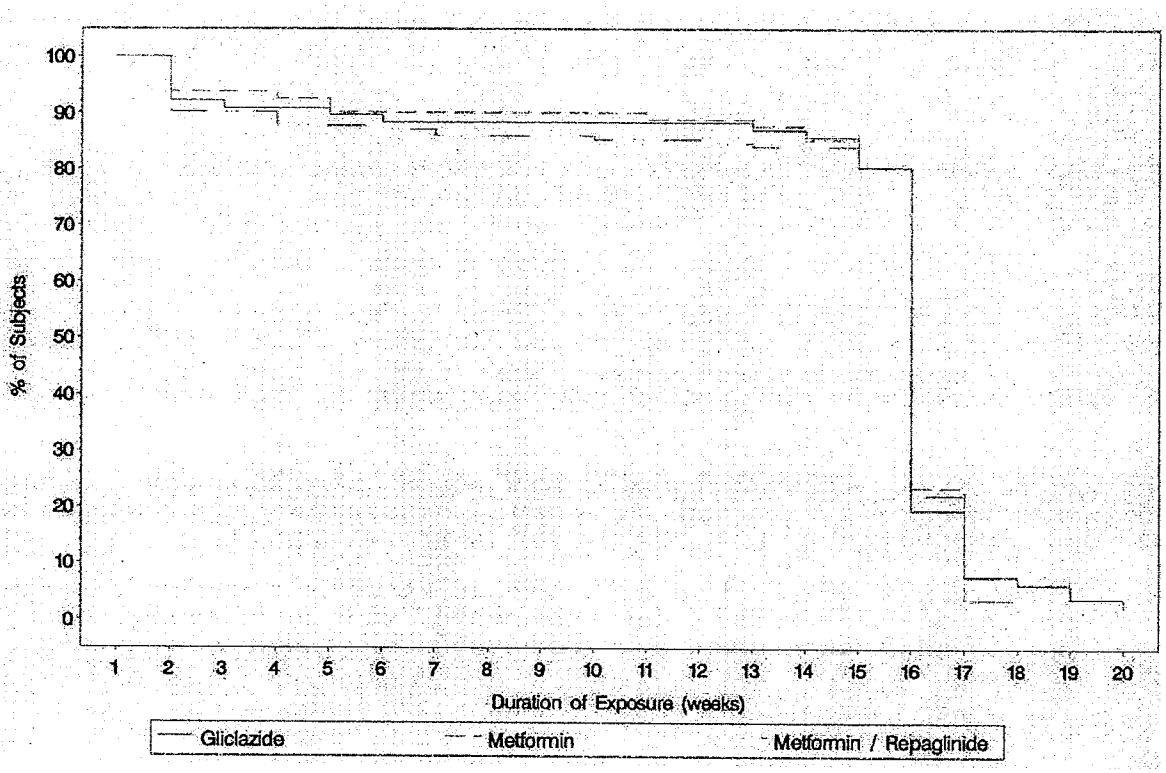
Patient Disposition

As summarised in Figure below, 322 subjects were randomised to three treatment groups in the ratio 2:1:1 with 163 subjects in repaglinide and metformin combination therapy, 82 subjects in metformin monotherapy and 77 subjects in gliclazide monotherapy.

One subject from the metformin monotherapy group was wrongly randomised to receive repaglinide and metformin therapy and thus excluded from ITT population.



Cumulative treatment exposure for the ITT population



The numbers of subjects exposed to study drug at the start of the trial were 81, 77, and 163 subjects in the gliclazide, metformin, and metformin/repaglinide groups, respectively. Twenty subjects across the three treatment groups (4, 5, and 11 subjects in the gliclazide, metformin, and metformin/repaglinide groups, respectively) did not have exposure information after the first treatment day (Visit 2). Although it is not known when these twenty subjects stopped taking treatment during the trial, they were removed from the cumulative exposure at Week 2.

As shown in Table below, 258 subjects completed the trial, with 129 subjects from repaglinide and metformin combination therapy and 129 subjects from the two monotherapy groups (68 subjects from metformin monotherapy and 61 subjects from gliclazide montherapy). Of the 321 subjects from ITT population, 175 subjects (54%) fulfilled the criteria for PP population.

Subject Disposition

	MET/GLI	MET+REP	Total
Screened			521
Randomised	159 (100%)	163 (100%)	322 (100%)
Withdrawals	30 (19%)	34 (21%)	64 (20%)
Primary Reason for Withdrawal			
Adverse Event	1 (0.6%)	1 (0.6%)	2 (0.6%)
Ineffective Therapy	1 (0.6%)	0 (0.0%)	1 (0.3%)
Non-Compliance with Protocol	9 (5.7%)	9 (5.5%)	18 (5.6%)
Other	19 (11.9%)	24 (14.7%)	43 (13.4%)
Completed	129 (81%)	129 (79%)	258 (80%)
Analysis Population			
Intention to Treat (ITT)	158 (99%)	163 (100%)	321 (100%)
Per Protocol (PP)	91 (57%)	84 (52%)	175 (54%)

1 subject from Metformin monotherapy was excluded from ITT analysis.

Demographic and Baseline Characteristics

The demographic and baseline characteristics are shown in Tables below.

Mean age was 50.7 years for combination therapy and 49.8 years for monotherapy groups. Overall, there were more female subjects (57.7% and 54.4%) than male subjects (42.3% and 45.6%) in both the combination therapy and monotherapy groups. Mean weight was similar in all treatment groups (67.1 kg and 67.0 kg). BMI was 26.1 kg/m2 for combination therapy and 25.8 kg/m2 monotherapy groups.

Demographic and Baseline Characteristics:

	MET/GLI	MET+REP
Number of Subjects Exposed	158	163
Age, years		
N	157	163
Mean (SD)	49.8 (10.7)	50.7 (11.5)
Median	50.0	51.0
Min - Max	19.0 - 75.0	21.0 - 79.0
Sex, N (%)		
Female	86 (54.4%)	94 (57.7%)
Male	72 (45.6%)	69 (42.3%)
Weight, kg		
N	158	163
Mean (SD)	67.0 (12.8)	67.1 (12.8)
Median	66.0	66.0
Min - Max	44.5 - 114.2	39.5 - 115.0
Height, cm		
N	158	163
Mean (SD)	1.61 (0.09)	1.60 (0.10)
Median	1.60	1.60
Min - Max	1.41 - 1.90	1.35 - 1.85
BMI, kg/m^2		
N	158	163
Mean (SD)	25.8 (3.9)	26.1 (3.9)
Median	25.6	25.5
Min - Max	19.1 - 39.5	19.1 - 38.2
BP Systolic, mmHg		
N	158	163
Mean (SD)	125 (17.8)	125 (17.5)
Median	125	120
Min - Max	90.0 - 177	90.0 - 179
BP Diastolic, mmHg		
N	158	163
Mean (SD)	78.9 (10.3)	78.0 (9.0)
Median	80.0	80.0
Min - Max	50.0 - 100	58.0 - 100
Pulse, beats/minute		
N	158	163
Mean (SD)	77.8 (9.6)	78.1 (10.2)
Median	78.0	78.0
Min - Max	55.0 - 111	50.0 - 119

No major imbalance is seen between the treatment arms.

As shown in Table below, there was not much difference in duration of diagnosed diabetes between the combination therapy group (2.70 years) and monotherapy group (2.48 years). Diabetes complications such as retinopathy, nephropathy, neuropathy and macroangiopathy were absent in 81.0% of the subjects in all treatment groups.

HbA1c at visit 1 was similar in both treatment groups at 9.2% for combination therapy and 9.1% for monotherapy groups.

Diabetes History:

	MET/GLI	MET+REP
Number of Subjects Exposed	158	163
Duration of Diagnosed Diabetes, years		
N	158	163
Mean (SD)	2.48 (3.4)	2.70 (4.1)
Median	1.19	1.12
Min - Max	0.00 - 21.35	0.00 - 32.96
Retinopathy, N (%)		
No	154 (97.5%)	159 (97.5%)
Yes	4 (2.5%)	4 (2.5%)
Nephropathy, N (%)		
No	155 (98.1%)	162 (99.4%)
Yes	3 (1.9%)	1 (0.6%)
Neuropathy, N (%)		
No	128 (81.0%)	132 (81.0%)
Yes	30 (19.0%)	31 (19.0%)
Macroangiopathy, N (%)		
No	149 (94.3%)	159 (97.5%)
Yes	9 (5.7%)	4 (2.5%)
HbA1c at Visit 1, %		
N	158	163
Mean (SD)	9.1 (1.4)	9.2 (1.3)
Median	9.0	9.1
Min - Max	7.0 - 12.0	7.0 - 12.0

Statistical Methodologies

The following is quoted from the Statistical Analysis Plan, dated Feb. 13, 2004:

"3 Analysis Sets

Patients once withdrawn or dropped out cannot be included again and patients leaving the trial prematurely will not be replaced.

The ITT population will consist of all subjects who were randomized, exposed to at least one dose of the trial product or who return for at least one visit after treatment initiation. This would include data from subjects who withdraw or drop out.

The PP population will consist of all subjects who were exposed to trial product, and who have not violated inclusion and exclusion criteria, and did not meet any withdrawal criteria or any other aspect in the protocol in general.

Overall compliance with the trial medication, based on the overall trial period assessment and the by visit assessment. As the dosing is relative to number of meals per day (between 2 and 4 per day), the drug compliance is interpreted in a broader manner. Compliance is defined as taking more than 80% of the lower range and less than 110% of the higher range of suggested medication during the period of treatment.

The exclusion of a subject or observation from the PP population must be a joint decision of the trial manager, medical writer and the statistician. The subjects or observations to be excluded and the reason for their exclusion must be documented and signed by all parties. All these must take place before the database release.

Efficacy analyses will be based on both ITT and PP populations.

Safety analyses will be based on the ITT population defined above.

All other tables and graphs will be based on ITT population unless otherwise stated.

Statistical Methodology

The null hypothesis of interest is: no difference between combination therapy (repaglinide and metformin) and monotherapy (gliclazide or metformin monotherapy).

Comparison of combination therapy versus the two individual monotherapies will not be made as the study is not powered to do so. Rather the two monotherapy groups will be combined together for testing.

The main statistical analysis will be made on ITT population. All tests will be two-sided with a significance level of 5%.

The analysis of FPG and mean delta PG will be carried out following the LOCF principle.

6.1 Efficacy Endpoints Primary Efficacy Endpoint

Change in HbAlc (from Visit 2 to 6)

6.2 Primary Analysis Analysis of variance (ANOVA) techniques will be used for comparison of HbAlc between the combination therapy and monotherapy groups. The two monotherapy groups will be combined together for testing.

Estimates for the mean difference for each of the three treatment groups will be given together with the 95% confidence interval. The treatment difference between combination and each of the two monotherapies will also be estimated. However, statistical testing will not be performed.

6.3 Presentation of Primary Endpoint The results of all statistical analyses will be tabulated. HbAlc results will be fwrther summarised by visit.

HbAIc will be presented graphically by visit, showing mean curve with 95% confidence limits. A subject-by-subject listing of HbAlc values at Visit 1,2 and 6 will be provided.

6.4 Secondary Endpoints Secondary Efficacy Endpoints

Change in FPG (Visit 2 to 6) Change in 2hr post-prandial plasma glucose (Visit 2 to 6) 7-point glucose profile (mean delta PG at Visit 6, Change in FPG from Visit 3 to 6) Change in Fasting lipids (Visit 2 to 6) Quality of life assessment Treatment satisfaction

6.5 Secondary Analyses Secondary Endpoints

As there are three 7-point plasma glucose profiles recorded in Visit 3, the average of the first two 7-point profiles will be presented as Pre-Visit 3 and the last one as Visit 3.

The change of FPG for analysis means the change of the plasma glucose before breakfast from Pre-Visit 3 to Visit 6.

All secondary endpoints, except Quality of life assessment and Treatment satisfaction, will be analysed using ANOVA model. Covariate adjustments will be made if indicated by the data. A superiority test will be performed between combination therapy and monotherapy groups. The treatment difference (combination therapy - monotherapy) will be estimated. However, statistical testing will not be performed for one to one comparison.

For the analysis of QoL endpoints, Kruskal-Wallis test will be applied between the combination therapy and monotherapy groups.

WHO-DTSQ questionnaire: scores of items 1,4, 5, 6,7 and 8 will be totaled. For items 2 and 3, analysis will be done separately.

WHO- 10 Well-Being Index questionnaire: scores will be totaled."

Results and Conclusions

The ITT analysis included 321 subjects while the PP analysis included 175 subjects.

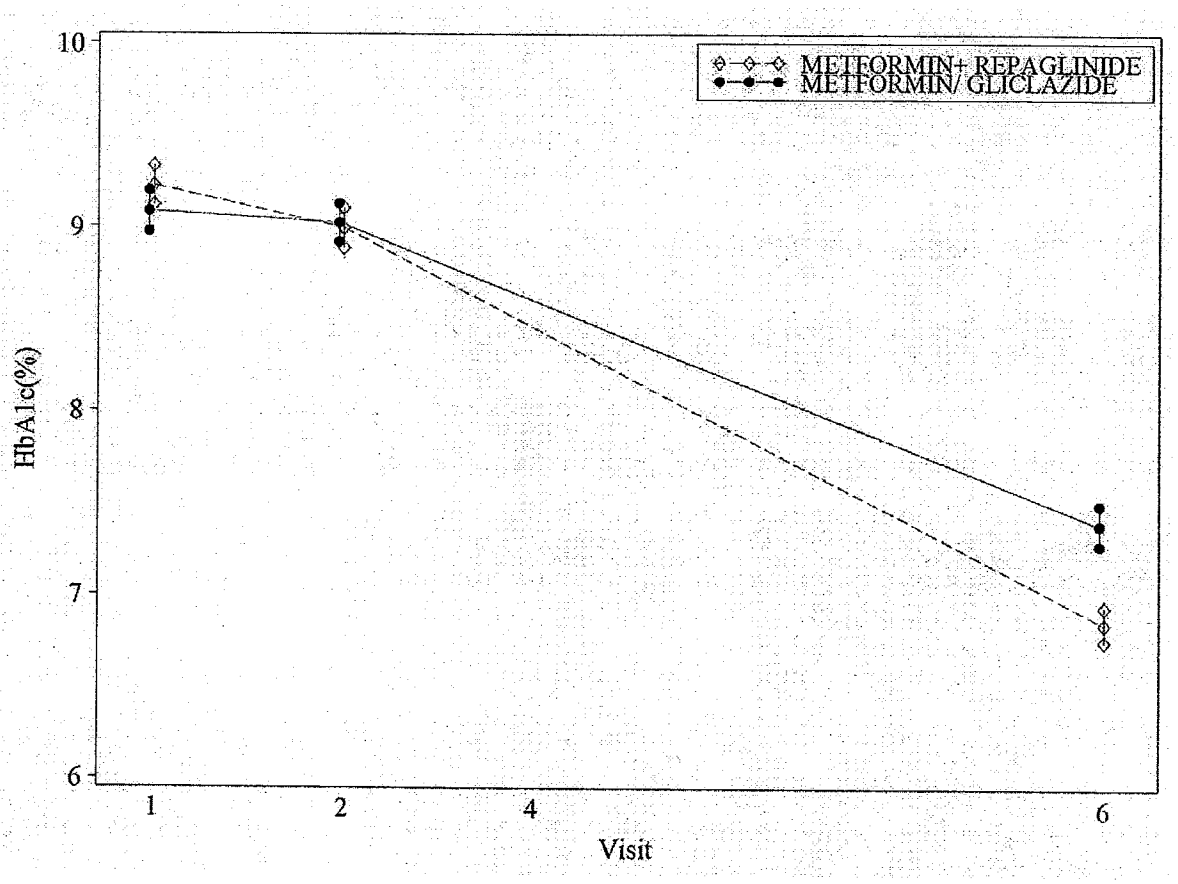
The primary efficacy endpoint was the change from baseline (visit 2) to visit 6 in HbA1c.

HbA1c

The mean HbA1c over time by visit is presented in the Figure below for the ITT population (and in EOT Table 18 for the PP population, in the NDA study report).

At baseline, there was not much difference in HbA1c between the repaglinide and metformin combination therapy group (9.00 ± 1.38%) and the metformin/gliclazide monotherapy group (9.02 ± 1.31%). At the end of the treatment period, both treatment groups showed a reduction in HbA1c from baseline. Mean HbA1c was lower in the combination therapy group (6.85 ± 1.12%) than in the monotherapy group (7.38 ± 1.32%). Similar results were observed in the PP population.

Mean HbA1c ± SEM by Visit – ITT population:



Analysis of Change in HbA1c

The analysis of change in HbA1c from baseline to visit 6 in each treatment group and between treatment groups is shown in Table below for the ITT population (and in EOT Table 19 for the PP population, in the NDA study report).

The reduction in mean HbA1c (SEM) at the end of the treatment period was greater in the combination therapy group (-2.129 ± 0.11%) compared with the monotherapy group (-1.639 ± 0.11%), without adjustment for centre effect. The result was the same after adjusting for centre effect between combination therapy and monotherapy groups.

There was a statistically significant difference in the treatment between combination therapy and monotherapy groups, with (-0.493 ± 0.15%, 95% CI=-0.782;-0.204, p=0.001) or without (-0.490 ± 0.15%, 95% CI=-0.789;-0.191, p=0.001) adjustment for centre effect.

Analysis of Change in HbA1c from Visit 2 to Visit 6 – ITT population

	MET/GLI	MET+REP	(MET+REP) - (MET/GLI)
Adjusting for centre			
N	148	146	
LS Mean(SE)	-1.525 (0.12)	-2.018 (0.12)	-0.493 (0.15)
95.0% C.I.	[-1.757;-1.292]	[-2.254;-1.781]	[-0.782;-0.204]
p-value			0.001*
No adjustment			
N	148	146	
LS Mean(SE)	-1.639 (0.11)	-2.129 (0.11)	-0.490 (0.15)
95.0% C.I.	[-1.850;-1.428]	[-2.342;-1.917]	[-0.789;-0.191]
p-value			0.001*

An asterisk(*) indicates statistical significance at 5% level.

The values of the cumulative distribution of patients at baseline (Visit 2) and at the end of the study (Visit 6) are presented below.

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On Original

	HbA1c value	Gliclazide	Metformin	Metformin/Repaglinide
Randomized		77	81	163
Visit 2	≤4.5%	0	0	1 (0.6%)
	≤5%	0	0	1 (0.6%)
	≤6%	0	0	1 (0.6%)
	≤6.5%	0	0	2 (1.2%)
	≤7%	4 (5.2%)	4 (4.9%)	10 (6.1%)
	≤8%	20 (26.0%)	24 (29.6%)	48 (29.4%)
	≤9%	34 (44.2%)	49 (60.5%)	89 (54.6%)
	≤10%	56 (72.7%)	64 (79.0%)	124 (76.1%)
	≤11%	71 (92.2%)	75 (92.6%)	147 (90.2%)
	≤12%	74 (96.1%)	81 (100.0%)	160 (98.2%)
	≤13%	76 (98.7%)	81 (100.0%)	162 (99.4%)
Visit 6	≤5%	0	0	2 (1.2%)
	≤6%	10 (13.0%)	8 (9.9%)	31 (19.0%)
	≤6.5%	25 (32.5%)	17 (21.0%)	62 (38.0%)
	≤7%	40 (51.9%)	35 (43.2%)	100 (61.3%)
	≤8%	52 (67.5%)	53 (65.4%)	129 (79.1%)
	≤9%	66 (85.7%)	68 (84.0%)	139 (85.3%)
	≤10%	67 (87.0%)	73 (90.1%)	145 (89.0%)
	≤11%	69 (89.6%)	76 (93.8%)	148 (90.8%)
	≤12%	69 (89.6%)	78 (96.3%)	148 (90.8%)
	≤13%	70 (90.9%)	78 (96.3%)	148 (90.8%)

Above in graphical form:

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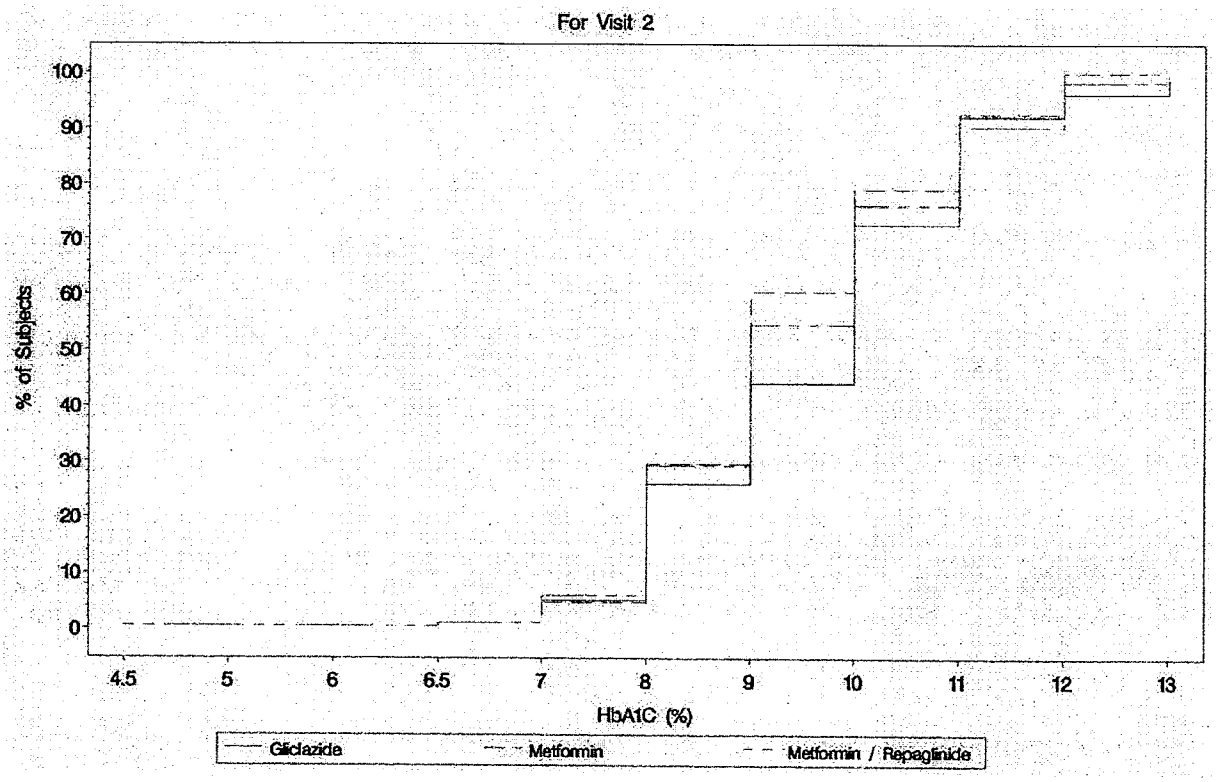

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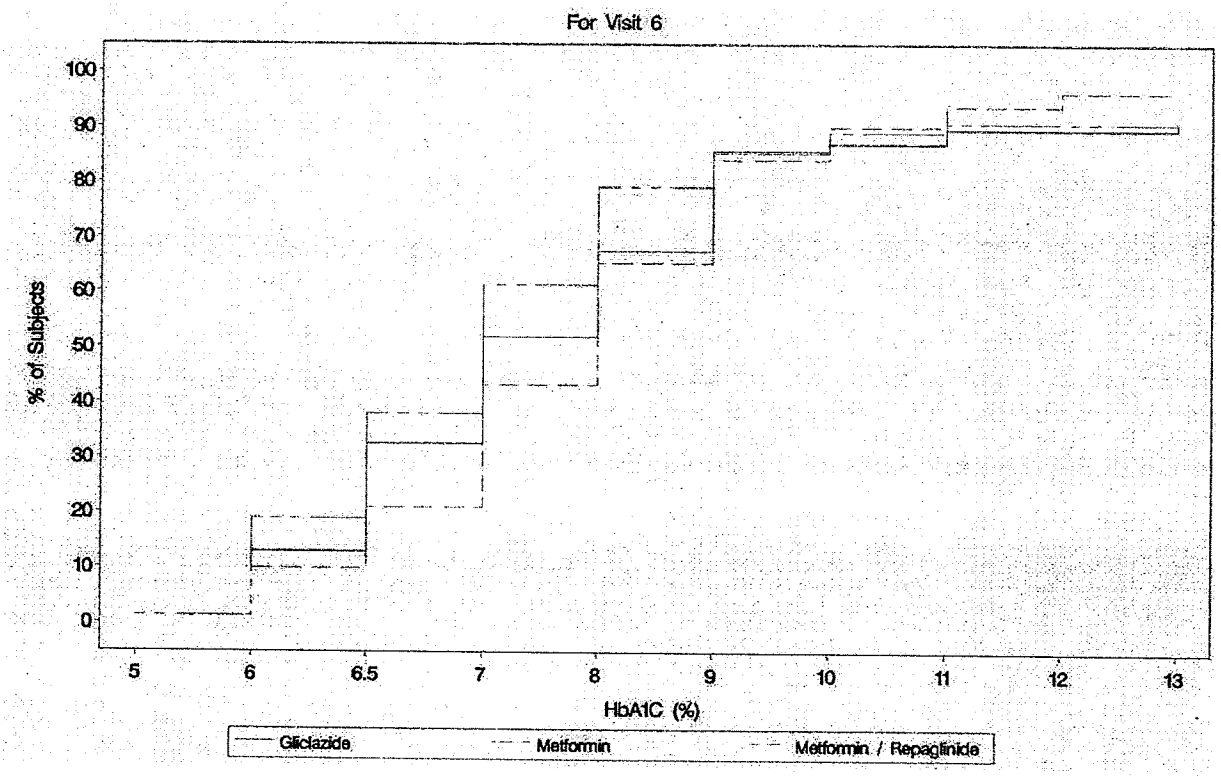


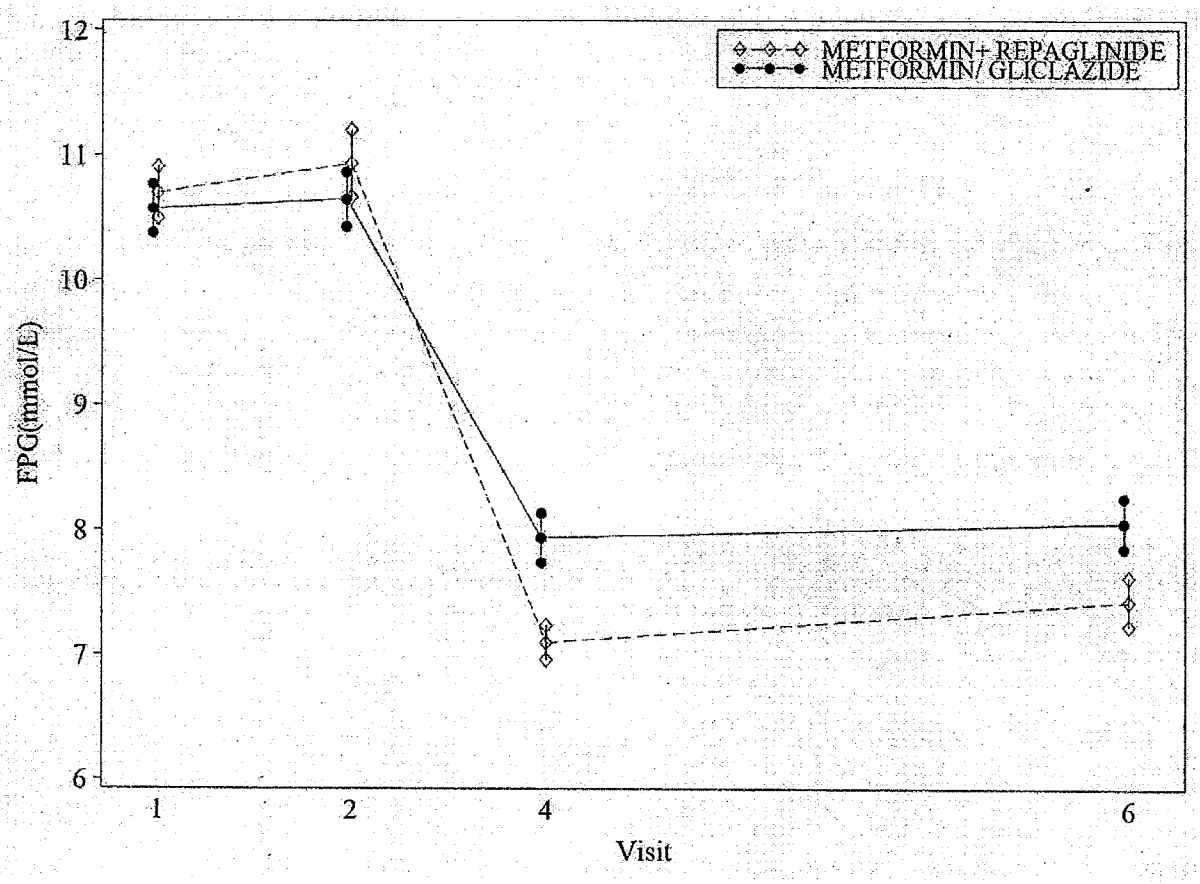
Secondary Evaluations

The secondary efficacy endpoints were the changes from baseline to visit 6 in FPG, 2-hr PPPG, 7-pt PG profile (change from pre-visit 3 to visit 6 in FPG and visit 6 mean delta PG), fasting lipids, QoL assessment and treatment satisfaction.

FPG

The mean FPG over time by visit is presented in Figure below (and EOT Table 8 for the ITT population and EOT Table 20 for the PP population, in the NDA study report).

FPG Mean ± SEM by Visit – ITT population:



At baseline, there was not much difference in mean FPG between the combination therapy group (10.93 ± 3.41 mmol/L) and monotherapy group (10.65 ± 2.74 mmol/L). At the end of the treatment period, FPG was lowered in both treatment groups with the combination group (7.43 ± 2.38 mmol/L) lower than the monotherapy group (8.05 ± 2.44 mmol/L). The slight increase observed from visit 4 (7.10 ± 1.57 mmol/L for combination therapy and 7.93 ± 2.27 mmol/L for monotherapy) to visit 6 is due to the non-optimal dosing or titration. Similar results were observed in the PP population (EOT Table 20 of the NDA study report).

Analysis of Change in FPG

The analysis of change in FPG from visit 2 to visit 6 in each treatment group and between treatment groups is shown in Table below for the ITT population (and EOT Table 21 for the PP population, in the NDA study report).

The reduction in FPG (SEM) at the end of the treatment was greater in the combination therapy group (-3.532 ± 0.24 mmol/L) than in the monotherapy group (- 2.562 ± 0.24 mmol/L), without

adjustment for centre effect. Similar results were observed in the PP population (EOT Table 21 of the NDA study report).

There was a statistically significant difference in the treatment between the combination therapy and monotherapy groups (-0.970 ± 0.34 mmol/L, 95% CI=- 1.633;-0.308, p=0.004), without adjustment for centre effect.

Analysis of Change in FPG from Visit 2 to Visit 6 – ITT population

	MET/GLI	MET+REP	(MET+REP) - (MET/GLI)
No adjustment			
N	152	156	
LS Mean(SE)	-2.562 (0.24)	-3.532 (0.24)	-0.970 (0.34)
95.0% C.I.	[-3.034;-2.090]	[-3.998;-3.067]	[-1.633;-0.308]
p-value			0.004*

An asterisk(*) indicates statistical significance at 5% level.

Note: The sponsor's and this reviewer's analyses of HBA1c and FPG provided statistically significant p-values for the comparisons pre-specified in the Statistical Analysis Plan.

3.2 Evaluation of Safety

This reviewer did not perform any formal safety evaluation but was available to the clinical reviewer for statistical consultation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Clinical trial AGEE/DCD/053/AUS was conducted in a patient population that had previously shown inadequate response to OAD monotherapy (metformin), and study AGEE-3017 was conducted in a population of OAD-naïve patients. There were differences in the baseline characteristics of these two patient populations which were consistent with such differences in the stage of disease progression/severity: subjects were slightly older in study

AGEE/DCD/053/AUS, as well as having a slightly longer duration of diabetes and a higher reported incidence of nephropathy.

The sponsor stated, "Taken together, available clinical trial data indicate that a repaglinide/metformin combination formulation (such as NN4440) will provide acceptable efficacy for use in patients who had previously failed to achieve glycemic control using OAD monotherapy, [redacted]

b(4)

Note: The absence of statistically significant interaction p-values does not assure that there is really no interaction.

On the other hand, adjustments for so many subgroups cannot be properly done, without pre-specifying which subgroup results will be confirmatory. Therefore, it is possible to see some significant interaction p-values out of so many p-values, even if there is really no interaction.

Results of these demographic characteristics (at baseline) and other prognostic factors were presented before. There were no major baseline imbalances.

4.1 Gender, Race, and Age

Efficacy Response by Age Group

Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Subjects < 65 Years): Study AGEE-3017 (ITT Population)

	MET	GLI	MET+REP	(MET+REP) - MET	(MET+REP) - GLI
Adjusting for centre					
N	69	63	130		
LS Mean (SE)	-1.200 (0.17)	-1.763 (0.17)	-1.966 (0.13)	-0.767 (0.18)	-0.204 (0.19)
95% C.I.	[-1.529,-0.870]	[-2.101,-1.425]	[-2.220,-1.713]	[-1.131,-0.403]	[-0.578,0.171]
p-value				<0.001*	0.285
No adjusting					
N	69	63	130		
LS Mean (SE)	-1.390 (0.15)	-1.898 (0.16)	-2.122 (0.11)	-0.732 (0.19)	-0.223 (0.20)
95% C.I.	[-1.695,-1.085]	[-2.217,-1.579]	[-2.344,-1.899]	[-1.109,-0.355]	[-0.612,0.166]
p-value				<0.001*	0.259

Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Subjects ≥ 65 Years): Study AGEE-3017 (ITT Population)

	MET	GLI	MET+REP	(MET+REP) - MET	(MET+REP) - GLI
Adjusting for centre					
N	9	7	18		
LS Mean (SE)	-1.036 (0.53)	-1.868 (0.61)	-2.581 (0.41)	-1.545 (0.75)	-0.712 (0.67)
95% C.I.	[-2.148,0.076]	[-3.142,-0.595]	[-3.447,-1.715]	[-3.105,0.016]	[-2.114,0.689]
p-value				0.052	0.301
No adjusting					
N	9	7	18		
LS Mean (SE)	-1.367 (0.45)	-2.114 (0.51)	-2.222 (0.32)	-0.856 (0.55)	-0.108 (0.60)
95% C.I.	[-2.283,-0.450]	[-3.154,-1.075]	[-2.871,-1.574]	[-1.978,0.267]	[-1.333,1.117]
p-value				0.130	0.859

The only statistically significant difference seen was in the age group <65 and between the repaglinide/metformin treatment arm and the metformin monotherapy arm.

Among subjects 65 years or older, there was no statistically significant differences between the repaglinide/metformin treatment arm and the metformin monotherapy arm; however, this observation may reflect the small sample size of elderly subjects available for analysis in the three treatment arms. Considering results without adjusting for center -- among subjects younger than 65 years, the LS mean change in HbA1c values during repaglinide/metformin combination therapy treatment was -2.122%. HbA1c reductions were very similar for the subset of subjects at least 65 years old who received the repaglinide/metformin combination therapy (LS mean change = -2.222%).

Efficacy Response by Gender

Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Male Subjects): Study AGEE-3017 (ITT Population)

	MET	GLI	MET+REP	(MET+REP) - MET	(MET+REP) - GLI
Adjusting for centre					
N	37	36	63		
LS Mean (SE)	-1.567 (0.22)	-2.263 (0.27)	-2.146 (0.18)	-0.579 (0.27)	0.116 (0.31)
95% C.I.	[-2.002,-1.133]	[-2.792,-1.733]	[-2.496,-1.797]	[-1.119,-0.039]	[-0.489,0.721]
p-value				0.036*	0.704
No adjusting					
N	37	26	63		
LS Mean (SE)	-1.549 (0.21)	-2.192 (0.25)	-2.183 (0.16)	-0.634 (0.27)	0.010 (0.30)
95% C.I.	[-1.969,-1.128]	[-2.694,-1.691]	[-2.505,-1.860]	[-1.163,-0.104]	[-0.586,0.606]
p-value				0.019*	0.974

Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Female Subjects): Study AGEE-3017 (ITT Population)

	MET	GLI	MET+REP	(MET+REP) - MET	(MET+REP) - GLI
Adjusting for centre					
N	41	44	85		
LS Mean (SE)	-1.158 (0.20)	-1.621 (0.20)	-2.117 (0.15)	-0.959 (0.24)	-0.496 (0.23)
95% C.I.	[-1.554,-0.762]	[-2.013,-1.230]	[-2.413,-1.821]	[-1.430,-0.489]	[-0.951,-0.040]
p-value				<0.001*	0.033*
No adjusting					
N	41	44	85		
LS Mean (SE)	-1.241 (0.20)	-1.759 (0.19)	-2.098 (0.14)	-0.856 (0.24)	-0.339 (0.24)
95% C.I.	[-1.637,-0.846]	[-2.141,-1.377]	[-2.372,-1.823]	[-1.338,-0.375]	[-0.809,0.132]
p-value				0.001*	0.157

Among the male and female subsets of subjects, repaglinide/metformin combination therapy showed a significantly greater reduction in HbA1c values than metformin monotherapy (Tables above). LS mean changes for HbA1c values from Visit 2 to Visit 6 were -2.183% among male subjects, and -2.098% among female subjects (without adjustment for center). In the male subpopulation, changes in HbA1c values were comparable for repaglinide/metformin and gliclazide treatment groups. In the female subpopulation, repaglinide/metformin combination therapy produced an LS mean change in HbA1c values which was significantly greater than that of gliclazide monotherapy (-2.117% vs. -1.621%), when changes were adjusted for treatment centre.

Efficacy Response by Race/Ethnic Origin

Clinical trial AGEE-3017 was conducted at 15 clinical sites, located in China, Malaysia, the Philippines, and Thailand. Ethnic origin data were not collected for subjects of this Asian clinical trial.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

These are open-label studies. I do not know how it has been guaranteed that no bias could occur; e.g., evaluation bias.

I do not agree with the sponsor's argument for open-label, "This trial was conducted as an open-label trial (see Section 5.1). Blinding was considered unfeasible due to the number of tablet administration necessary to maintain blinding, given the different timing of administration of the different treatments." Placebo tablets can easily be used for all the time-slots, even if the drug does not need to be administered for a particular arm, to maintain the blind.

In Study 3017, the sponsor did not plan to show that the combination is superior to each component. The primary analysis was the comparison between the repaglinide/metformin combination therapy arm and the pooled gliclazide and metformin monotherapy arms.

Apart from issues of credibility, the data available to me provide the statistical evidence in favor of the superiority of the combination repaglinide/metformin to the pooled group of the two arms metformin alone and gliclazide alone. The data does not provide the statistical evidence in favor of the superiority of the combination repaglinide/metformin to gliclazide alone.

5.2 Conclusions and Recommendations

These are open-label studies. I do not know how it has been guaranteed that no bias could occur; e.g., evaluation bias.

Apart from issues of credibility, the data available to me provide the statistical evidence in favor of the superiority of the combination repaglinide/metformin to the pooled group of the two arms metformin alone and gliclazide alone. The data do not provide the statistical evidence in favor of the superiority of the combination repaglinide/metformin to gliclazide alone.

Appendix I

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AUC	area under the curve
BMI	body mass index
Cmax	peak concentration
CRF	Case Record Form
DBP	diastolic blood pressure
ECG	electrocardiogram
EOT	End-of-Text
FPG	fasting plasma glucose
HbA1c	glycosylated haemoglobin
HDL	high density lipoprotein
ICTR	integrated clinical trial report
IEC	Independent Ethics Committee
IPS	International Product Safety
ITT	intent-to-treat
IUD	intra-uterine device
i.v.	intravenous
LDH	lactate dehydrogenase
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
NTF	Note-to-File
NYHA	New York Heart Association
PG	plasma glucose
7-pt PG profile	7-point plasma glucose profile
PGR	prandial glucose regulator
PP	per-protocol
2-hr PPPG	2-hour post-prandial plasma glucose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	severe acute respiratory syndrome
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of mean
t½	half-life

URTI	upper respiratory tract infection
WHO-DTSQ	World Health Organization-Diabetes Treatment Satisfaction Questionnaire

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J.Choudhury:x61184: 6/02/08

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/s/

Japobrata Choudhury
6/2/2008 08:44:50 AM
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Todd Sahlroot
6/2/2008 11:09:08 AM
BIOMETRICS