CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-386

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-232	Submission Date(s): 8/15/07, 10/19/07
Brand Name	Prandi*Met*
Generic Name	Repaglinide and Metformin Hydrochloride Fixed Dose Combination Tablets
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	DCP-2
OND Division	Metabolic and Endocrine Products
Sponsor	Novo Nordisk
Submission Type	505 (b) (2)
Formulation; Strength(s)	1 mg/500 mg and 2 mg/500 mg repaglinide/metformin tablets for oral administration; 2 to 3 times daily with meals
Indication	Treatment of Type 2 Diabetes Mellitus

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I Executive Summary

Novo Nordisk has developed Prandi*Met* fixed-dose combination (FDC) tablets containing repaglinide and metformin.

In the original approval of Prandin (repaglinide), it is indicated for use not only as monotherapy, but also in combination therapy with metformin. Prandin is available in 0.5 mg, 1 mg and 2 mg strength tablets. Based on the package insert, there is no fixed dosage regimen for the management of type 2 diabetes with Prandin. The recommended dose range is 0.5 mg to 4 mg taken with meals. Prandin may be dosed preprandially 2, 3, or 4 times a day in response to changes in the patient's meal pattern. The maximum recommended daily dose is 16 mg.

The most common strengths of metformin are 500, 850, and 1000 mg tablets (other available strengths include 625 mg and 750 mg) and is approved for individualized treatment up to a maximum daily dose of 2550 mg in adults. Typically metformin is administered twice per day with meals.

The sponsor has developed two FDC tablet strengths – 1 mg/500 mg and 2 mg/500 mg (repaglinide/metformin). To aid in the approval of this application the sponsor has submitted one pivotal bioequivalence study. There were no clinical studies done with the to-be marketed combination product and the bioequivalence study was designed to bridge the proposed combination tablets to the clinical safety and efficacy database supporting the use of repaglinide in combination with metformin. In addition, the sponsor has submitted two efficacy clinical trials where repaglinide and metformin were co-administered: AGEE/DCD/053/AUS (included in the original NDA 20-741 for repaglinide) and AGEE-3017, [redacted] b(4)

A Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the information provided in the NDA 22-232 for Prandi*Met* (repaglinide/metformin) fixed dose combination tablets. Recommendation and comments should be sent to sponsor as appropriate.

- OCP/DCP-2 finds the NDA *acceptable* pending requested DSI inspection for the bioequivalence study (NN4440-1753).
- OCP/DCP-2 finds the NDA *acceptable* pending agreement on the language of package insert.

Clinical Pharmacology briefing was held on 5/19/08 and the attendees were Drs. Chandra Sahajwalla, Suresh Doddapaneni, Sally Choe, Jayabharathi Vaidyanathan, Sandra Suarez-Sharp and Project Manager Julie Marchik.

B Phase 4 Commitments

None.

C Summary of Clinical Pharmacology Findings

The summary of the results from the pharmacokinetic studies are provided below.

- *Bioequivalence:*
    - Metformin in the FDC tablet (2/500 mg) was bioequivalent to concomitant administration of individual tablets of 2 mg repaglinide and 500 mg metformin. The 90% CI of the geometric mean ratios for the primary PK parameters were contained within the prespecified intervals of 80-125% (AUCinf, [102.39 (98.53 – 106.40)]; AUC0-t, [102.19 (98.22 – 106.31)]; and Cmax, [103.11 (98.49 – 107.96)]).
    - Repaglinide in the FDC tablet (2/500 mg) was bioequivalent to concomitant administration of individual tablets of 2 mg repaglinide and 500 mg metformin. The 90% CI of the geometric mean ratios for the primary PK parameters were contained within the prespecified intervals of 80-125% (AUCinf, [98.66 (94.77 – 102.71)]; AUC0-t, [98.52 (94.63 – 102.57)]; and Cmax, [108.49 (94.26 – 124.86)]).
- *Dose proportionality:* Dose-proportionality of the repaglinide plasma concentrations resulting from the administration of the FDC tablet 2/500 mg and 1/500 mg was also determined as a secondary PK endpoint. The approach of dose-proportionality was analogous to that of bioequivalence. The repaglinide dose-adjusted primary PK parameters (AUC/dose and Cmax/dose) were used to determine the BE assessment of the 2/500 mg FDC tablets versus 1/500 mg FDC tablets. The results indicated that the two formulations were dose-proportional with respect to repaglinide PK parameters.
- Secondary PK parameters for both metformin and repaglinide (Tmax, t1/2, λz, Cl/f, and Vz/f) appeared to be similar between the FDC tablets and the co-administration of individual tablets. Metformin PK parameters also appeared to be similar between the two FDC tablet strengths (1/500 mg and 2/500 mg).

II Question Based Review

A General Attributes

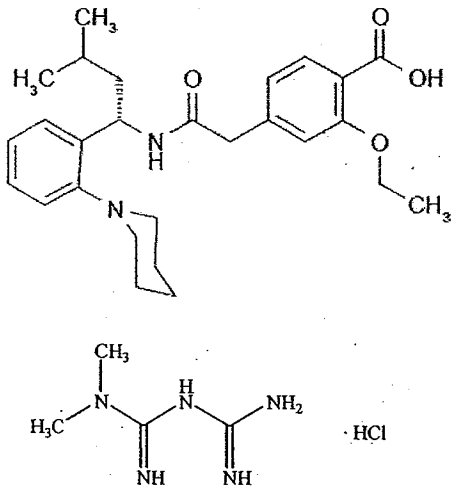
What are the highlights of the chemistry and physico-chemical properties of repaglinide and metformin FDC tablets?

Prandi*Met* FDC tablets contain 2 oral antihyperglycemic drugs used in type 2 diabetes, repaglinide and metformin hydrochloride.

Repaglinide [S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl)phenyl)-butyl)amino)-2-oxoethyl)benzoic acid] is an insulin secretagogue of the meglitinide class. Repaglinide is a white to off-white powder with molecular formula $C_{27}H_{36}N_2O_4$ and a molecular weight of 452.6. The chemical structure is shown in Figure 1.

Metformin hydrochloride (*N,N* -dimethylimidodicarbonimidic diamide hydrochloride) (Figure 1) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white crystalline powder with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.62.

Figure 1: Chemical structure of repaglinide (top) and metformin (bottom).



What is the proposed mechanism (s) of action and therapeutic indication?

Prandi*Met* tablets combine two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes.

Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta cells in the pancreatic islets. Insulin release is glucose dependent and diminishes at low glucose concentrations.

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both 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 therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

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

What is the proposed dose and dosage form?

Prandi*Met* is proposed in two dosage strengths: 1 mg/500 mg and 2 mg/500 mg (repaglinide/metformin) tablets.

The sponsor's proposed package insert states the following regarding dosage and administration:

[redacted] b(4)

B General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical trials conducted by the sponsor to support the approval of the FDC product are summarized in the following table:

Table 1: Clinical trials in support of the FDC tablets

Trial ID	Study Type	Duration	Total Subjects	Endpoints
NN4440-1753	Bioequivalence trial	Single dose; 3 way crossover	55 healthy volunteers (18-45 years)	Primary: Cmax, AUC, AUC0-24, AUC0-t Secondary: Tmax, CL/f, Vz/f, t1/2, λz

AGEE/DCD/053/AUS	Efficacy and safety (Oral antidiabetic drug monotherapy failures)	4 to 5 months	83 patients with type 2 diabetics	Primary: HbA1c, FPG Secondary: Fasting insulin, fasting C-peptide, lipids, home blood glucose profile
AGEE-3017	Efficacy and safety (Oral antidiabetic drug-Naive)	16 weeks	322 patients with type 2 diabetics	Primary: HbA1c Secondary: FPG, 2-hr PPG, 7-point glucose profiles, fasting lipids

The clinical trial NN4440-1753 provides bioequivalence data regarding the new repaglinide/metformin combination tablet, while clinical trials AGEE/DCD/053/AUS (included in the original NDA 20-741 for repaglinide) and AGEE-3017 (both studies were conducted with separate repaglinide and metformin formulations) provide efficacy and safety data relevant to the repaglinide and metformin combination therapy. The

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C Intrinsic Factors

The effects of various intrinsic factors (e.g., hepatic, renal, gender, elderly) were provided in the original NDA for each drug. Please see Clinical Pharmacology reviews for Prandin NDA 20-741 (repaglinide) and Glucophage NDA 20-357 (metformin).

D Extrinsic Factors

Is there any drug-drug interaction between repaglinide and metformin?

No drug interaction study was conducted with the fixed-dose combination tablet.

The mode of excretion and elimination of repaglinide and metformin are different: repaglinide is metabolized in the liver, while metformin is primarily eliminated by renal excretion. Therefore, there is no mechanism to suspect that an interaction between the FDC tablet and other drugs will be different from the interactions that have been observed with individual agent with other drugs.

E General Biopharmaceutics

What is the formulation of repaglinide and metformin combination tablets?

The FDC formulation containing different doses of repaglinide were developed and used in the pivotal BE Study NN4440-1753. The components of the tablets are described in Table 2.

Table 2: Components of repaglinide + metformin FDC tablets used in clinical trials

Ingredient	Function	NN4440 Tablet (1 mg repaglinide/ 500 mg metformin) Quantity per tablet (mg)	NN4440 Tablet (2 mg repaglinide/ 500 mg metformin) Quantity per tablet (mg)
Active Ingredients			
Repaglinide	Active	1.00	2.00
Poloxamer 188			
Povidone			
Meglumine			
Cellulose, Microcrystalline			
Metformin Hydrochloride	Active	500	500
Povidone			
Sorbitol			
Macrogol			
Non-active Ingredients			
Cellulose, Microcrystalline			
Polacrillin Potassium			
Magnesium Stearate			
Yellow			
Hypromellose 6cP			
Talc			
Titanium Dioxide,			
Macrogol			
Iron Oxide Yellow,			
Red		–	
Hypromellose 3cP		–	
Talc		–	
Titanium Dioxide,		–	
Propylene Glycol		–	
Iron Oxide Red,		–	
		–	
Hypromellose 6cP		–	
Titanium Dioxide,		–	
Macrogol		–	
		–	

q.s. = sufficient quantity.

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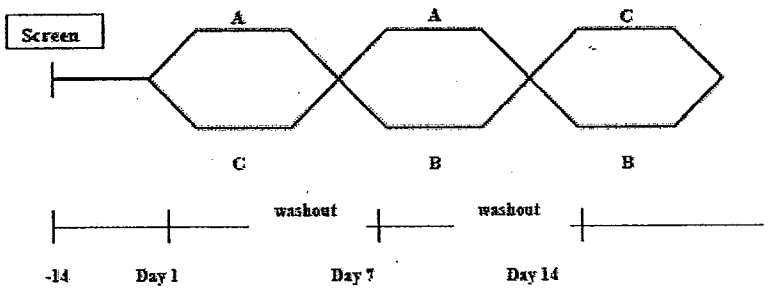
Are the combination tablets of repaglinide and metformin (2/500 mg) bioequivalent to concomitant dosing of repaglinide 2 mg and metformin 500 mg individual tablets in healthy subjects?

The FDC 2 mg/500 mg strength tablets were bioequivalent to individual tablet of 2 mg repaglinide and 500 mg metformin.

This study was a single-blind, randomized, three-period crossover study in healthy male and female subjects. The subjects received either the FDC tablets 1/500 mg, 2/500 mg, or 2 mg repaglinide and 500 mg metformin co-administered as separate tablets. The treatment was administered immediately prior to a high-fat breakfast. Subjects received a single dose of treatment A, B, or C during each period at Day 1, Day 7 ± 3 and Day 14 ± 3 of the study. An overview of the study design is shown below:



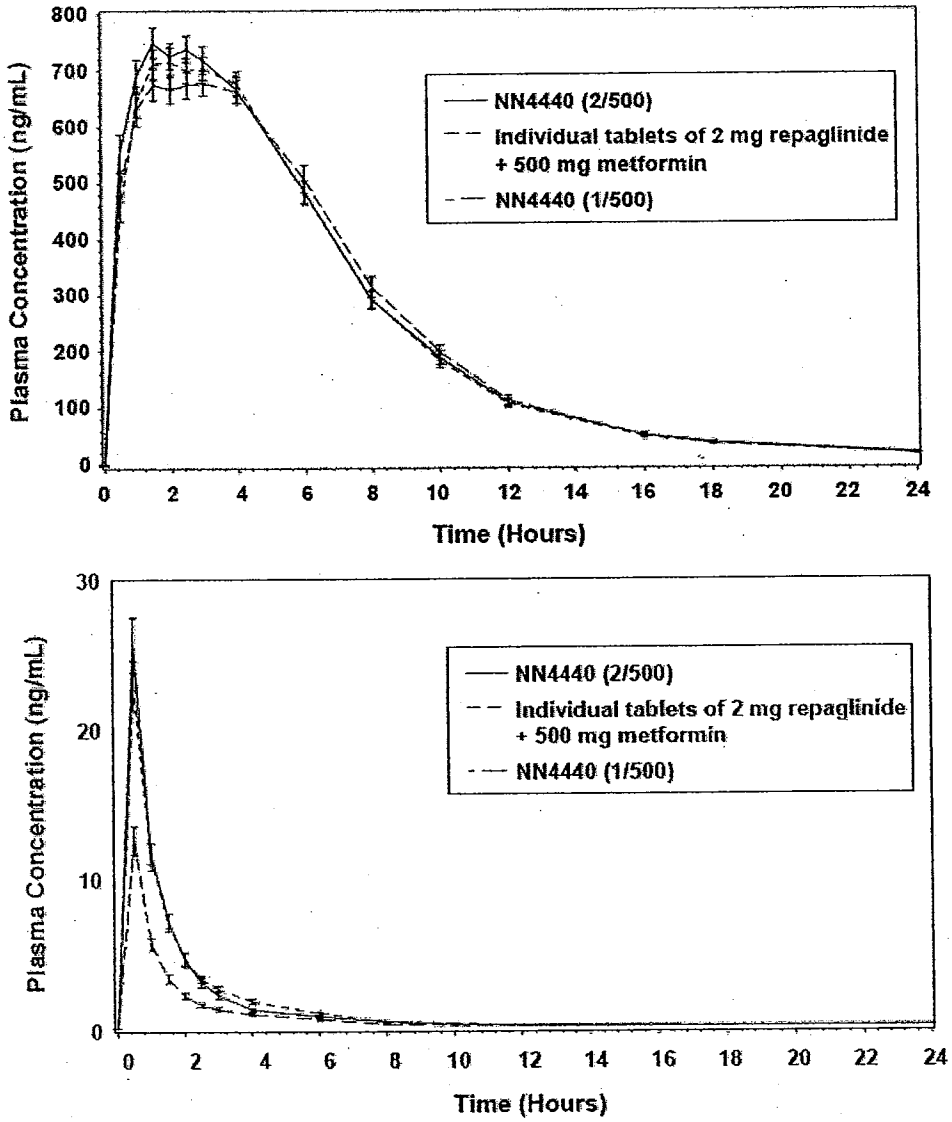
Only two of 2 of 6 possible treatment sequences (Williams design) are shown.

A = NN4440 (2/500)
B = Individual tablets of 2 mg repaglinide + 500 mg metformin
C = NN4440 (1/500)

Blood was sampled at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 18, and 24 hours after dosing for repaglinide and metformin assay. 55 subjects completed the study and 38 subjects withdrew. Sponsor has stated that these 38 subjects did not withdraw from the trial due to an adverse event but due to logistical problems that these subjects were unavailable for later visits. The primary PK endpoints were repaglinide and metformin AUC, AUC0-24, AUC0-t, and Cmax. Sponsor used all of these four endpoints to establish bioequivalence between the FDC (2/500) and concomitantly administered individual tablets of 2 mg repaglinide and 500 mg metformin.

The mean plasma drug concentrations over time are shown in the Figure 2 for metformin and repaglinide. As shown below, the metformin plasma profiles following various treatments were superimposing except at Tmax of around 2-4 hours post-dose, where there was some variability between treatments. In case of repaglinide, the concentrations following 2/500 mg FDC tablet administrations were similar to that following the individual tablet (Figure 2).

Figure 2: Mean metformin (top) and repaglinide (bottom) plasma concentration (ng/mL) over time by treatment for the PK population



Sponsor concluded that both metformin and repaglinide PK parameters (AUC, AUC(0-24), AUC(0-t), and Cmax) from the FDC (2/500 mg) were bioequivalent to concomitantly administered individual tablets of 2 mg repaglinide and 500 mg metformin. This was demonstrated based on the limits of the 90% CI of the mean treatment ratio of the PK parameters was contained within the predetermined interval of 0.8 to 1.25 (Table 3). The reviewer also conducted the BE analysis using both SAS and WinNonlin and the results were similar to that of the sponsor (Table 4). [Results were similar with both WinNonlin and SAS; Table 4 shows results obtained from WinNonlin].

Table 3: Primary PK parameters - Sponsor's analysis

PK Parameter	Metformin			Repaglinide		
	LS Mean Reference (N=55)	LS Mean Test (N=55)	Ratio (90% CI)	LS Mean Reference (N=55)	LS Mean Test (N=55)	Ratio (90% CI)
AUCinf (ng. h/mL)	5740.6	5877.8	102.39 (98.53 – 106.40)	32.8	32.3	98.66 (94.77 – 102.71)
AUC(0-24) (ng. h/mL)	5633.0	5756.1	102.19 (98.22 – 106.31)	32.3	31.8	98.50 (94.64 – 102.52)
AUC(0-t) (ng. h/mL)	5633.0	5756.1	102.19 (98.22 – 106.31)	32.1	31.6	98.52 (94.63 – 102.57)
Cmax (ng/mL)	792.0	816.7	103.11 (98.49 – 107.96)	20.4	22.1	108.49 (94.26 – 124.86)

Table 4: Primary PK parameters - Reviewer's analysis

PK Parameter	Metformin			Repaglinide		
	LS Mean Reference (N=55)	LS Mean Test (N=55)	Ratio (90% CI)	LS Mean Reference (N=55)	LS Mean Test (N=55)	Ratio (90% CI)
AUCinf (ng. h/mL)	5740.61	5798.60	102.39 (98.53 – 106.40)	32.75	32.31	98.66 (94.77 – 102.71)
AUC(0-t) (ng. h/mL)	5632.95	5756.11	102.19 (98.22 – 106.31)	32.079	31.60	98.52 (94.63 – 102.57)
Cmax (ng/mL)	792.04	816.69	103.11 (98.49 – 107.96)	20.37	22.10	108.49 (94.26 – 124.86)

Are the repaglinide PK parameters following administration of FDC 2 /500 mg and FDC 1/500 mg dose-proportional?

Yes.

The dose proportionality was addressed for the two strengths of the FDC tablets, 2/500 mg and 1/500 mg with regard to repaglinide drug concentrations. The approach was analogous to that of the bioequivalence using dose-adjusted primary PK parameters. Sponsor concluded that the FDC 2/500 mg tablet strength demonstrated dose proportionality to FDC 1/500 mg strength since for all the repaglinide PK parameters analyzed (AUC, AUC0-t, AUC0-24, and Cmax), and the 90% CI for the ratio of FDC

(2/500)/FDC (1/500) (dose normalized) were within the predetermined limit of 0.8 – 1.25 (Table 5).

Table 5: Primary repaglinide PK parameters (dose normalized for 1/500 mg): Sponsor's analysis

PK parameter	LS Mean 2/500 mg (N=55)	LS Mean 1/500 mg (N=55)	Ratio (90% CI)
AUCinf (ng. h/mL)	32.3	33.0	97.99 (94.13 – 102.02)
AUC(0-24) (ng. h/mL)	31.8	32.3	98.51 (94.65 – 102.53)
AUC(0-t) (ng. h/mL)	31.6	31.9	99.05 (95.14 – 103.12)
Cmax (ng/mL)	22.1	21.5	102.72 (89.25 – 118.22)

Metformin AUC and Cmax from the two treatments (1/500 mg and 2/500 mg) were bioequivalent. The log-transformed geometric mean ratio (90% CI) for metformin AUC0-t, AUCinf, and Cmax were 98.79 (94.95 – 102.77), 98.65 (94.93 – 102.51) and 95.81 (91.51 – 100.32) respectively [Reviewer's analysis]. Secondary PK parameters (Tmax, t1/2, CL/f, ke [elimination rate constant], Vz/f) seemed similar for metformin and repaglinide among all 3 treatments (Table 6).

Table 6: Secondary PK parameters (Mean ± SD) for metformin and repaglinide

PK Parameter	Metformin			Repaglinide		
	FDC (2/500 mg) (N=55)	Individual tablets (2 mg + 500 mg) (N=55)	FDC (1/500 mg) (N=55)	FDC (2/500 mg) (N=55)	Individual tablets (2 mg + 500 mg) (N=55)	FDC (1/500 mg) (N=55)
Tmax (hour)	2.08 (1.04)	2.57 (1.2)	2.62 (1.5)	0.65 (0.25)	0.77 (0.61)	0.86 (0.80)
t1/2 (hour)	4.41 (0.71)	4.27 (0.51)	4.22 (0.57)	3.07 (2.38)	2.89 (1.65)	2.24 (1.65)
ke (L/h)	0.161 (0.02)	0.164 (0.01)	0.167 (0.02)	0.28 (0.11)	0.28 (0.10)	0.38 (0.16)
CL/f (mL/h)	89.77 (22.90)	91.26 (20.97)	90.63 (21.90)	68.22 (26.49)	66.91 (25.47)	67.49 (26.66)
Vz/f (mL)	584.38 (233.38)	570.33 (180.86)	559.73 (189.81)	291.44 (207.5)	273.42 (165.46)	213.36 (214.2)

Comments:

- The schedule of the PK blood sampling was chosen to be consistent with the half life for metformin (3-5 hours) and repaglinide (1-2 hours).
- Minimum washout period between doses was 4 days which is acceptable based on the half-life of both metformin and repaglinide.
- Prematurely withdrawn subjects were replaced until 54 evaluable subjects completed the study. Replacement subjects were either assigned to the next available subject number with the same treatment code or they were given a prefix of 1 and assigned the same exact treatment sequence as the subject they replaced (e.g., withdrawn subject 41 [A-B-C] was replaced by subject 141 [A-B-C].
- BE study was conducted with the proposed highest tablet strength.
- All treatments were administered just prior (5 min) to a high fat meal (repaglinide is generally administered immediately prior to meals and metformin is administered with meals).
- Actual time values were used for all PK calculations. PK values below the lower limit of quantitation were treated as 0 at time 0. At other time points, the data below the limit of quantitation was treated as missing. This is acceptable.
- The protocol was amended following the hypoglycemic episodes experienced by the first cohort of subjects in spite of drug being administered immediately prior to a high fat meal. The sponsor added the following: more frequent plasma glucose monitoring, midnight carbohydrate snack (Days 0, 6, and 13), an algorithm for starting glucose infusion and general guidelines for treating possible hypoglycemic events.

5.32%. The accuracy (expressed as % relative error, or %RE) ranged from -9.38% to 2.00% (Table 6).

Table 6:

Intra-Batch Precision and Accuracy of Quality Controls

Batch No.	Metformin, ng/mL		
	15	300	750
T01	12.272*	292.714	743.363
	12.841	293.436	728.978
	13.570	297.876	728.903
	13.197	298.944	712.868
	13.367	290.900	750.932
	12.983	300.212	734.009
Mean	13.038	295.680	733.176
SD	0.457	3.813	13.176
%CV	3.51	1.29	1.80
%RE	-13.08	-1.44	-2.24

Inter-Batch Precision and Accuracy of Quality Controls

Batch No.	Metformin, ng/mL		
	15	300	750
Mean	13.593	306.002	760.995
SD	0.723	10.990	25.414
%CV	5.32	3.59	3.34
%RE	-9.38	2.00	1.47

Repaglinide

Method: Repaglinide was analyzed in human plasma using a LC/MS/MS procedure. Briefly, EDTA human plasma samples containing repaglinide was spiked with internal standard (repaglinide-d5) and extracted using liquid-liquid extraction.

Results: The lower limit of quantitation (LLOQ) was 0.1 ng/mL and linearity of repaglinide in human plasma was demonstrated over the range of 0.1 to 50 ng/mL. Recovery of repaglinide ranged from 95.33% to 97.67% over this concentration range. The intra-batch precision of QC samples (%CV) ranged from 1.37% to 3.2%, while accuracy (%RE) ranged from 4.63% to 9.33%. The inter-batch of QC samples precision (%CV) ranged from 0.45% to 4.51%, and accuracy (%RE) ranged from -3.15% to 2.62% (Table 7). The chromatography was acceptable in terms of column efficiency, linearity and sensitivity.

Table 7:

Intra-Batch Precision and Accuracy of Quality Control Samples of Repaglinide

Batch No.	Repaglinide, ng/mL		
	0.3	15	37.5
V01	0.330	14.846	39.419
	0.331	15.444	41.263
	0.334	16.075	39.837
	0.324	15.704	39.226
	0.322	16.250	39.495
	0.327	15.846	40.632
Mean	0.3280	15.6941	39.9786
SD	0.0045	0.5018	0.8014
%CV	1.37	3.20	2.00
%RE	9.33	4.63	6.61

Inter-Batch Precision and Accuracy of Quality Control Samples of Repaglinide

Batch No.	Repaglinide, ng/mL		
	0.3	15	37.5
Mean	0.3220	15.5015	38.9134
SD	0.0152	0.5862	1.7520
%CV	4.72	3.78	4.50
%RE	7.35	3.34	3.77

[Note: Analytical procedure was carried out by 55 subjects completed all test periods and 38 subjects participated in dosing but did not complete the study. Only samples from subjects completing the study were analyzed as per instructions from the sponsor.]

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III Labeling Recommendations

The Office of Clinical Pharmacology (OCP/DCP-2) has reviewed the package insert labeling for Prandi*Met* and finds it acceptable pending the following revision:

(~~Strikethrough text~~ is recommended to be deleted and **underlined text** is recommended to be added.)

Comment: It is noted that there was significant drug interaction when gemfibrozil (when given alone or with itraconazole) was co-administered with repaglinide. This was based on literature data. The plasma concentrations in this study were measured only for 7 hours. The mean AUC0-7 increased to about 20 fold (the maximum increase in individual AUC was ~ 25 fold). The plasma concentration at 7 hour was increased 70 fold with the combination of gemfibrozil-itraconazole. In this study they also looked at PD and glucose-lowering effect of repaglinide was prolonged in presence of the combination, potentially leading to severe hypoglycemia. Two (out of 12) subjects required carbohydrate supplementation because of symptomatic hypoglycemia during the combination phase. Please refer to Clinical Pharmacology review by Dr. Sang Chung for details. Thus, we recommend the following:

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The other labeling recommendations are as follows:

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18 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio-1

B Individual Study Synopsis

2 Synopsis

PACT Number – Not applicable.	IND Number – 70,959
Title of Trial A Randomised, Single-Blind, Three-Period Crossover Study Examining the Single-Dose Pharmacokinetics of Concomitantly Administered Repaglinide and Metformin Versus Combination Tablet Dosing (NN4440) in Fed Healthy Volunteers	
Investigator [redacted]	
Trial Site One site in the U.S.: [redacted]	
Publications None.	
Trial Period 1 June 2006 to 5 August 2006	**Development Phase** Phase 1
Objectives **Primary Objective:** • To compare the single-dose repaglinide (2 mg) and metformin (500 mg) AUC and C_{max} as co-administered tablets and in NN4440 combination tablet (2 mg repaglinide /500 mg metformin) dosing under fed conditions. **Secondary Objectives:** • To compare the repaglinide dose proportionality of NN4440 (1 mg repaglinide/500 mg metformin) and NN4440 (2/500). • To compare secondary pharmacokinetic parameters of repaglinide and metformin in single dose and combination therapy. • To examine the safety and tolerability of repaglinide and metformin in combination tablet therapy.	
Methodology This trial was a single-blind, randomised, three-period crossover study. Subjects were randomised to 1 of 6 possible treatment sequences (Williams design). Subjects received a single dose of NN4440 (1/500), NN4440 (2/500), or 2 mg repaglinide and 500 mg metformin co-administered as individual tablets per study period. All trial products were administered immediately prior to a standard high-fat breakfast.	
Number of Subjects Planned and Analysed Planned to Randomise: 58 Randomised: 93 Completed: 55	
Diagnosis and Main Criteria for Inclusion Healthy male and female volunteers ≥ 18 and ≤ 45 years with a BMI ≥ 19 and ≤ 29 kg/m^2	
Test Product, Dose and Mode of Administration, Batch Number	

Trial Products	Batch Number	Expiry Date
NN4440 (1/500) (repaglinide 1 mg, metformin 500 mg) tablet	SBBN012	03 January 2007
NN4440 (2/500) (repaglinide 2 mg, metformin 500 mg) tablet	SBBN018	03 January 2007

• Products were administered as a single oral dose. Only 1 dose of each of the 3 treatments was administered to each subject in the study (1 dose per study period).
• Test products were administered immediately prior to a high-fat breakfast.

Duration of Treatment A single dose of each of the three treatments was administered per study period. Each dose was separated by a washout period of at least 4 days.	

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Reference Therapy, Dose and Mode of Administration, Batch Number

Trial Product	Batch Number	Expiry Date
Repaglinide, 2 mg tablets (Prandin®, Novo Nordisk)	5060601	31 May 2010
Metformin, 500 mg tablets (Glucophage®, Bristol-Myers Squibb)	6A12719	31 October 2009

- Repaglinide 2 mg and metformin 500 mg were concomitantly administered as a single oral dose.
- Reference products were administered immediately prior to a high-fat breakfast.

Criteria for Evaluation – Efficacy

Primary

- Pharmacokinetic parameters from drug concentration measurements: repaglinide and metformin AUC, AUC_{0-t}, AUC_{0-24}, and C_{max} for NN4440 (2/500) and individual tablets of 2 mg repaglinide and 500 mg metformin.

Secondary

- Pharmacokinetic parameters from drug concentration measurements: repaglinide AUC, AUC_{0-t}, AUC_{0-24}, and C_{max} for NN4440 (2/500) and NN4440 (1/500).
- Pharmacokinetic parameters from drug concentration measurements: repaglinide and metformin t_{max}, $t_{1/2}$, λz, Cl/f, MRT, and Vz/f for NN4440 (2/500), individual tablets of 2 mg repaglinide and 500 mg metformin, and NN4440 (1/500).

Criteria for Evaluation – Safety

- Treatment-emergent adverse events and treatment-emergent serious adverse events
- Incidence of hypoglycaemic episodes
- Clinical assessments (vital signs, standard 12-lead ECG, complete/targeted physical examination, height, body weight)
- Clinical laboratory tests (urinalysis, haematology with differential, biochemistry, pregnancy, hepatitis B and C, HIV, urine drug screen)
- Concomitant medications

Statistical Methods

Primary Efficacy

- The PK population was used for all efficacy parameters. The PK population consisted of all subjects who fulfilled the following criteria:
  - Complied with all entry criteria
  - Had not violated the protocol such that pharmacokinetic data collection was compromised.
  - Subjects who completed all required evaluations at all scheduled visits.
  - Subjects with valid blood concentrations so that their primary PK parameters could be assessed in all 3 periods.
- Bioequivalence was assessed for the treatments of repaglinide (2 mg) and metformin (500 mg) as co-administered tablets and the combination tablet NN4440 (2 mg repaglinide /500 mg metformin). A 90% confidence interval for $\eta_1 - \eta_2$ (difference of log-transformed AUC or C_{max}), which is equivalent to the Shuirmann's two 1-sided t-tests at 5% level, was constructed. If the 90% confidence intervals for the group mean differences of the log-transformed AUC and C_{max} fell within the range $-\ln 1.25$ to $\ln 1.25$, then the null hypotheses were rejected at the 5% level and the average bioequivalence was demonstrated. Subsequently, these differences and confidence intervals were exponentiated (to estimate geometric means ratios) and assessed relative to the bioequivalence interval [0.80, 1.25]. The 90% confidence intervals used the estimated least-square difference of the means and mean square error based on a 3 x 6 Williams design with three treatment periods, and 6 treatment sequences.

Secondary efficacy

- The approach of dose-proportionality was analogous to that of bioequivalence since the study consisted of only two different doses of a drug. The dose-adjusted primary pharmacokinetic parameters (AUC/dose and C_{max}/dose) were used to determine the bioequivalence assessment of NN4440 (2/500) and NN4440 (1/500). Dose proportionality of NN4440 (2/500) and NN4440 (1/500) was established if the dose-adjusted primary pharmacokinetic parameters were bioequivalent.
- Descriptive statistics and 90% confidence intervals were provided for other pharmacokinetic parameters (MRT, t_{max}, λ_z and $t_{\frac{1}{2}}$, CL/f, Vz/f) using appropriate statistical methodology.

Safety

- All enrolled and randomised subjects that received at least one dose of study drug were included in the safety population and analysis.
- If a safety variable was evaluated at each visit (i.e., for each treatment), then that particular safety variable was summarised by treatment. Otherwise, safety evaluations were summarised by treatment sequence and for overall subjects.
- Treatment-emergent AEs and SAEs were summarised and presented. No formal statistical analysis was performed.
- Descriptive statistics, and change from baseline were tabulated for vital signs.
- Clinical laboratory tests were tabulated. Descriptive statistics and change from baseline for each subsequent visit were presented. Values outside of the reference ranges were flagged as being high or low.
- Number and percentage of subjects with abnormality at Screening in complete physical examination by body system and Investigator's overall assessment was provided. For targeted physical examination, number and percentage of subjects with no new or worsening symptoms since last visit were presented.
- Descriptive ECG statistics for the raw data at Visit 1 and the end of the trial, and Investigator's overall interpretations of ECG were presented.
- Frequencies of subjects experiencing any episode of hypoglycaemia were tabulated for episodes occurring after Amendment #2 of the Protocol.

Demography of Trial Population

	A-B-C (N=17)	C-A-B (N=14)	B-C-A (N=16)	C-B-A (N=15)	B-A-C (N=16)	A-C-B (N=15)	Total (N=93)
Sex (n (%))							
Male	6 (35.3%)	7 (50.0%)	6 (37.5%)	7 (46.7%)	7 (43.8%)	7 (46.7%)	40 (43.0%)
Female	11 (64.7%)	7 (50.0%)	10 (62.5%)	8 (53.3%)	9 (56.3%)	8 (53.3%)	53 (57.0%)
Race (n (%))							
AMERICAN INDIAN - ALASKA NATIVE	0	0	0	0	0	1 (6.7%)	1 (1.1%)
ASIAN	0	0	1 (6.3%)	2 (13.3%)	0	0	3 (3.2%)
AFRICAN AMERICAN	2 (11.8%)	3 (21.4%)	3 (18.8%)	3 (20.0%)	2 (12.5%)	2 (13.3%)	15 (16.1%)
CAUCASIAN	15 (88.2%)	11 (78.6%)	11 (68.8%)	10 (66.7%)	13 (81.3%)	12 (80.0%)	72 (77.4%)
OTHER	0	0	1 (6.3%)	0	1 (6.3%)	0	2 (2.2%)
Ethnicity (n (%))							
HISPANIC	4 (23.5%)	6 (42.9%)	5 (31.3%)	4 (26.7%)	3 (18.8%)	5 (33.3%)	27 (29.0%)
NOT HISPANIC	13 (76.5%)	8 (57.1%)	11 (68.8%)	11 (73.3%)	13 (81.3%)	10 (66.7%)	66 (71.0%)
Age (Years)							
N	17	14	16	15	16	15	93
Mean	27.8	26.6	30.9	26.9	26.6	31.4	28.4
SD	5.3	4.9	7.7	7.5	7.6	8.3	7.1
Median	27.8	25.4	31.6	26.4	23.8	30.2	27.6
Min	19.6	19.6	18.3	19.3	20.0	18.8	18.3
Max	40.5	39.9	44.2	43.2	43.5	45.9	45.9
Height (cm)							
N	17	14	16	15	16	15	93
Mean	168.7	171.2	167.7	170.3	172.5	172.8	170.5
SD	8.4	11.4	9.3	9.0	12.5	8.9	9.9
Median	168.1	169.4	168.1	171.3	173.4	176.2	170.3
Min	154.4	156.2	151.6	156.9	154.0	156.5	151.6
Max	183.6	193.2	185.4	185.8	196.4	184.0	196.4
Weight (kg)							
N	17	14	16	15	16	15	93
Mean	67.6	70.0	68.5	71.7	74.1	73.2	70.8
SD	11.3	10.2	11.1	15.3	13.1	10.5	12.0
Median	69.3	68.5	67.1	69.9	73.2	72.9	69.6
Min	51.2	54.3	46.9	46.9	54.4	55.2	46.9
Max	88.0	87.6	91.5	96.0	108.4	94.3	108.4
BMI (kg/m^2)							
N	17	14	16	15	16	15	93
Mean	23.6	23.8	24.3	24.5	24.8	24.4	24.2
SD	2.5	3.0	2.0	3.3	2.1	2.4	2.4
Median	24.4	23.7	24.7	25.5	24.4	23.2	24.4
Min	19.1	20.3	19.8	19.1	20.4	21.5	19.1
Max	27.2	27.5	27.4	29.0	26.1	28.5	29.0

Treatment A = NN4440 (2/500); B = Individual tablets of 2 mg repaglinide + 500 mg metformin; C = NN4440 (1/500).

Efficacy Results

- Metformin in the NN4440 (2 mg repaglinide/500 mg metformin) fixed dose combination tablet was demonstrated to be bioequivalent to concomitantly administered individual tablets of 2 mg repaglinide and 500 mg metformin for primary pharmacokinetic parameters. Bioequivalence was demonstrated because the 90% CIs of the mean treatment ratios were contained within the predetermined bioequivalence interval [0.8, 1.25] (AUC, [0.9853, 1.0640]; AUC_{0-24}, [0.9822, 1.0631]; AUC_{0-t}, [0.9822, 1.0631]; C_{max}, [0.9849, 1.0796]).
- Repaglinide in NN4440 (2 mg repaglinide/ 500 mg metformin) was demonstrated to be bioequivalent to concomitantly administered individual tablets of 2 mg repaglinide and 500 mg metformin for primary pharmacokinetic parameters. Bioequivalence was demonstrated because the 90% CIs of the mean treatment ratios were contained within the predetermined bioequivalence interval [0.8, 1.25] (AUC, [0.9477, 1.0271]; AUC_{0-24}, [0.9464, 1.0252], AUC_{0-t}, [0.9463, 1.0257]; C_{max}, [0.9426, 1.2486]).
- NN4440 (2/500) was demonstrated to be dose proportional to NN4440 (1/500) for all repaglinide pharmacokinetic parameters (AUC, AUC_{0-24}, AUC_{0-t} and C_{max}). Dose proportionality was demonstrated since the 90% CIs for the ratio of NN4440 (2/500)/NN4440 (1/500)(dose normalised) were within the predetermined limit of [0.8, 1.25] (AUC, [0.9413, 1.0202]; AUC_{0-24}, [0.9465, 1.0253], AUC_{0-t}, [0.9514, 1.0312]; C_{max}, [0.8925, 1.1822]).
- Secondary metformin and repaglinide pharmacokinetic parameters (t_{max}, $t_{1/2}$, λz, Cl/f, MRT, and Vz/f) appeared similar between the combination tablets and the co-administered individual tablets.

Safety Results

- A total of 56 subjects (60.2%) experienced 141 treatment-emergent adverse events; 24 (33.8%) subjects treated with NN4440 (2/500), 25 (36.8%) subjects treated with individual tablets of 2 mg repaglinide + 500 mg metformin, and 16 (23.9%) subjects treated with NN4440 (1/500).
- A total of 26 subjects (28%) had 26 treatment emergent serious adverse events which were listed as serious due to a non-standard classification of hypoglycaemic events in the original version of the Protocol that led to an artificially elevated estimate of hypoglycaemic events that were characterized as TESAEs; 12 (16.9%) subjects treated with NN4440 (2/500), 9 (13.2%) subjects treated with individual tablets of 2 mg repaglinide + 500 mg metformin, 5 (7.5%) subjects treated with NN4440 (1/500). All TESAEs were classified as "hypoglycaemia" and occurred prior to Amendment #2 of the Protocol which instituted more frequent blood glucose monitoring and a glucose infusion algorithm. Prior to Amendment #2 of the Protocol, when these events occurred, hypoglycaemic events with a plasma glucose value < 56 mg/dL, with or without symptoms were classified as TESAEs.
- The majority of TEAEs in each of the treatment periods were considered possibly or probably related to study drug (NN4440 [2/500], 47 of 60 events; individual tablets of 2 mg repaglinide + 500 mg metformin, 42 of 55 events; NN4440 [1/500], 25 of 26 events).
- The most frequently occurring TEAEs (occurring in ≥ 5% of subjects in any treatment group) were hypoglycaemia, headache, diarrhoea, dizziness, and nausea, and were similar across treatment groups.
- No deaths or withdrawals due to adverse events were reported in this study.
- No clinically notable changes in physical examinations, vital signs, ECG parameters, or clinical laboratory parameters occurred in this study.
- After Amendment #2 of the Protocol, all episodes of hypoglycaemia were classified as major, minor, or symptoms only. All reported hypoglycaemic episodes were minor (NN4440 [2/500], 18 [25.4%] subjects, 32 episodes; individual tablets of 2 mg repaglinide + 500 mg metformin, 24 [35.3%] subjects, 33 episodes; NN4440 [1/500], 18 [26.9%] subjects, 26 episodes).

Conclusions

- In this study, metformin and repaglinide in the combination tablet of NN4440 (2 mg repaglinide/500 mg metformin) were demonstrated to be bioequivalent to concomitantly administered individual tablets of 2 mg repaglinide and 500 mg metformin.
- Repaglinide dose proportionality was demonstrated for NN4440 (2 mg repaglinide/500 mg metformin) and NN4440 (1 mg repaglinide/500 mg metformin) fixed-dose tablets.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

C OCP Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	22-232	Brand Name	PrandiMet
OCP Division	DCP 2	Generic Name	repaglinide/metformin HCl
Medical Division	DMEP	Drug Class	
OCP Reviewer	Filing by Sally Choe, Ph.D. on behalf of Jayabharathi Vaidyanathan, Ph.D.	Indication(s)	An adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
OCP Pharmacometrics Reviewer	N/A	Dosage Form	Tablet; 1/500 and 2/500 (mg/mg)
OCP Team Leader	Sally Choe, Ph.D. (Acting)	Dosing Regimen	1/500 mg through 10/2500 mg 2 to 3 times daily with meals
Date of Submission	August 10, 2007	Route of Administration	Oral
Estimated Due Date of OCP Review	May 20, 2008 (review due in DFS)	Sponsor	Novo Nordisk
PDUFA Due Date	June 15, 2008	Priority Classification	S
Division Due Date	June 12, 2008		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	X	1		
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

Filability		
	"X" if yes	Comments
Application filable ?	X	The formulations used in the bioequivalence study are identical to the fixed dose combination (FDC) formulations intended for the market. DSI inspection is requested for BE study (NN4440-1753) trial site and its analytical site.

Submission In Brief:

Prandin (repaglinide) Tablets was approved on December 22, 1997, for the treatment of type 2 diabetes. Repaglinide is approved for use in combination with metformin as second line therapy with frequency of dosing two to three times daily, with meals. The sponsor has submitted NDA 22-232 requesting approval of the fixed dose combination (FDC) product, PrandiMet, a combination product with repaglinide and metformin HCl for an indication of an adjunct to diet and exercise to improve glycemic control in type 2 diabetics.

The Agency had earlier accepted that a bioequivalence (BE) trial will be adequate to support the approval of the FDC tablet. In response, the sponsor conducted a BE trial, NN4440-1753 to show that the FDC tablets are bioequivalent to concomitantly administered repaglinide and metformin. In addition, the sponsor submitted a factorial efficacy and safety clinical trial AGEE-053, which originally submitted with the repaglinide NDA 20-741 and another efficacy and safety clinical trial AGEE-3017 in type 2 diabetics no adequately controlled using diet and exercise alone (OAD naïve patients).

The Agency has accepted previously that the sponsor will not conduct a repaglinide-metformin HCl interaction trial and a food interaction trial with the FDC.

The pivotal BE study NN4440-1753 is described below:

NN4440-1753

Title: A Randomised, Single-Blind, Three-Period Crossover Study Examining the Single-Dose Pharmacokinetics of Concomitantly Administered Repaglinide and Metformin versus Combination Tablet Dosing (NN4440) in Fed Healthy Volunteers

Trial Site: [redacted] b(4)

Analytical Site: [redacted] b(4)

Bioanalytical Investigator: [redacted]

Primary Objective:

• To compare the single-dose repaglinide (2 mg) and metformin (500 mg) AUC and Cmax as co-administered tablets and in NN4440 combination tablet (2 mg repaglinide /500 mg metformin) dosing under fed conditions.

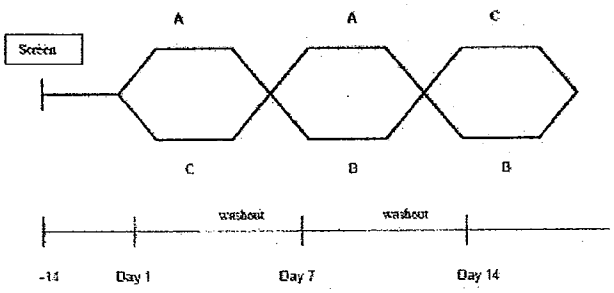
Secondary Objectives:

• To compare the repaglinide dose proportionality of NN4440 (1 mg repaglinide/500 mg metformin) and NN4440 (2/500).

• To compare secondary pharmacokinetic parameters of repaglinide and metformin in single dose and combination therapy.

• To examine the safety and tolerability of repaglinide and metformin in combination tablet therapy.

Study Design:



Only two of 2 of 6 possible treatment sequences (Williams design) are shown.

Allowable treatment sequences include:

A-B-C
C-A-B
B-C-A
C-B-A
B-A-C
A-C-B

Where:
A = NN4440 (2/500)
B = Individual tablets of 2 mg repaglinide + 500 mg metformin
C = NN4440 (1/500)

Investigational Products:

Table 9–1 Batch Numbers and Expiry Dates of Trial Products

Trial Product	Batch Number	Expiry Date
NN4440 (1/500) (repaglinide 1 mg, metformin 500 mg) tablet	SBBN012	03 January 2007
NN4440 (2/500) (repaglinide 2 mg, metformin 500 mg) tablet	SBBN018	03 January 2007
Repaglinide, 2 mg tablets (Prandin®, Novo Nordisk)	5060601	31 May 2010
Metformin, 500 mg tablets (Glucophage®, Bristol-Myers Squibb)	6A12719	31 October 2009

Study Results:

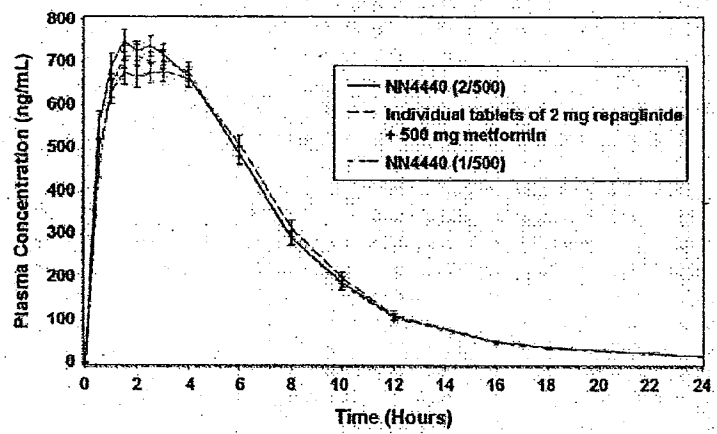


Figure 11–1 Mean Metformin Plasma Concentration (ng/mL) Over Time by Treatment – PK Population

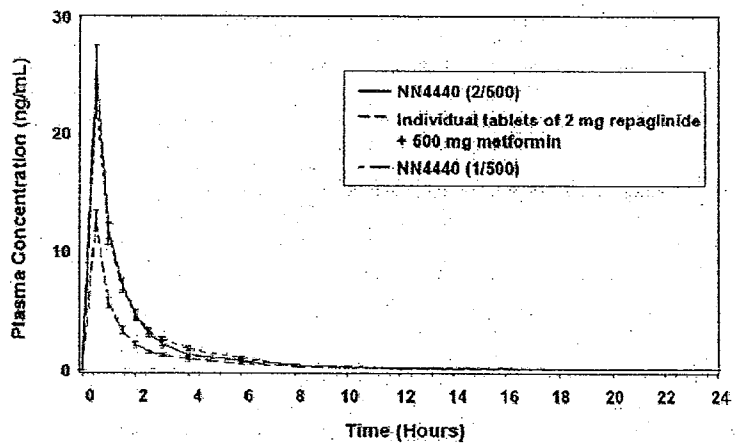


Figure 11–2 Mean Repaglinide Plasma Concentration (ng/mL) Over Time by Treatment – PK Population

Table 11–3 Primary Pharmacokinetic Parameters for Metformin Bioequivalence – PK Population

Parameter	A (N=55)	B (N=55)	90% CI for the Ratio (A/B)	Bioequivalence Achieved?[a]
AUC (ng*h/mL)				
N	55	55	[0.9853, 1.0640]	Yes
Mean	6041.911	5971.621		
SD	1494.582	1352.617		
Median	5870.996	5809.320		
Min	3266.09	3319.35		
Max	9796.40	10411.87		
LS Means	5877.8	5740.6		
AUC(0-24) (ng*h/mL)				
N	55	55	[0.9822, 1.0631]	Yes
Mean	5920.496	5762.298		
SD	1479.846	1328.531		
Median	5791.920	5692.760		
Min	3114.54	3244.95		
Max	9638.92	10117.21		
LS Means	5756.1	5633.0		
AUC(0-t) (ng*h/mL)				
N	55	55	[0.9822, 1.0631]	Yes
Mean	5920.496	5762.298		
SD	1479.846	1328.531		
Median	5791.920	5692.760		
Min	3114.54	3244.95		
Max	9638.92	10117.21		
LS Means	5756.1	5633.0		
Cmax (ng/mL)				
N	55	55	[0.9849, 1.0796]	Yes
Mean	838.840	805.906		
SD	210.192	160.328		
Median	794.382	803.451		
Min	472.64	473.70		
Max	1465.24	1183.61		
LS Means	816.7	792.0		

Treatment A = NN4440 (2/500); B = Individual tablets of 2 mg repaglinide + 500 mg metformin; CI = confidence interval; AUC = area under the concentration time curve calculated for the linear trapezoidal rule time 0 extrapolated to infinity; AUC_{0-24} = area under the concentration time curve calculated by the linear trapezoidal rule time 0 hr to 24 hours after dosing; AUC_{0-t} = area under the concentration time curve calculated by the linear trapezoidal rule time 0 hr to the time of the last measurable concentration; C_{max} = maximum drug concentration.

a: Metformin bioequivalence was demonstrated if the 90% CI of the mean treatment ratios (A/B) for the primary PK parameters were contained within the interval [0.8, 1.25].

Table 11–4 Primary Pharmacokinetic Parameters for Repaglinide Bioequivalence – PK Population

Parameter	A (N=55)	B (N=55)	90% CI for the Ratio (A/B)	Bioequivalence Achieved?[a]
AUC (ng*h/mL)				
N	55	55	[0.9477, 1.0271]	Yes
Mean	34.536	35.016		
SD	11.292	13.184		
Median	31.963	33.378		
Min	13.64	15.13		
Max	71.22	75.67		
LS Means	32.3	32.8		
AUC(0-24) (ng*h/mL)				
N	55	55	[0.9464, 1.0252]	Yes
Mean	34.094	34.613		
SD	13.309	13.186		
Median	31.589	33.167		
Min	13.30	15.09		
Max	71.19	75.24		
LS Means	31.8	32.3		
AUC(0-t) (ng*h/mL)				
N	55	55	[0.9463, 1.0257]	Yes
Mean	33.867	34.369		
SD	13.292	13.166		
Median	31.362	32.815		
Min	13.24	14.98		
Max	70.99	75.09		
LS Means	31.6	32.1		
Cmax (ng/mL)				
N	55	55	[0.9426, 1.2486]	Yes
Mean	25.966	23.711		
SD	13.685	12.523		
Median	27.059	21.798		
Min	4.20	5.19		
Max	67.11	59.72		
LS Means	22.1	20.4		

Treatment A = NN4440 (2/500); B = Individual tablets of 2 mg repaglinide + 500 mg metformin; CI = confidence interval; AUC = area under the concentration time curve calculated for the linear trapezoidal rule time 0 extrapolated to infinity; AUC_{0-24} = area under the concentration time curve calculated by the linear trapezoidal rule time 0 hr to 24 hours after dosing; AUC_{0-t} = area under the concentration time curve calculated by the linear trapezoidal rule time 0 hr to the time of the last measurable concentration; C_{max} = maximum drug concentration.

a: Repaglinide bioequivalence was demonstrated if the 90% CI of the mean treatment ratios (A/B) for the primary PK parameters were contained within the interval [0.8, 1.25].

Cross reference: EOT Table 14.2-6.

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

/s/

Jayabharathi Vaidyanathan
5/30/2008 03:00:06 PM
BIOPHARMACEUTICS

Sally Choe
5/30/2008 03:38:14 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-232	Brand Name	PrandiMet
OCP Division	DCP 2	Generic Name	repaglinide/metformin HCl
Medical Division	DMEP	Drug Class	
OCP Reviewer	Filing by Sally Choe, Ph.D. on behalf of Jayabharathi Vaidyanathan, Ph.D.	Indication(s)	An adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
OCP Pharmacometrics Reviewer	N/A	Dosage Form	Tablet; 1/500 and 2/500 (mg/mg)
OCP Team Leader	Sally Choe, Ph.D. (Acting)	Dosing Regimen	1/500 mg through 10/2500 mg 2 to 3 times daily with meals
Date of Submission	August 10, 2007	Route of Administration	Oral
Estimated Due Date of OCP Review	May 20, 2008 (review due in DFS)	Sponsor	Novo Nordisk
PDUFA Due Date	June 15, 2008	Priority Classification	S
Division Due Date	June 12, 2008		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	X	1		
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

Filability		
	"X" if yes	**Comments**
Application filable ?	X	The formulations used in the bioequivalence study are identical to the fixed dose combination (FDC) formulations intended for the market. DSI inspection is requested for BE study **(NN4440-1753)** trial site and its analytical site.

Submission In Brief:

Prandin (repaglinide) Tablets was approved on December 22, 1997, for the treatment of type 2 diabetes. Repaglinide is approved for use in combination with metformin as second line therapy with frequency of dosing two to three times daily, with meals. The sponsor has submitted NDA 22-232 requesting approval of the fixed dose combination (FDC) product, PrandiMet, a combination product with repaglinide and metformin HCl for an indication of an adjunct to diet and exercise to improve glycemic control in type 2 diabetics.

The Agency had earlier accepted that a bioequivalence (BE) trial will be adequate to support the approval of the FDC tablet. In response, the sponsor conducted a BE trial, NN4440-1753 to show that the FDC tablets are bioequivalent to concomitantly administered repaglinide and metformin. In addition, the sponsor submitted a factorial efficacy and safety clinical trial AGEE-053, which originally submitted with the repaglinide NDA 20-741 and another efficacy and safety clinical trial AGEE-3017 in type 2 diabetics no adequately controlled using diet and exercise alone (OAD naïve patients).

The Agency has accepted previously that the sponsor will not conduct a repaglinide-metformin HCl interaction trial and a food interaction trial with the FDC.

The pivotal BE study NN4440-1753 is described below:

NN4440-1753

Title: A Randomised, Single-Blind, Three-Period Crossover Study Examining the Single-Dose Pharmacokinetics of Concomitantly Administered Repaglinide and Metformin versus Combination Tablet Dosing (NN4440) in Fed Healthy Volunteers

Trial Site: One site in the U.S.: b(4)

Analytical Site: b(4)

Bioanalytical Investigator: Jing Ke, PhD

Primary Objective:

• To compare the single-dose repaglinide (2 mg) and metformin (500 mg) AUC and Cmax as co-administered tablets and in NN4440 combination tablet (2 mg repaglinide /500 mg metformin) dosing under fed conditions.

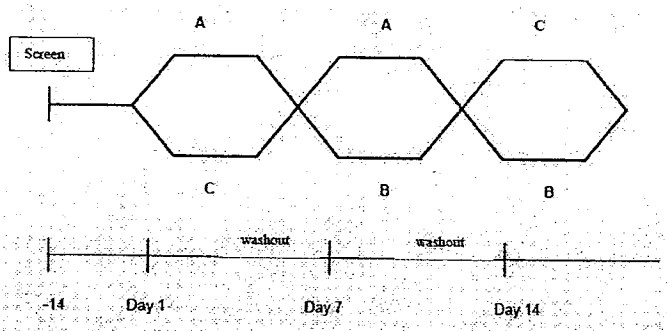
Secondary Objectives:

• To compare the repaglinide dose proportionality of NN4440 (1 mg repaglinide/500 mg metformin) and NN4440 (2/500).

• To compare secondary pharmacokinetic parameters of repaglinide and metformin in single dose and combination therapy.

• To examine the safety and tolerability of repaglinide and metformin in combination tablet therapy.

Study Design:



Only two of 2 of 6 possible treatment sequences (Williams design) are shown.

Allowable treatment sequences include:

A-B-C
C-A-B
B-C-A
C-B-A
B-A-C
A-C-B

Where:
A = NN4440 (2/500)
B = Individual tablets of 2 mg repaglinide + 500 mg metformin
C = NN4440 (1/500)

Investigational Products:

Table 9–1 Batch Numbers and Expiry Dates of Trial Products

Trial Product	Batch Number	Expiry Date
NN4440 (1/500) (repaglinide 1 mg, metformin 500 mg) tablet	SBBN012	03 January 2007
NN4440 (2/500) (repaglinide 2 mg, metformin 500 mg) tablet	SBBN018	03 January 2007
Repaglinide, 2 mg tablets (Prandin®, Novo Nordisk)	5060601	31 May 2010
Metformin, 500 mg tablets (Glucophage®, Bristol-Myers Squibb)	6A12719	31 October 2009

Study Results:

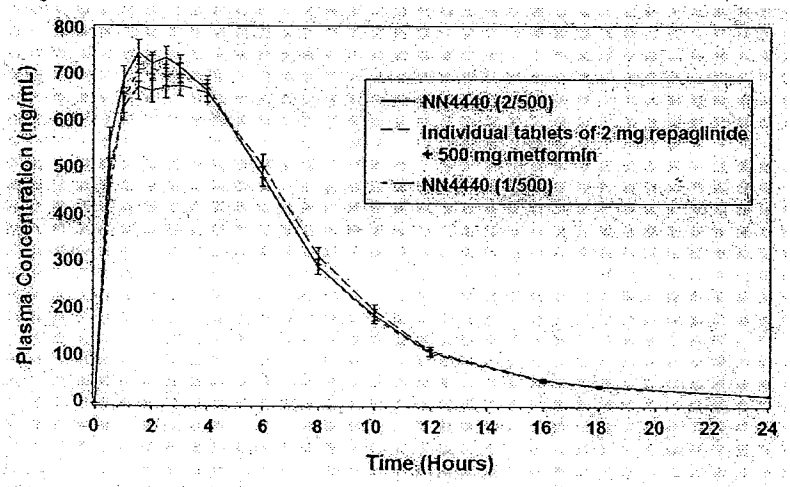


Figure 11–1 Mean Metformin Plasma Concentration (ug/mL) Over Time by Treatment – PK Population

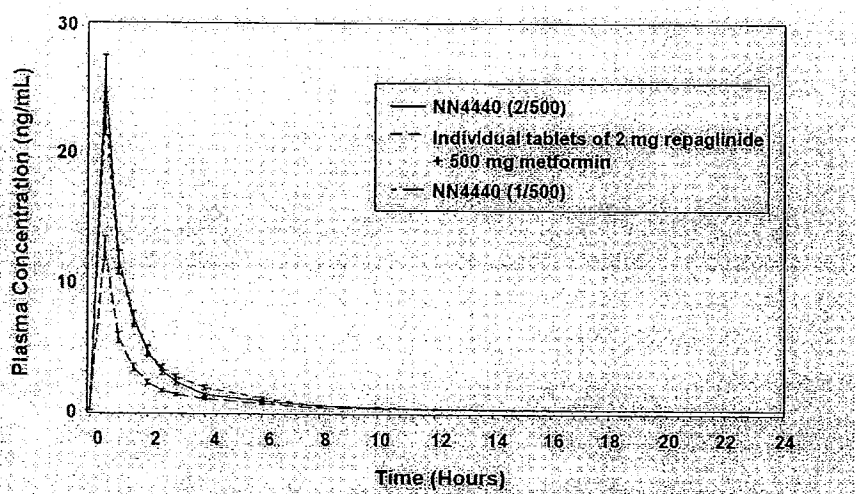


Figure 11–2 Mean Repaglinide Plasma Concentration (ug/mL) Over Time by Treatment – PK Population

Table 11–3 Primary Pharmacokinetic Parameters for Metformin Bioequivalence – PK Population

Parameter	A (N=55)	B (N=55)	90% CI for the Ratio (A/B)	Bioequivalence Achieved?[a]
AUC (ng*h/mL)				
N	55	55	[0.9853, 1.0640]	Yes
Mean	6041.911	5871.621		
SD	1494.582	1352.617		
Median	5870.996	5808.320		
Min	3266.09	3319.35		
Max	9796.40	10411.87		
LS Means	5877.8	5740.6		
AUC(0-24) (ng*h/mL)				
N	55	55	[0.9822, 1.0631]	Yes
Mean	5920.496	5762.298		
SD	1479.846	1328.531		
Median	5791.920	5692.760		
Min	3114.54	3244.95		
Max	9638.92	10117.21		
LS Means	5756.1	5633.0		
AUC(0-t) (ng*h/mL)				
N	55	55	[0.9822, 1.0631]	Yes
Mean	5920.496	5762.298		
SD	1479.846	1328.531		
Median	5791.920	5692.760		
Min	3114.54	3244.95		
Max	9638.92	10117.21		
LS Means	5756.1	5633.0		
Cmax (ng/mL)				
N	55	55	[0.9849, 1.0796]	Yes
Mean	838.840	805.906		
SD	210.192	160.328		
Median	794.382	803.451		
Min	472.64	473.70		
Max	1465.24	1183.61		
LS Means	816.7	792.0		

Treatment A = NN4440 (2/500), B = Individual tablets of 2 mg repaglinide + 500 mg metformin, CI = confidence interval; AUC = area under the concentration time curve calculated for the linear trapezoidal rule time 0 extrapolated to infinity, AUC_{0-24} = area under the concentration time curve calculated by the linear trapezoidal rule time 0 hr to 24 hours after dosing, AUC_{0-t} = area under the concentration time curve calculated by the linear trapezoidal rule time 0 hr to the time of the last measurable concentration, C_{max} = maximum drug concentration.

a: Metformin bioequivalence was demonstrated if the 90% CI of the mean treatment ratios (A/B) for the primary PK parameters were contained within the interval [0.8, 1.25].

Table 11–4 Primary Pharmacokinetic Parameters for Repaglinide Bioequivalence – PK Population

Parameter	A (N=55)	B (N=55)	90% CI for the Ratio (A/B)	Bioequivalence Achieved?[a]
AUC (ng*h/mL)				
N	55	55	[0.9477, 1.0271]	Yes
Mean	34.536	35.016		
SD	13.293	13.184		
Median	31.963	33.378		
Min	13.64	15.33		
Max	71.22	75.67		
LS Means	32.3	32.8		
AUC(0-24) (ng*h/mL)				
N	55	55	[0.9464, 1.0252]	Yes
Mean	34.094	34.613		
SD	13.309	13.186		
Median	31.589	33.167		
Min	13.38	15.09		
Max	71.19	75.24		
LS Means	31.8	32.3		
AUC(0-t) (ng*h/mL)				
N	55	55	[0.9463, 1.0257]	Yes
Mean	33.867	34.369		
SD	13.292	13.166		
Median	31.362	32.835		
Min	13.24	14.98		
Max	70.99	75.09		
LS Means	31.6	32.1		
Cmax (ng/mL)				
N	55	55	[0.9426, 1.2486]	Yes
Mean	25.966	23.711		
SD	13.685	12.523		
Median	27.059	21.798		
Min	4.20	5.19		
Max	67.11	59.72		
LS Means	22.1	20.4		

Treatment A = NN4440 (2/500); B = Individual tablets of 2 mg repaglinide + 500 mg metformin; CI = confidence interval; AUC = area under the concentration time curve calculated for the linear trapezoidal rule time 0 extrapolated to infinity; AUC_{0-24} = area under the concentration time curve calculated by the linear trapezoidal rule time 0 hr to 24 hours after dosing; AUC_{0-t} = area under the concentration time curve calculated by the linear trapezoidal rule time 0 hr to the time of the last measurable concentration; C_{max} = maximum drug concentration.

a. Repaglinide bioequivalence was demonstrated if the 90% CI of the mean treatment ratios (A/B) for the primary PK parameters were contained within the interval [0.8, 1.25].

Cross reference: EOT Table 14.2-6.

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/s/

Sally Choe
9/26/2007 03:58:39 PM
BIOPHARMACEUTICS