CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-386

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22232
Letter Date	8/15/07
Stamp Date	8/15/07
PDUFA Goal Date	6/15/08
Reviewer Name	Robert I Misbin
Review Completion Date	June 5, 2008
Established Name	repaglinide/metformin
(Proposed) Trade Name	Prandi*Met*
Therapeutic Class	Antidiabetic agents
Applicant	Novo Nordisk
Priority Designation	standard
Formulation	1mg/500mg, 2mg/500mg
Dosing Regimen	twice or thrice daily with meals
Indication	type 2 diabetes

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

As a fixed dose combination (FDC), PrandiMet can be expected to provide convenience for patients taking repaglinide (REP) and metformin (MET) as separate dosage forms. However the data submitted in this NDA do NOT form a basis for use of PrandiMet [b(4)

]

[b(4)

]

[b(4)

]

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity None recommended

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Commitments

[b(4)

]

1.3 Summary of Clinical Findings

Pivotal trials:

The Sponsor has identified two clinical trials as being "most relevant" to demonstrating efficacy and safety of the repaglinide/metformin fixed dose combination (FDC). These are AGEE 053 and AGEE 3017. I believe results of trial 1411 are also relevant.

Study AGEE053

Study AGEE053 was reviewed as part of the original Prandin NDA (NDA 20-741). This trial enrolled patients who had been treated with metformin for at least 6 months and had had an inadequate response as manifested by HbA1c of >7%. Patients were randomized to repaglinide add-on to metformin, repaglinide monotherapy, or continued metformin monotherapy. The mean HbA1c at baseline was about 8.5% .There was a 4 to 8 week repaglinide titration followed by the 12 week maintenance period. The mean dose of metformin at baseline was about 1.8 g in the repaglinide/metformin and metformin monotherapy treatment arms. The baseline dose of metformin was continued in patients randomized to metformin monotherapy and REP/MET. The dose of repaglinide was individually titrated (starting at 0.5 mg three times daily) for FBG > 140 mg/dl without hypoglycemia. Repaglinide was given before each of the three main meals. The maximum daily dose was 12 mg. At end of trial the mean dose of metformin was 1.85 g in the MET monotherapy arm and 1.75g in the REP/MET arm. The mean dose of repaglinide was 8.22 mg in the REP monotherapy arm and 6.28 in the REP/MET arm. The mean change in HbA1c was -0.38% for REP monotherapy, -0.33 for MET monotherapy and -1.41 for REP/MET.

There was a higher frequency of gastrointestinal events in the metformin group (44.4%) compared to REP monotherapy (29.6%) and REP/MET (21.4%). Hypoglycemia was reported in 0% with MET, 10.7% with REP and 33.3% with REP/MET. There were no severe hypoglycemic events in any group. There was a weight gain of about 2 to 3 kg with REP or REP/MET and a 0.9 kg weight loss with MET monotherapy. The difference in weight between REP/MET and MET monotherapy was statistically significant.

Study AGEE 3017

A new trial submitted in this NDA is AGEE 3017. This was an open label study in drug naïve patients. There were three treatment arms: repaglinide plus metformin combination therapy, metformin monotherapy and gliclazide monotherapy. Randomization was 2:1:1. Gliclazide is a sulfonylurea that is not available in the USA.

The study consisted of a four week run-in, a four week dose titration and a 12 week maintenance period. The trial was performed at 15 sites in China, Malaysia, the Philippines and Thailand. 340 patients were randomized (163 for the combo, 81 for MET monotherapy and 77 to GLI monotherapy) to achieve 300 evaluable patients. The ITT population was 163 for the combo, 81 for MET monotherapy and 77 to GLI monotherapy. Completers were 129 for the combo, 68 for MET monotherapy and 61 to GLI monotherapy. The statistical power calculation was based on a

comparison of the combo arm to the pooled monotherapy arms. It was not powered for comparison between the two monotherapy arms. Patients were approximately 55% female. The mean age was about 50 years, mean duration of diabetes about 2.5 years. The mean BMI was about 26. The mean HbA1c at baseline was about 9.0%. Ethnic origin was not specified because the trial was done completely in Asia.

Patients had diabetes for at least three months and had not received pharmaceutical treatment for at least three months. The range of acceptable glycemia for randomization was HbA1c 7-12% and FPG > 131 mg/dl, PPG > 208 mg/dl. The initial dose of metformin was 500 mg bid in the MET monotherapy arm. This could be titrated to a maximum of 2500 mg/d based on FPG target range of 76-112 mg/dl. The initial dose of gliclazide was 80 mg per day. This could be titrated to a maximum of 160 mg bid based on FPG targets. In the REP/MET arm, the initial dose of metformin was 500 mg given with dinner. This could be increased to a maximum of 1500 mg based on FPG targets. The initial dose of repaglinide was 0.5 mg tid with meals. This could be increased to a maximum of 2 mg based on a PPG target of < 187 mg/dl. The mean titrated dose of metformin was 1632 mg in the monotherapy arm and 865 mg in the combo arm. The mean doses of REP were 2.65 mg and GLI 208 mg.

Mean HbA1c fell in all groups. The reduction with REP/MET (-2.13) was greater then the reduction with MET monotherapy (-1.39). However the reduction with GLI monotherapy (-1.92) was not statistically different from the change with REP/MET. Similar results were found with respect to FPG. Mean FPG fell in all groups. The reduction with REP/MET (-3.52 mol/L)) was greater then the reduction with MET monotherapy (-2.13). However the reduction with GLI monotherapy (-3.00) was not statistically different from the change with REP/MET. There were no statistically significant differences among the groups with respect to postprandial glucose or lipid measures. Mean changes in body weight were REP/MET +0.81 kg, MET -1.43 kg, and GLI +1.14 kg.

Symptomatic hypoglycemia was reported in 24% in the REP/MET arm and 5% and 9% in the MET and GLI monotherapy arms respectively. Hypoglycemia confirmed with meter < 2.9 mmol/L (< 52mg/dl) occurred in 4% in the REP/MET arm and none in the monotherapy arms. A major hypoglycemic event occurred in one patient (subject S296 screen ID 4343) in the REP/MET arm and none in the monotherapy arms.

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The product in this NDA is a fixed dose combination of repaglinide (REP) and metformin (MET). REP was approved in the USA in 1997 and is marketed as Prandin. Metformin was approved in the USA in 1995. It was marketed initially as Glucophage but is now available as generics. Metformin had been used extensively elsewhere in the world before it was approved in the USA.

The Division of Medication Errors Prevention has objected to the trade name Prandi*Met*. They expressed concern about possible confusion between Prandi*Met* and Prandin, Avandamet, and Prednisone.

Of the concerns expressed by The Division of Medication Errors Prevention, the potential for confusion with prednisone seems the most serious. They cite a medication error that occurred in 2004 in which prandin was prescribed but prednisone was dispensed. The consequences of this mistake were not reported, but one might expect that giving a diabetic patient prednisone instead of prandin would greatly exacerbate hyperglycemia. Without additional information, it is not clear to me whether or not this error resulted from name confusion. The presumption of name confusion between prandin and prednisone would be more convincing if the Division of Medication Errors Prevention were able to provide evidence that switches with prednisone do not occur with drugs whose names are very different.

The potential for confusion with Prandin is unavoidable because "Prandin" is a component of "Prandi*Met*". To give "Prandi*Met*" a name unrelated to "Prandin" would lead to possible overdoses because patients taking Prandin might be given the new drug in addition.

I believe that the names Prandi*Met* and Avandamet are sufficiently different that confusion is not likely. Furthermore, both drugs are used in the same types of patients. The standard of practice is to add an insulin secretagogue (like Prandin) or an insulin sensitizer (like Avandia) in patients whose hyperglycemia is not controlled adequately by metformin alone. It is unlikely that a switch between these two drugs will result in major harm.

It is proposed that Prandi*Met* be marketed in dosage strengths of 1mg/500mg and 2mg/500mg. The prescriber will need to specify which strength is to be dispensed. Thus, the likelihood of name confusion is likely reduced by the need to specify the dose.

As of completion of this review, a decision about the tradename has not been finalized. For the sake of simplicity, I have used PrandiMet elsewhere in this review.

2.2 Currently Available Treatment for Indications

Sulfonylureas are insulin secretagogues that have been the mainstay of treatment of type 2 diabetes since the 1950's. Repaglinide is also an insulin secretagogue. Although it is chemically distinct from sulfonylureas, its pharmacology is similar. Metformin inhibits glucose production by the liver. Metformin is available as fixed dose combinations with three sulfonylureas, glyburide, glipizide and glimeperide. Metformin is also available as fixed dose combinations with the thiazolidinediones rosiglitazone and pioglitazone.

2.3 Presubmission Regulatory Activity

Letter from Dr Parks dated Aug 29, 2006 under IND 70959

A bioequivalence study should be conducted. Assuming that the fixed-dose combination (FDC) is bioequivalent to the individual components, it could receive labeling to allow it to be used BID or TID for patients who need additional glycemic control while taking metformin or repaglinide alone or patients taking a combination of both drugs.

Appears This Way
On Original

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES: NO COMMENT

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor has identified two clinical trials as being "most relevant" to demonstrating of efficacy of the repaglinide/metformin FDA. These are trials AGEE 053 and AGEE 3017. Study reports were provided in the submission. The efficacy and safety results of these pivotal trials are reviewed in subsequent sections.

The following other trials were said to be "not pertinent for purposes of the current submission" for the reasons given below. Efficacy data from some of these trials are reviewed briefly at the end of section 6.

b(4)

4.2 Review Strategy

The Sponsor has identified trials AGEE053 and AGEE 3017 to be pivotal and submitted study reports. Additional efficacy data from other trials are reviewed briefly at the end of section 6.

Section 7 includes safety data from the pivotal trials AGEE053 and AGEE 3017. Safety are also given from a newly completed comparison of PrandiMet to Avandamet. These data were submitted in a 120 data safety update Dec 2007.

4.3 Compliance with Good Clinical Practices

The studies appear to have been conducted in accordance with generally accepted principles that apply to treatment of patient volunteers in clinical trials. I did not personally review the consent documents.

4.4 Financial Disclosures

The Sponsor submitted debarment and financial disclosure documents. These documents are acceptable. The debarment statement indicated that the Sponsor did not and will not use the services of any individual or organization that had been debarred.

The Sponsor makes reference to FDA form 3454. The following financial disclosure information has been submitted:

1 Form OMB No. 0910-0396. The applicant certifies that the Sponsor has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study.

2 The applicant furthers certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in the Sponsor

3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from the Sponsor.

5 CLINICAL PHARMACOLOGY: SEE BIOPHARMACY REVIEW

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor is seeking the indication for use of repaglinide/metformin FDC (PrandiMet) in patients with type 2 diabetes who had been taking other antidiabetic agents,

The Sponsor has identified two clinical trials as being "most relevant" to demonstration of efficacy of the repaglinide/metformin FDC. Study AGEE053 supports the indication for the use of PrandiMet in patients who had been taking other oral agents.

b(4)

6.1.1 Methods

Data were reviewed from hard copies of study summaries submitted to the electronic document room

6.1.2 General Discussion of Endpoints

The primary endpoint was change in HbA1c.

6.1.3 Study Design

Design is given under each study.

6.1.4 Efficacy Findings

Pivotal trials:

The Sponsor has identified two clinical trials as being "most relevant" to demonstration of efficacy of the repaglinide/metformin FDA. These are AGEE053 and AGEE 3017.

Study AGEE053

Study AGEE053 was reviewed as part of the original Prandin NDA (NDA 20-741). This trial enrolled patients who had been treated with metformin for at least 6 months and had had an inadequate response as manifested by HbA1c of >7%. Patients were randomized to repaglinide add-on to metformin, repaglinide monotherapy, or continued metformin monotherapy. Patients were approximately 60% female and 92% white. The mean age was about 58 years, mean duration of diabetes about 4 years. The mean BMI was about 32. The mean HbA1c at baseline was about 8.5% .There was a 4 to 8 week repaglinide titration followed by the 12 week maintenance period. The mean dose of metformin at baseline was about 1.8 g in the REP/MET and metformin monotherapy arms. The baseline dose of metformin was continued in patients randomized to metformin monotherapy and REP/MET. The dose of repaglinide was individually titrated for FBG > 140 mg/dl without hypoglycemia. Repaglinide was given before each of the three main meals. The maximum daily dose was 12 mg. At end of trial the mean dose of metformin was 1.85 g in the MET monotherapy arm and 1.75g in the REP/MET arm. The mean dose of repaglinide was 8.22 mg in the REP monotherapy arm and 6.28 in the REP/MET arm. The mean change in HbA1c was -0.38% for REP monotherapy, -0.33 for MET monotherapy and -1.41 for REP/MET. The mean change in FPG was -0.49 mmol/L for REP monotherapy, -0.25 for MET monotherapy and -2.18 for REP/MET. This study demonstrated the superiority of repaglinide plus metformin to each of the monotherapies. There was a higher frequency of gastrointestinal events in the metformin group (44.4%) compared to REP monotherapy (29.6%) and REP/MET (21.4%). Hypoglycemia was reported in 0% with MET, 10.7% with REP and 33.3% with REP/MET. There were no severe hypoglycemic events in any group. There was a weight gain of about 2 to 3 kg in with REP or REP/MET and 0.9 kg weight loss

with MET monotherapy. The difference in weight between REP/MET and MET monotherapy was statistically significant.

Study AGEE 3017

A new trial submitted in this NDA is AGEE 3017. This was an open label study in drug naïve patients. There were three treatment arms: repaglinide plus metformin combination therapy (REP/MET), metformin monotherapy (MET) and gliclazide monotherapy (GLI). Randomization was 2:1:1. Gliclazide is a sulfonylurea that is not available in the USA.

The study consisted of a four week run-in, a four week dose titration and a 12 week maintenance period. The trial was performed at 15 sites in China, Malaysia, the Philippines and Thailand. 340 patients were randomized (163 for REP/MET., 81 for MET monotherapy and 77 to GLI monotherapy) to achieve 300 evaluable patients. The ITT population was 163 for REP/MET, 81 for MET monotherapy and 77 to GLI monotherapy. Completers were 129 for REP/MET, 68 for MET monotherapy and 61 to GLI monotherapy. The statistical power calculation was based on a comparison of the combo arm to the pooled monotherapy arms. It was not powered for comparison between the two monotherapy arms. Patients were approximately 55% female. The mean age was about 50 years, mean duration of diabetes about 2.5 years. The mean BMI was about 26. The mean HbA1c at baseline was about 9.0%. Ethnic origin was not specified because the trial was done completely in Asia.

Patients had diabetes for at least three months and had not received pharmaceutical treatment for at least three months. The range of acceptable glycemia for randomization was HbA1c 7-12% and FPG > 131 mg/dl, PPG > 208 mg/dl. The initial dose of metformin was 500 mg bid in the MET monotherapy arm. This could be titrated to a maximum of 2500 mg/d based on FPG target range of 76-112 mg/dl. The initial dose of gliclazide was 80 mg per day. This could be titrated to a maximum of 160 mg bid based on FPG targets. In the combo arm, the initial dose of metformin was 500 mg given with dinner. This could be increased to a maximum of 1500 mg based on FPG targets. The initial dose of repaglinide was 0.5 mg tid with meals. This could be increased to a maximum of 2 mg based on a PPG target of < 187 mg/dl. The mean titrated dose of metformin was 1632 mg in the monotherapy arm and 865 mg in the combo arm. The mean dose of REP was 2.65 mg and GLI 208 mg.

Mean HbA1c fell in all groups. The reduction with REP/MET (-2.13) was greater (p=?) then the reduction with MET monotherapy (-1.39). However the reduction with GLI monotherapy (-1.92) was not statistically different from the change with REP/MET. Similar results were found with respect to FPG. Mean FPG fell in all groups. The reduction with REP/MET (-3.52 mmol/L) was greater then the reduction with MET monotherapy (-2.13). However the reduction with GLI monotherapy (-3.00) was not statistically different from the change with REP/MET. There were no statistically significant differences among the groups with respect to postprandial glucose or

lipid measures. Mean changes in body weight were REP/MET +0.81 kg, MET -1.43 kg, and GLI +1.14 kg.

Efficacy data by Subsets:

As shown in the following tables, there was little difference among the various subsets with respect to change in HbA1c. The combination of REP/MET was significantly better than MET monotherapy in all subsets except subjects > 65 years old. Although REP/MET tended to be better in the subjects > 65 as well, the difference was of marginal statistical significance (this finding is likely explained by the small sample size of only 7-18 patients in the elderly subset, which reduced statistical power). REP/MET was significantly better than GLI monotherapy only in female patients.

Table 1 Summary of HbA1c Values (%) by Visit (Subjects with Baseline HbA1c < 9%): Study AGEE-3017
AGEE-3017 (ITT Population) January 14, 2008 16:32 Page 1 of 1

	MET	GLI	MET+REP
Number of Subjects Randomized	48	29	84
VISIT 1			
N	48	29	84
Mean (SD)	8.10 (0.78)	7.95 (0.95)	8.39 (0.96)
Median	8.00	7.50	8.30
Min - Max	7.00 - 10.20	7.00 - 10.40	7.00 - 11.30
VISIT 2			
N	48	28	83
Mean (SD)	7.99 (0.62)	7.79 (0.64)	7.90 (0.65)
Median	8.10	7.60	7.90
Min - Max	7.00 - 8.90	6.60 - 8.90	6.40 - 8.90
VISIT 6			
N	46	26	76
Mean (SD)	7.00 (0.99)	6.78 (0.85)	6.49 (0.68)
Median	6.80	6.60	6.40
Min - Max	5.40 - 10.00	5.50 - 8.60	4.90 - 8.70

Table 2 Summary of HbA1c Values (%) by Visit (Subjects with Baseline HbA1c ≥ 9%): Study AGEE-3017

AGEE-3017 (ITT Population) January 14, 2008 16:32 Page 1 of 1

	MET	GLI	MET+REP
Number of Subjects Randomized	33	48	79
VISIT 1			
N	33	48	79
Mean (SD)	10.29 (1.03)	9.92 (1.08)	10.11 (1.10)
Median	10.30	10.00	10.20
Min - Max	8.30 - 11.70	7.60 - 12.00	7.40 - 12.00
VISIT 2			
N	33	48	78
Mean (SD)	10.24 (0.74)	9.94 (0.90)	10.16 (0.91)
Median	10.10	9.60	9.90
Min - Max	9.00 - 11.50	9.00 - 12.60	9.00 - 12.80
VISIT 6			
N	32	44	72
Mean (SD)	8.28 (1.52)	7.49 (1.37)	7.22 (1.22)
Median	8.25	7.15	6.95
Min - Max	5.90 - 11.50	5.60 - 12.10	5.30 - 11.00

Table 3 Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Subjects with Baseline HbA1c <9%): Study AGEE-3017

AGEE-3017 (ITT Population) January 15, 2008 12:51 Page 1 of 1

	MET	GLI	MET+REP	(MET+REP) - MET	(MET+REP) - GLI
Adjusting for centre					
N	46	26	76		
LS Mean (SE)	-0.860 (0.15)	-0.854 (0.19)	-1.230 (0.12)	-0.369 (0.17)	-0.376 (0.20)
95% C.I.	[-1.151,-0.570]	[-1.232,-0.477]	[-1.469,-0.991]	[-0.696,-0.042]	[-0.775,0.024]
p-value				0.027*	0.065
No adjusting					
N	46	26	76		
LS Mean (SE)	-1.007 (0.14)	-1.054 (0.19)	-1.434 (0.11)	-0.428 (0.18)	-0.380 (0.21)
95% C.I.	[-1.282,-0.731]	[-1.430,-0.687]	[-1.649,-1.220]	[-0.777,-0.079]	[-0.805,0.044]
p-value				0.017*	0.079

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

Table 4 Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Subjects with Baseline HbA1c ≥ 9%): Study AGEE-3017

AGEE-3017 (ITT Population) January 15, 2008 12:51 Page 1 of 1

	MET	GLI	MET+REP	(MET+REP) - MET	(MET+REP) - GLI
Adjusting for centre					
N	32	44	72		
LS Mean (SE)	-1.869 (0.23)	-2.364 (0.20)	-2.793 (0.16)	-0.929 (0.25)	-0.434 (0.22)
95% C.I.	[-2.315,-1.423]	[-2.758,-1.969]	[-3.123,-2.473]	[-1.418,-0.439]	[-0.882,0.014]
p-value				<0.001*	0.057
No adjusting					
N	32	44	72		
LS Mean (SE)	-1.934 (0.22)	-2.432 (0.19)	-2.872 (0.15)	-0.938 (0.27)	-0.440 (0.24)
95% C.I.	[-2.376,-1.493]	[-2.809,-2.055]	[-3.167,-2.578]	[-1.469,-0.407]	[-0.919,0.038]
p-value				0.001*	0.071

Table 5 Summary of HbA1c Values (%) by Visit (Subjects < 65 Years): Study AGEE-3017

AGEE-3017 (ITT Population) January 16, 2008 Page 1 of 1

	MET	GLI	MET+REP
Number of Subjects Randomized	72	68	144
VISIT 1			
N	72	68	144
Mean (SD)	9.10 (1.40)	9.19 (1.41)	9.27 (1.34)
Median	8.80	9.20	9.25
Min - Max	7.00 - 11.70	7.00 - 12.00	7.00 - 12.00
VISIT 2			
N	72	68	142
Mean (SD)	8.98 (1.32)	9.15 (1.30)	9.01 (1.41)
Median	8.70	9.10	8.85
Min - Max	7.00 - 11.50	6.90 - 12.60	6.40 - 12.80
VISIT 6			
N	69	63	130
Mean (SD)	7.61 (1.14)	7.21 (1.20)	6.88 (1.15)
Median	7.30	7.00	6.70
Min - Max	5.40 - 11.50	5.50 - 12.10	4.90 - 11.60

Table 6 Summary of HbA1c Values (%) by Visit (Subjects ≥ 65 Years): Study AGEE-3017

AGEE-3017 (ITT Population) January 16, 2008 11:47 Page 1 of 1

	MET	GLI	MET+REP
Number of Subjects Randomized	9	9	19
VISIT 1			
N	9	9	19
Mean (SD)	8.16 (1.69)	9.09 (1.50)	8.85 (1.35)
Median	7.90	8.70	8.80
Min - Max	7.00 - 10.50	7.00 - 11.70	7.10 - 11.30
VISIT 2			
N	9	8	19
Mean (SD)	8.28 (0.90)	9.14 (1.56)	8.85 (1.17)
Median	8.40	9.75	8.50
Min - Max	7.10 - 9.90	6.60 - 11.10	7.10 - 11.20
VISIT 6			
N	9	7	18
Mean (SD)	6.91 (0.43)	7.39 (1.60)	6.58 (0.84)
Median	6.80	6.50	6.40
Min - Max	6.20 - 7.50	6.10 - 10.50	5.30 - 8.60

Table 7 Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Subjects < 65 Years): Study AGEE-3017

AGEE-3017 (ITT Population) January 16, 2008 11:48 Page 1 of 1

	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)	-1.393 (0.15)	-1.858 (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

Table 8 Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Subjects ≥ 65 Years): Study AGEE-3017
AGEE-3017 (ITT Population) January 16, 2008 11:48 Page 1 of 1

	MET	GLI	MET+REP	(MET+REP) - MET	(MET+REP) - GLI
Adjusting for centre					
N	9	7	18		
LS Mean (SE)	-1.035 (0.53)	-1.468 (0.61)	-2.581 (0.41)	-1.545 (0.75)	-0.722 (0.67)
95% C.I.	[-2.148,0.078]	[-3.142,-0.595]	[-3.447,-1.715]	[-3.105,0.015]	[-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

Table 9 Summary of HbA1c Values (%) by Visit (Male Subjects): Study AGEE-3017
AGEE-3017 (ITT Population) January 14, 2008 16:06 Page 1 of 1

	MET	GLI	MET+REP
Number of Subjects Randomized	40	32	69
VISIT 1			
N	40	32	69
Mean (SD)	8.88 (1.35)	9.41 (1.45)	9.26 (1.31)
Median	8.70	9.40	9.10
Min - Max	7.00 - 11.70	7.00 - 13.80	7.10 - 12.00
VISIT 2			
N	40	31	67
Mean (SD)	8.79 (1.25)	9.34 (1.37)	8.87 (1.30)
Median	8.50	9.10	8.60
Min - Max	7.00 - 11.50	6.60 - 12.30	6.70 - 12.00
VISIT 6			
N	37	26	63
Mean (SD)	7.24 (1.20)	7.00 (0.79)	6.68 (1.01)
Median	7.00	6.90	6.70
Min - Max	5.40 - 11.10	5.80 - 8.50	4.90 - 9.40

Table 10 Summary of HbA1c Values (%) by Visit (Female Subjects): Study AGEE-3017
AGEE-3017 (ITT Population) January 14, 2008 16:06

	MET	GLI	MET+REP
Number of Subjects Randomized	41	45	94
VISIT 1			
N	41	45	94
Mean (SD)	9.10 (1.43)	9.02 (1.35)	9.21 (1.37)
Median	8.80	9.00	9.20
Min - Max	7.00 - 11.70	7.00 - 12.00	7.00 - 12.00
VISIT 2			
N	41	45	94
Mean (SD)	9.02 (1.35)	9.08 (1.30)	9.08 (1.43)
Median	8.70	9.10	9.05
Min - Max	7.00 - 11.40	7.00 - 12.60	6.40 - 12.80
VISIT 6			
N	41	44	85
Mean (SD)	7.78 (1.49)	7.36 (1.45)	6.97 (1.18)
Median	7.30	6.95	6.80
Min - Max	5.90 - 11.50	5.50 - 12.10	5.00 - 11.50

Table 11 Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Male Subjects): Study AGEE-3017

AGEE-3017 (ITT Population) January 15, 2008 12:41 Page 1 of 1

	MET	GLI	MET+REP	(MET+REP) - MET	(MET+REP) - GLI
Adjusting for centre					
N	37	26	63		
LS Mean (SE)	-1.507 (0.22)	-2.263 (0.27)	-2.166 (0.18)	-0.579 (0.22)	0.116 (0.31)
95% C.I.	[-2.002,-1.139]	[-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

Best Possible Copy

Table 12 Analysis of Changes in HbA1c (%) from Visit 2 to Visit 6 (Female Subjects): Study AGEE-3017

AGEE-3017 (ITT Population) January 15, 2008 12:41 Page 1 of 1

	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,-0.845]	[-2.141,-1.377]	[-2.372,-1.825]	[-1.338,-0.375]	[-0.809,0.132]
p-value				0.001*	0.157

Safety

There were no deaths. A single subject (71 year old female, S306, subject ID 4420) had two SAE's (pneumonia and TIA) after two months of REP/MET. There were no SAE's in the monotherapy arms. Symptomatic hypoglycemia was reported in 24% in the REP/MET arm and 5% and 9% in the MET and GLI monotherapy arms respectively. Hypoglycemia confirmed with meter < 2.9 mmol/L (< 52mg/dl) occurred in 4% in the REP/MET arm and none in the monotherapy arms. A major hypoglycemic event occurred in one patient (subject S296 screen ID 4343) in the REP/MET arm and none in the monotherapy arms. One patient on MET monotherapy withdrew because of gastrointestinal complaints (S123 screen ID 3305). One patient on REP/MET withdrew because of headache and nausea (S124 screen ID 3312).

Critique of study 3017

1 Study 3017 was open label and study drugs were titrated individually. Metformin was given once or twice daily. Repaglinide was given three times daily with meals. This study provides little insight into how a fixed dose combination of repaglinide and metformin should be dosed.

2 The mean final dose in the combination arm was 865 mg of metformin and 2.65 mg repaglinide. This cannot be achieved with the two dose strengths of PrandiMet (1mg or 2 mg of REP with 500 mg MET) that are proposed.

3 Instead of comparing the combination of REP/MET to each of the monotherapies, the comparison here is to Gliclazide, a sulfonylurea not available in the USA.

4 Although the combination REP/MET was more effective than MET monotherapy, it was only marginally more effective than GLI monotherapy. Hypoglycemia seemed more prominent with REP/MET than with GLI.

5. This study was conducted exclusively in Asians. It is unknown whether a similar efficacy and safety profile would be seen in other races/ethnicities that are more representative of the U.S. population.

Conclusions from Study 3017

The combination REP/MET was marginally more effective in lowering HbA1c than was GLI monotherapy. One might expect that the use of REP + MET would be associated with less hypoglycemia than with GLI alone. But this was not the case. If anything, hypoglycemia was more prominent with REP/MET than with GLI.

b(4)

Non-pivotal trials

The following other trials were said to be "not pertinent for purposes of the current submission". Additional information about these trials was requested by FDA in a letter dated January 29, 2008. The Sponsor responded with an eleven page submission dated Feb 15, 2008. Results are taken from summaries in the original NDA and the submission of Feb 15, 2008:

b(4)

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 2

Other trials:

[redacted]

b(4)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Repaglinide and metformin have each been marketed for many years. Like all insulin secretagogues, repaglinide can cause hypoglycemia. Patients treated with insulin secretagogues commonly gain weight. Metformin causes gastrointestinal symptoms.

Safety issues associated with the use of the individual drugs as monotherapy will not be discussed here. The review focused on whether use of the two drugs in combination appeared to exacerbate adverse events or resulted in unexpected adverse events. Safety data from the two pivotal trials are presented separately. This is followed by safety data from study 1794, a trial that compared the REP/MET fixed dose combination with Avandamet. These data were submitted in the 120 day safety update of 13 Dec 2007.

Trial 053

There was a higher frequency of gastrointestinal events in the metformin group (44.4%) compared to REP monotherapy (29.6%) and REP/MET (21.4%). Hypoglycemia was reported in 0% with MET, 10.7% with REP and 33.3% with REP/MET. There were no severe hypoglycemic events in any group. There was a weight gain of about 2 to 3 kg in with REP or REP/MET and 0.9 kg weight loss with MET monotherapy. The difference in weight between REP/MET and MET monotherapy was statistically significant.

Trial 3017

There were no deaths. A single subject (71 year old female, S306, subject ID 4420) had two SAE's (pneumonia and TIA) after two months of combination therapy. There were no SAE's in the monotherapy arms. Symptomatic hypoglycemia was reported in 24% in the combo arm and 5% and 9% in the MET and GLI monotherapy arms respectively. Hypoglycemia confirmed with meter < 2.9 mmol/L (< 52mg/dl) occurred in 4% in the combo arm and none in the monotherapy arms. A major hypoglycemic event occurred in one patient (subject S296 screen ID 4343) in the combo arm and none in the monotherapy arms. One patient on MET monotherapy withdrew because of gastrointestinal complaints (S123 screen ID 3305). One patient on combination therapy withdrew because of headache and nausea (S124 screen ID 3312).

b(4)

Table 2 HbA_{1c} Values at Baseline and End-of-study (ITT Population)

	NN4440 BID		NN4440 TID		Avandamet BID	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Baseline	177	8.42 (0.083)	178	8.27 (0.074)	176	8.43 (0.083)
End-of-study (LOCF)	177	7.44 (0.085)	178	7.26 (0.083)	174	7.41 (0.093)

There were 12 SAE's with PrandiMet (both arms combined) and 7 with Avandamet. None appeared to be drug related.

As shown in the tables below, there appeared to be more hypoglycemia with PrandiMet than with Avandamet but there were no cases of major hypoglycemia in any arm. Diarrhea was the most common treatment emergent adverse events, reported in 10.6% of patients on PrandiMet bid, 12.9% on PrandiMet tid and 5.4% on Avandamet. Peripheral edema was reported in 2.1% of patients on PrandiMet bid, 2.2% on PrandiMet tid and 6.5% on Avandamet. Headache was reported in 6.4% of patients on PrandiMet bid, 5.9% on PrandiMet tid and 5.4% on Avandamet. No other differences appear noteworthy.

Table 4 Incidence of Adverse Events: Study NN4440-1794

	BID NN4440			TID NN4440			BID Avandamet		
	N	%	E	N	%	E	N	%	E
Subjects exposed	188	100		186	100		186	100	
Adverse events	102	54.3	277	118	63.4	313	110	59.1	284
Serious adverse events	7	3.7	7	5	2.7	6	7	3.8	7
Hypoglycaemic episodes[a]	73	38.8	469	84	45.2	566	19	10.2	52

a: All episodes (major, minor, and symptoms only).
Cross reference: Clinical Trial Report NN4440-1794, End-of-Text Tables 14-3-1-1-1 and 14-3-6-6-1.

8 ADDITIONAL CLINICAL ISSUES:

8.1 Dosing regimen and labeling

b(4)

b(4)

b(4)

8.2 Pediatrics - Not labeled to be used in children

8.3 Postmarketing Risk Management Plan – None recommended

9 OVERALL ASSESSMENT

9.1 CONCLUSIONS:

As a fixed dose combination, PrandiMet can be expected to provide convenience for patients taking repaglinide and metformin as separate dosage forms. PrandiMet may also be useful in patients on metformin in whom repaglinide is to be started or patients on repaglinide in whom metformin is to be started.

b(4)

Naïve patients are generally started on 500 mg metformin once or twice a day. The dose is increased to 1.5 to 2 g in divided doses based on gastrointestinal tolerability. The initial dose of repaglinide in naïve patients is 0.5 mg two to four times per day with meals. The dose is increased as needed to control hyperglycemia.

b(4)

9.2 Recommendation on Regulatory Action

The application can be approved provided that the label does not say that PrandiMet should be

b(4)

b(4)

b(4)

Appears This Way
On Original

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Misbin
6/4/2008 04:46:52 PM
MEDICAL OFFICER

Hylton Joffe
6/8/2008 07:52:19 PM
MEDICAL OFFICER
Please see clinical team leader memo.