CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-204

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Supplemental Review

NDA:	21-204	**Relevant IND:**	[ ]
Brand Name:	Starlix™	**Generic Name:**	Nateglinide Tablets
Strength(s):	60 mg, 120 mg, 180 mg		
Sponsor:	Novartis Pharmaceuticals Corporation 59 Route 10, East Hanover, NJ 07936-1080		
Submission Date:	17-DEC-1999; 13-APR-2000; 20-OCT-2000; 6-NOV-2000; **15-DEC-2000**		
Submission Type:	New Drug Application – appendix to dissolution section		
Reviewer:	Steven B. Johnson, B.S.Pharm, Pharm.D.		

Synopsis

In response to the Clinical Pharmacology and Biopharmaceutics "Comments to Sponsor," Novartis Pharmaceuticals submitted batch release data to supplement the concerns OCPB had with Starlix™ dissolution specifications (refer to CPB review of NDA 21-204). Thirty-minute release data from 5 batches of 60 mg tablets and 185 batches of 120 mg tablets were included. Based upon this new data, OCPB and Novartis have agreed to the following conditions:

1. Novartis will test 6 tablets for the release of routine production batches.

2. Dissolution tolerances are set at Q = —% @ 30 minutes.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed this submission and finds the resultant responses to be acceptable.

[/S/] 12.15.00

Steven B. Johnson, B.S.Pharm, Pharm.D.
CPB Reviewer

[/S/] 12/15/00

Hae-Young Ahn, Ph.D.
CPB Team Leader

CC: NDA 21-204, HFD-510 (WeberJ), HFD-870 (MalinowskiH, AhnH, JohnsonST), CDR

NOV 28 2000

Clinical Pharmacology and Biopharmaceutics Review

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Terms and Abbreviations

Agency	Food and Drug Administration
ADA	American Diabetes Association
AUC	Area under the plasma-concentration-time curve
BA	Bioavailability
BE	Bioequivalence
CPB	Clinical Pharmacology and Biopharmaceutics
C_{max}	Maximum drug concentration
DMEDP	Division of Metabolic and Endocrine Drug Products
FD&C	Food, Drug, and Cosmetic [act]
IV	Intravenous [administration]
NDA	New Drug Application
NME	New Molecular Entity
OCPB	Office of Clinical Pharmacology and Biopharmaceutics
PO	Oral [administration]
T_{max}	Time of maximum drug concentration
$t_{1/2}$	Drug elimination half-life

Synopsis

Novartis Pharmaceuticals has submitted NDA 21-204 for Starlix™ (nateglinide) Tablets in 60 mg, 120 mg, and 180 mg strengths. The proposed indication for Starlix™ is for the management of type 2 diabetes mellitus (DM) not controlled by diet and exercise alone. This product is a new molecular entity (NME) and is the second to belong to the drug class meglitinide – non-sulfonylurea insulin secretogogues. Nateglinide appears to bind preferentially to potassium channels in the pancreatic β cells, which in turn stimulate insulin secretion. The proposed initial and maintenance dose of Starlix™ is 120 mg administered 30 minutes before a meal. The Agency recommends initial and maintenance dose of Starlix™ is 120 mg administered between 1 and 10 minutes prior to a meal.

Included in this submission were 52 pharmacokinetic studies which attempted to characterize and evaluate the disposition of nateglinide in humans. Of these 52 studies, approximately 30 were thought to have a direct impact on the approval of Starlix™ from the OCPB perspective. The respective study synopses have been included in the appendix of this review.

After oral administration, peak concentrations of nateglinide usually occur within one hour when given approximately 10 minutes before a meal. The half-life in both normal subjects and type 2 DM patients is about 2 hours. Dosage form proportionality is present among the three strengths.

In an ADME study conducted in normal subjects, total clearance was determined to be approximately 7.36 L/hr, steady-state volume of distribution about 10.5 L, and absolute bioavailability about 73%. Nateglinide is highly protein bound (~98%) to albumin (and to a lesser extent α_1-acid glycoprotein) and is extensively metabolized by cytochrome P450 2C9 to its hydroxylated metabolites. The relative activity of the major metabolites, M1, M2, and M3, is approximately 5 to 6, and 3 times less potent than the parent compound, respectively. The minor isoprene metabolite M7 is active and shows similar potency as the parent (nateglinide).

Both the parent drug (nateglinide) and metabolites are rapidly and completely eliminated, with 75% of the dose excreted in urine within 6 hours and 84% within 24 hours. The remaining portion of the dose is eliminated in the feces or lost in transit within 72 hours of dosing.

The formulation of nateglinide has changed significantly since its inception ten years ago. The first formulation was Japanese in origin ——— The subsequent formulations included 4 ——— Novartis (SDZ DJN 608) drug formulations, with FMI-2 being the final to-be-marketed formulation. Bioequivalence was never established between the ——— formulation and the SDZ DJN 608 formulations.

This issue of bioequivalence came up again when the sponsor attempted to show similarity between the phase III and FMI-2 formulations. The extent of absorption was consistent between products, but the rate was incredibly variable. The variability was so significant with regard to C_{max} that replicate design studies were necessary for the 60 mg and 180 mg strengths. Bioequivalence was ultimately established for all of the to-be-marketed formulations and their respective phase III formulations.

Nateglinide does exhibit a food effect, both with regard to fed vs. fasting conditions AND with the timing of the dose in relation to a meal. Multiple studies demonstrate that when nateglinide is taken either under fasting conditions OR when taken immediately after or during a meal, the rate and maximum concentration are significantly altered. Timing studies showed the need for Starlix™ to be administered between 1 and 10 minutes prior to a meal, which corresponds to the greatest insulin response, compared to either fasting or post-meal administration.

When *in vitro* studies demonstrated the inhibitory potential of nateglinide towards tolbutamide, *in vivo* studies were conducted with known CYP2C9 substrates (e.g., warfarin). The *in vivo* warfarin study revealed no relevant change in the pharmacokinetics or the pharmacodynamics (prothrombin time) of warfarin; both the less active R- and active S-warfarin isomers were evaluated. Additional studies addressed potential interactions with glyburide, metformin, diclofenac, and digoxin. No significant interactions were noted between nateglinide and any of these agents.

As mentioned previously, nateglinide is highly protein bound (~98%), primarily to albumin. Protein displacement studies were conducted in a variety of known highly protein bound drugs (e.g., phenytoin). Based upon these studies, it was concluded that there were little to no binding alterations related to the addition of nateglinide, nor did these agents alter the binding of nateglinide. However, caution should be observed in hemodialysis patients, who exhibited a statistically significant reduction in the protein binding of nateglinide.

Studies were performed that examined the effect of hepatic disease on the pharmacokinetics of nateglinide. Compared with normal subjects, those with hepatic insufficiency demonstrated a 30% increase in AUC_{0-t}, a 37% increase in C_{max}, a shorter T_{max} and $t_{½}$, increased renal clearance, and reduced total clearance. The hepatic subjects used in this study had relatively low Childs-Pugh scores indicating only mild hepatic dysfunction. It would be extremely prudent to exercise caution when administering Starlix™ to patients with hepatic dysfunction given these findings.

A study evaluating renal dysfunction showed no "difference" in nateglinide AUC and C_{max} between the type 2 DM subjects with moderate to severe renal failure with their matched normal counterparts. However, there was a 75% reduction in the clearance of parent drug (11% vs. 3%) in these renal subjects. Because there was no difference shown between the extent of absorption and the fact that renal subjects demonstrated a shorter half-life (2.8 hours vs. 1.9 hours) for nateglinide, this finding is inconclusive..

Finally, a population evaluation was conducted to explore the PK/PD relationship of nateglinide, and to determine which demographic variables might contribute to alterations in the behavior of nateglinide. Results of this analysis suggest that alcohol use, increasing body weight, and increasing creatinine clearance were predictors of nateglinide PK. Nateglinide concentrations were increased with alcohol use and decreased with increasing body weight and creatinine clearance. Age, gender, and race were not considered to be significant covariates. This was confirmed in the statistical review.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-204 submitted 17-DEC-1999. The overall Clinical Pharmacology and Drug Interactions Sections are **acceptable** to OCPB pending sponsor response to the questions described at the end of this review. Please convey ***Comments to Firm*** and ***Labeling Comments*** to the sponsor as appropriate.

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Background

Starlix™ is a second generation insulin secretogogue from the drug class meglitinide. The first member of this class is repaglinide (Prandin™). A general characteristic of these drugs is that they have a short insulinotropic action corresponding with a short half-life.

The sponsor claims that the purported benefit of Starlix™ over existing insulin secretogogues is due to its ability to induce "significant early insulin secretion within the first 15 minutes following a meal, which results in suppression of hepatic glucose production and reduced meal-related glucose excursions ..." This may be true, however, there has never been any correlation established between post-prandial glucose excursion and long term benefit (i.e., lowering of HbA_{1C}). Also, because the insulinotropic effect is directly related to drug levels there is the potential that fewer hypoglycemic reactions will occur. It is also true that if drug levels are erratic, then so to will be the desired response.

Starlix™ is indicated for the management of type 2 diabetes mellitus that is not controlled by diet and exercise alone. Based upon the pharmacokinetic studies submitted in this application, Starlix™ should be taken between 1 and 10 minutes before each meal for optimal effect. The meal type is an important consideration with Starlix™. This product will be available in three strengths: 60 mg, 120 mg, and 180 mg.

Drug Formulation

Is the composition of each strength tablet similar?

The 120 mg strength tablet formulation is a direct 2X multiple of the 60 mg strength tablet and the two differ only in their respective color coatings. In contrast, the 180 mg strength tablet is not a direct multiple of the 60 mg strength tablet, nor is it proportionality similar to either the 60 mg or 120 mg strength tablets. The 180 mg strength tablet is, however, composed of the same exipients as the two other formulations. This non-proportionality issue is addressed in the review section ***Bioequivalence***.

Components and Composition				
Component	Compendial Grade	60 mg Amount Per Tablet (mg)	120 mg Amount Per Tablet (mg)	180 mg Amount Per Tablet (mg)
Active				
Nateglinide	In-house	60.00	120.00	180.00
Excipients (Core)				
Lactose Monohydrate	NF			
Microcrystalline Cellulose	NF			
Croscarmellose Sodium	NF			
Povidone	USP			
Colloidal Silicon Dioxide	NF			
Magnesium Stearate	NF			
	USP			
Sub-Total		315	630	610

Coating Premix[2]				
Hydroxypropylmethyl Cellulose	USP			
Titanium Dioxide	USP			
Polyethylene Glycol	NF			
Talc	USP			
- Red	NF			
- Yellow	NF			
Total Coating - Pink	—			
Total Coating - Yellow (II)	—			
Total Coating - Red	—			
	USP			
Total Weight		**324**	**648**	**628**

1.
2. The coating premix is a commercially available product.

Dissolution

Has the sponsor proposed appropriate dissolution methods and specifications?
Was sufficient data submitted for evaluation of the dissolution methods and specifications?
Was a profile comparison made between the tablets used in phase III clinical studies and the final market image (FMI-2) tablet formulations?

Solubility

24 Hour Equilibrium Solubility of Nateglinide in Aqueous Solvents at 37°C	
Solvent	**mg Nateglinide / mL Solvent**
0.1 N Hydrochloric Acid	0.024
0.01 N Hydrochloric Acid	0.026
pH 4.0 Acetate Buffer	0.100
pH 4.0 Citrate Buffer	0.080
pH 5.0 Citrate Buffer	0.230
pH 6.8 Phosphate Buffer*	**> 1.0 ***
0.1 N HCl + 0.1% Sodium Lauryl Sulfate	0.105
0.1 N HCl + 0.5% Sodium Lauryl Sulfate*	**0.628***
0.01 N HCl + 0.1% Sodium Lauryl Sulfate	0.024
0.01 N HCl + 0.5% Sodium Lauryl Sulfate*	**0.668***

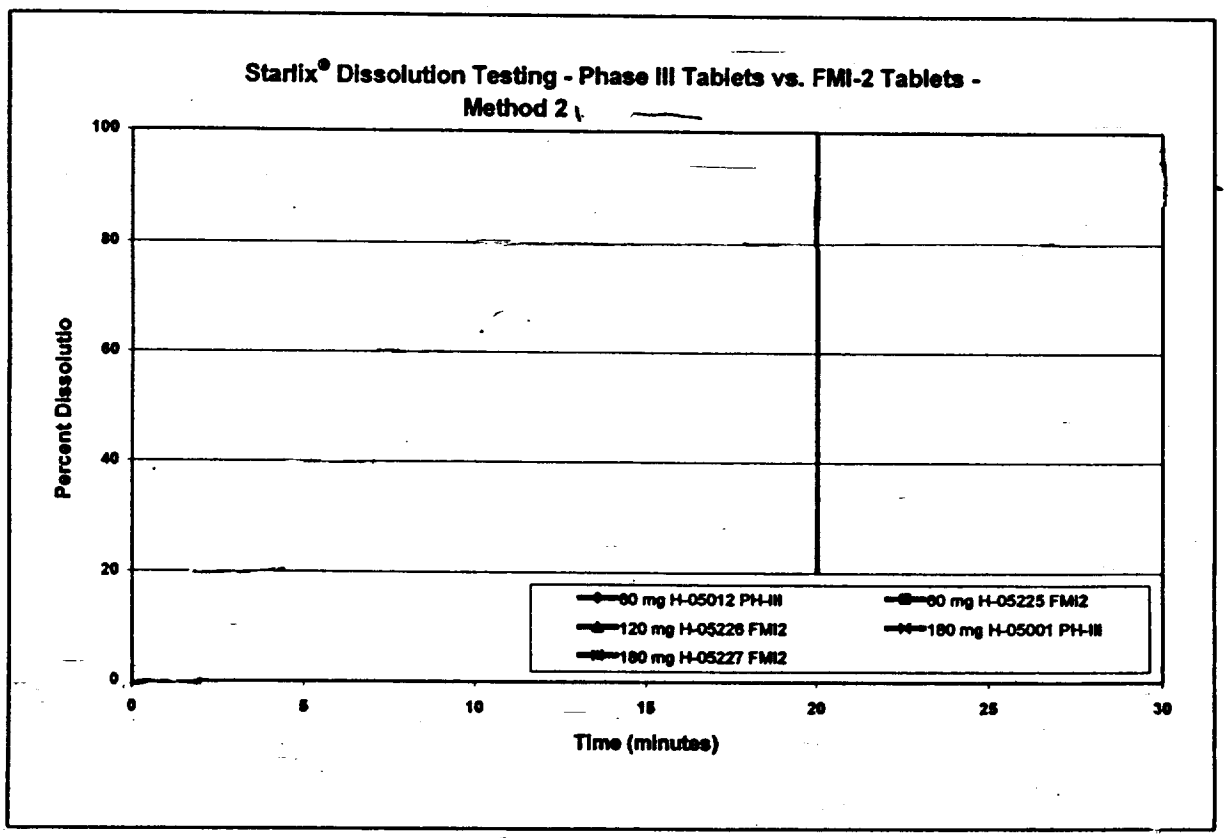
In order to maintain sink conditions for the 180 mg strength tablets, the dissolution solution must be capable of permitting the solubilization of > 540 mg (i.e., 3 x 180 mg) of nateglinide per liter of media. Three of the 10 solvent systems evaluated for nateglinide were capable of maintaining sink conditions and are indicated in the above table with asterisks. Of these three media, the pH 6.8 phosphate buffer and the 0.01 N HCl + 0.5% Sodium Lauryl Sulfate were incorporated into formal dissolution methodologies and are presented below.

	Dissolution Method	
	Method 1	**Method 2**
Apparatus:	2 (paddles)	2 (paddles)
Speed:	75 RPM	50 RPM
Medium:	pH 6.8 Phosphate Buffer	0.01 N HCl + 0.5% SLS
Volume:	1000 mL	1000 mL
Units Tested:	6	6
Time Points:	15, 30, 45, & 60 minutes	10, 20, & 30 minutes
Specifications:	Q = __% @ 60 minutes	Q = __% @ 30 minutes

Method 1 was used to evaluate process validation, target, and initial final image (FMI1) formulations. This method was found to be unsatisfactory for the following reasons: 1) there is a lack of discrimination between samples manufactured with varying process parameters; and 2) the dissolution of the tablet appears to be due to an erosive process rather than disintegration based on visual inspection – despite the high solubility of the nateglinide drug substance in the pH 6.8 phosphate buffer.

Method 2 was developed to overcome the shortcomings seen in method 1. Method 2 allows for a faster rate of tablet dissolution, compared to method 1, and shows a similar rate of drug release between different tablet lots known to be bioequivalent (see plot and table below).

Of the two methods presented, method 2 was determined to be acceptable pending the following required changes: ***Units Tested*** – stage 2 dissolution testing (i.e., 12 units tested vs 6 units tested); ***Specifications*** – Q = —% @ 20 minutes. See ***Comments to Firm.***



Similarity (f_2) Calculations for Bioequivalence Batches		
Batches Compared (T vs. R)	**Dose (mg) T/R**	**f_2**
H-05012 (phase III) vs. H-05225 (FMI-2)	60 / 60	79.4
H-05001 (phase III) vs. H-05227 (FMI-2)	180 / 180	72.7
H-05012 (phase III) vs. H-05001 (phase III)	60 / 180	89.4
H-05225 (FMI-2) vs. H-05227 (FMI-2)	60 / 180	81.2
H-05225 (FMI-2) vs. H-05226 (FMI-2)	60 / 120	70.4
H-05226 (FMI-2) vs. H-05227 (FMI-2)	120 / 180	61.5

Similarity (f_2) calculation results showed adequate similarity between the phase III and FMI-2 formulations, and among the 60 mg and 180 mg strength tablets. Inadequate data was submitted to fully

evaluate the 120 mg strength tablet (see ***Comments to Firm***). Refer to ***Appendix*** for individual tablet dissolution results. However, this data was subsequently submitted per reviewer request and found to be adequate.

Analytical Methodology
Were the bioanalytical assays sufficiently validated and cross-validated between analytical sites for the PK studies conducted in this application?

Cross-validation reports suggest acceptable consistency between the different analytical sites. Human plasma samples containing nateglinide were analyzed using a assay with The assay was originally developed for samples and was subsequently validated for human plasma samples by Novartis Pharmaceuticals Corporation, respectively. A few modifications were made during the validation and implementation process between each analytical site; which included the use of slightly different used in the United States as compared to Europe and Japan.

Assay Validation from the Four Analytical Sites

Parameter		Novartis			
LOQ (ng/mL)					
Linearity (ng/mL)					
Precision (%RSD)					
Accuracy (Observed / Theoretical)(100%)					
Specificity					
Stability	NS				
Recovery	NS				

Bioavailability and Bioequivalence
What is the absolute bioavailability of nateglinide?

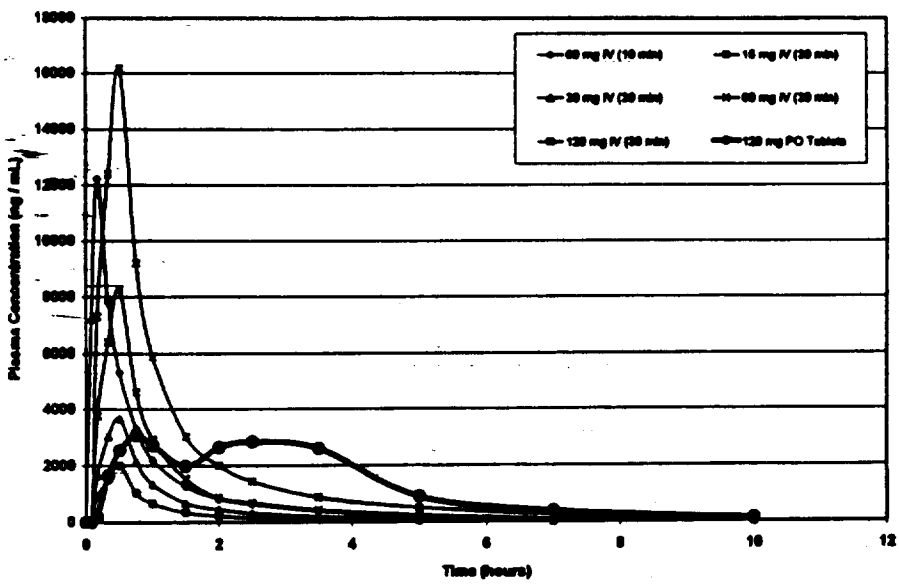
The absolute bioavailability of nateglinide was evaluated in two studies, one for an oral solution and the other for oral tablets. The first was a two-period ADME study (P114) in 6 healthy male subjects given a single PO (120 mg solution [80 µCi]) and IV (60 mg [20 µCi]) dose of [^{14}C]-labeled SDZ-608. Plasma samples were measured for both radioactivity and SDZ-608 concentrations. The second study (P113) was a six-period ascending single-dose study in 20 healthy subjects administered 15 mg to 120 mg nateglinide IV over either 10 or 30 minutes, and/or 2 x 60 mg tablets administered orally. SDZ-608 was administered in both studies under fasting conditions.

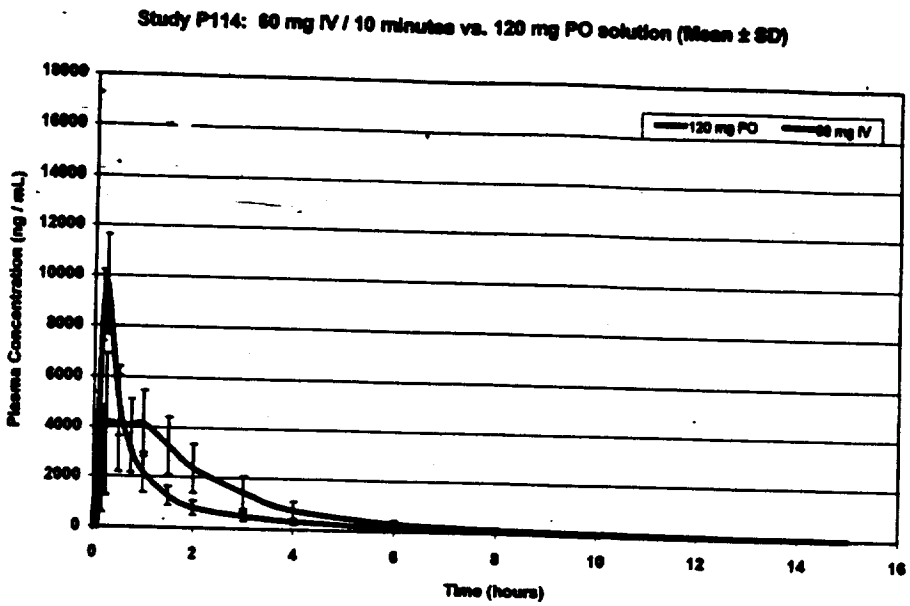
Results of these studies are presented in the following table and plot. The absolute bioavailability of nateglinide in healthy subjects was determined to be approximately 73% to 75%.

Note: The discrepancy in AUC between the 60 mg IV dose administered over 10 minutes in the two studies is due to the considerable differences in variability: P114 %CV AUC_{0-t} = 29.4% vs P113 %CV AUC_{0-t} = 13.4%.

Absolute Bioavailability Determinations for Nateglinide: Studies P114 and P113								
Parameter	120 mg PO SLN (P114)	60 mg IV 10 min (P114)	60 mg IV 10 min (P113)	15 mg IV 30 min (P113)	30 mg IV 30 min (P113)	60 mg IV 30 min (P113)	120 mg IV 30 min (P113)	120 mg PO Tab (P113)
AUC_{0-t} (µg*hr/mL)	11.7±2.05	8.05±2.37	8.73±1.17	1.84±0.2	3.95±0.5	8.65±1.1	17.48±2.2	13.[illegible]±1.7
$AUC_{0-\infty}$ (µg*hr/mL)	—	—	8.95±1.15	1.96±0.2	4.13±0.5	8.85±1.2	17.72±2.3	13.33±1.8
C_{max} (µg/mL)	5.69±1.80	—	12.24±1.5	1.99±0.1	3.77±0.3	8.28±0.7	16.19±1.3	5.21±1.2
T_{max} (hr)	0.83±0.66	—	—	—	—	—	—	1.93 ± 1.3
$t_{1/2}$ elimination (hr)	1.70	1.50	1.71±0.31	1.14±0.4	1.59±0.26	1.77±0.31	1.88±0.11	1.58±0.16
$t_{1/2}$ distribution (hr)	0.69	—	—	—	—	—	—	—
$t_{1/2}$ absorption (hr)	0.20	—	—	—	—	—	—	—
Cl (L/hr)	—	7.36	6.79±0.82	7.78±1.09	7.36±0.9	6.89±0.95	6.87±0.9	6.82±0.9
Vd (L)	—	10.5[1]	16.61±2.7	12.32±3.3	16.71±2.6	17.29±2.3	18.62±2.6	15.63±2.9
$f_{absolute}$ (%)[2]	72.7	—	—	—	—	—	—	75 ± 9.2
Mean ± SD; 1. Steady-state Vd								

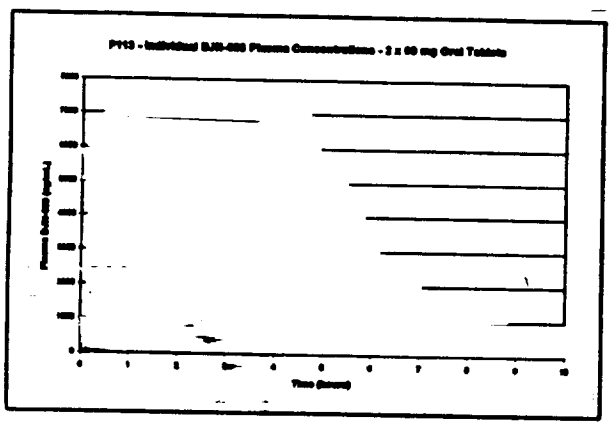
Study P113: Acending Dose Escalation - 15 mg to 120 mg (Mean)

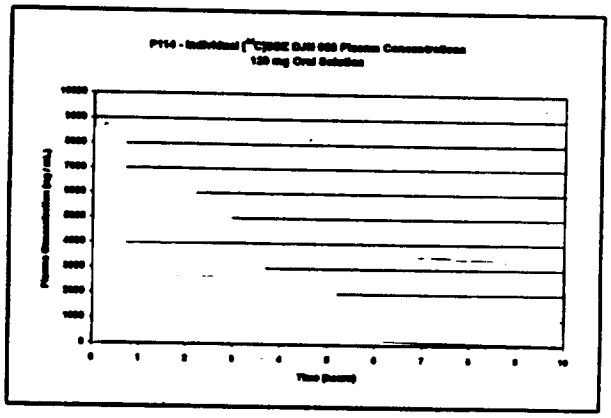




Why does a secondary plasma peak occur after the oral administration of nateglinide?

The sponsor has suggested that the "apparent" double peak in study P113 is attributable to the variability associated with the T_{max} (1.93 ± 1.30; %CV = 67.4). This is true, however, 4 of the 7 subjects demonstrated plasma profiles with two distinct peaks. This secondary peak is also evident in 4 of 6 subjects in study P114, which exhibits a similar (high) variability around the T_{max} (0.83 ± 0.66; %CV = 79.5). In both of these studies nateglinide was administered under fasting conditions. Enterohepatic recycling is a consideration, but nateglinide is rapidly and presumed to be well absorbed after oral administration, and there is no evidence of recycling from the IV data.





In a food effect study, P110, the secondary peak was also evident when either 30 mg or 60 mg tablets were administered under fasting conditions. However, the peak is not evident when the 30 mg or 60 mg tablets are administered either 10 minutes before or 10 minutes after a high fat meal. Also of note, is the relatively poor solubility of nateglinide in acidic pHs and considerably higher solubility at higher pHs (e.g., pH 6.8 phosphate buffer) or when surfactants are added to acidic media (see ***Dissolution***). Additionally, based on absorption studies in Caco-2 cells, the transport of nateglinide from the mucosal to the serosal side of the Caco-2 cell monolayer appears to be a passive diffusion process AND that there appears to be an "absorption window" when the pH is in the range of 5.5 to 7.0.

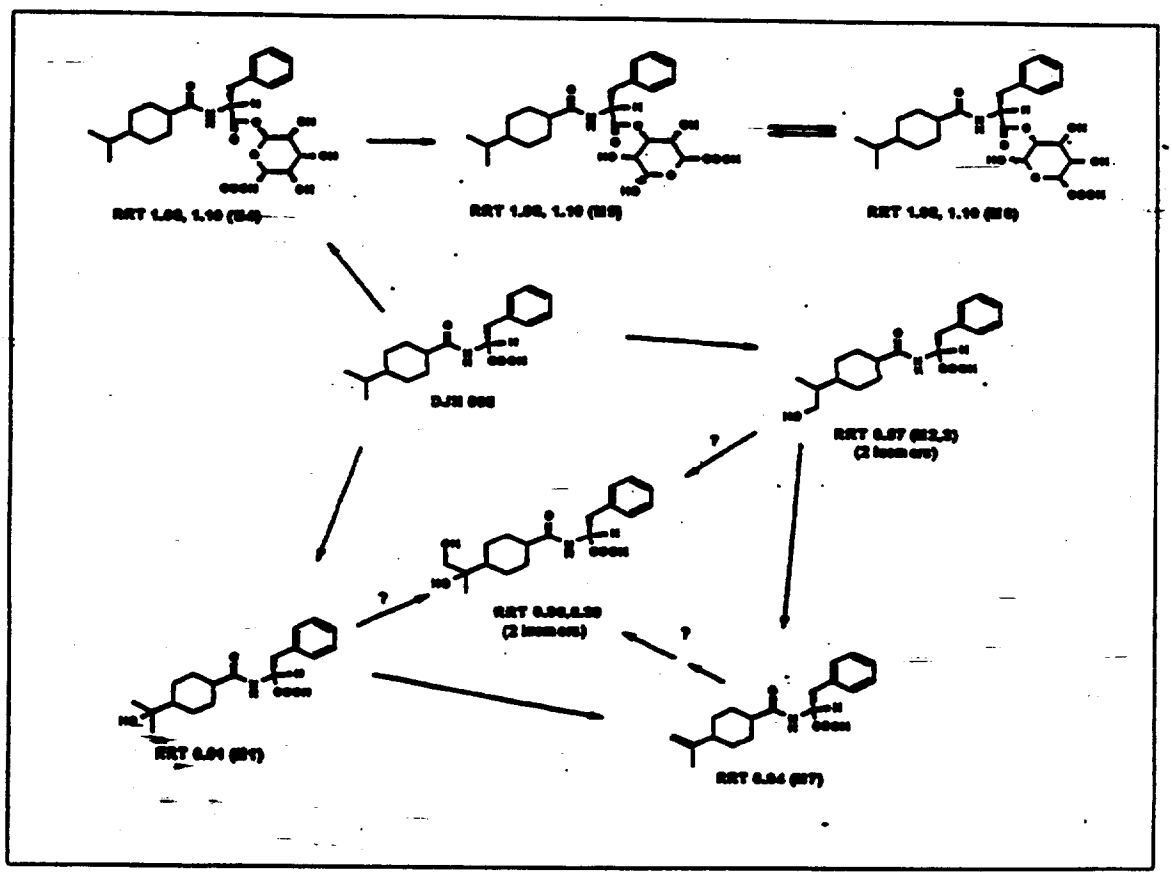
Therefore, it is reasonable to assume that the secondary plasma peak seen with the oral administration of nateglinide is due to gastric emptying, which is "normalized" when administered with food. This is an

important consideration since C_{max} appears to be associated with the magnitude of insulin release and the resultant glucose lowering effect of Starlix™.

Metabolism

How is nateglinide metabolized, and if metabolism is via the cytochrome P450 enzyme system, which specific isoform(s) is/are involved?

Nateglinide is extensively metabolized by the mixed-function oxidase system after absorption and prior to elimination (moderate first-pass effect ($f_{absolute}$ = 73%)). *In vitro* metabolism studies were performed using human liver microsomes and found that CYP2C9 (70%), followed by CYP3A4 (30%) were the dominant enzymes responsible for the hydroxylation of nateglinide to its major metabolites, M1, M2, and M3 (refer to the biotransformation chart below). These hydroxylated metabolites are subsequently glucuronidated. Based on results from study P114, M1 is the major metabolite formed and represents approximately 9% of metabolite exposure relative to the nateglinide parent – the remaining metabolites represent only 3% to 4%.



Are the metabolites of nateglinide active?

One of the minor isoprene metabolites (M7) conveys a similar potency as the nateglinide parent. The relative activity (to nateglinide) of the major metabolites, M1, and M2 and M3, is approximately 5 to 6 and 3 times less potent, respectively.

Bioequivalence

Was bioequivalence established between the phase III and to-be-marketed formulations?

The formulation for nateglinide has changed considerably over the course of the Starlix™ genesis. The original —— tablets differed not only in total weight, but also in exipient type relative to the —— Novartis drug products. Studies (# 5 – see ***Appendix***) utilizing this formulation were linked to the Novartis product through a five-period, partially randomized, crossover study under fasting conditions. Results of this study clearly show that the first —— Novartis formulation was not bioequivalent to the —— With the —— tablet used as the reference, the AUC from the —— Novartis product fell within the 90% confidence intervals, but the C_{max} was considerably lower (90% CI = 0.57 – 0.94). No additional bioequivalence studies were conducted between these formulations.

The C_{max} issue was raised again when the sponsor attempted to establish bioequivalence between its phase III and final market image (FMI-2) tablets for both the 60 mg and 180 mg strengths; AUC and C_{max} did fall within the 90% CI for the 120 mg tablets. In order to overcome the failed bioequivalence for the 60 mg and 180 mg tablet strengths, the sponsor repeated the two respective bioequivalence studies. This time, however, the studies were of a two-treatment, four-period crossover design (i.e., replicate design). Study CDJN608 0124 evaluated the bioequivalence of the 60 mg tablets and CDJN608 0125 evaluated the 180 mg tablets. Average bioequivalence analysis between the phase III and FMI-2 drug showed that the two formulations met bioequivalence requirements. Of interest in these studies was the degree of intra-subject %CV for the C_{max} of each product (60 mg: FMI-2 = 28% vs. phase III = 37%; 180 mg: FMI-2 = 39% vs. phase III = 47%). The variability in C_{max} was a recurring theme throughout many of the PK studies submitted in this application.

Problem: The pivotal bioequivalence studies were conducted under <u>fed</u> conditions. The current policy of OCPB dictates that all pivotal bioequivalence studies be conducted under fasting conditions such that introduced variability or muting effect from food is eliminated – unless there is a safety concern. In the case of Starlix™ there is no substantial safety concern in healthy volunteers, despite the fact that it is an insulin secretogogue. A high degree of variability in C_{max} does not and should not preclude a drug from being subject to fasting bioequivalence studies. Therefore, based on these findings, OCPB should recommend an "approvable" to DMEDP pending the outcome of fasting BE studies .

However, it seems unreasonable to request fasting bioequivalence studies with this particular drug in view of the fact that C_{max} is extremely erratic when administered under fasting conditions as demonstrated by the multiple peak phenomenon, which is ameliorated when administered just prior to a meal. This case was presented to Drs. Larry Lesko and Henry Malinowski. Based on these meetings and the evidence presented, it was determined that in this particular case, non-fasting bioequivalence studies were likely to be more reliable than fasting studies for measuring C_{max}. Therefore, OCPB would recommend an approval to DMEDP for Starlix™.

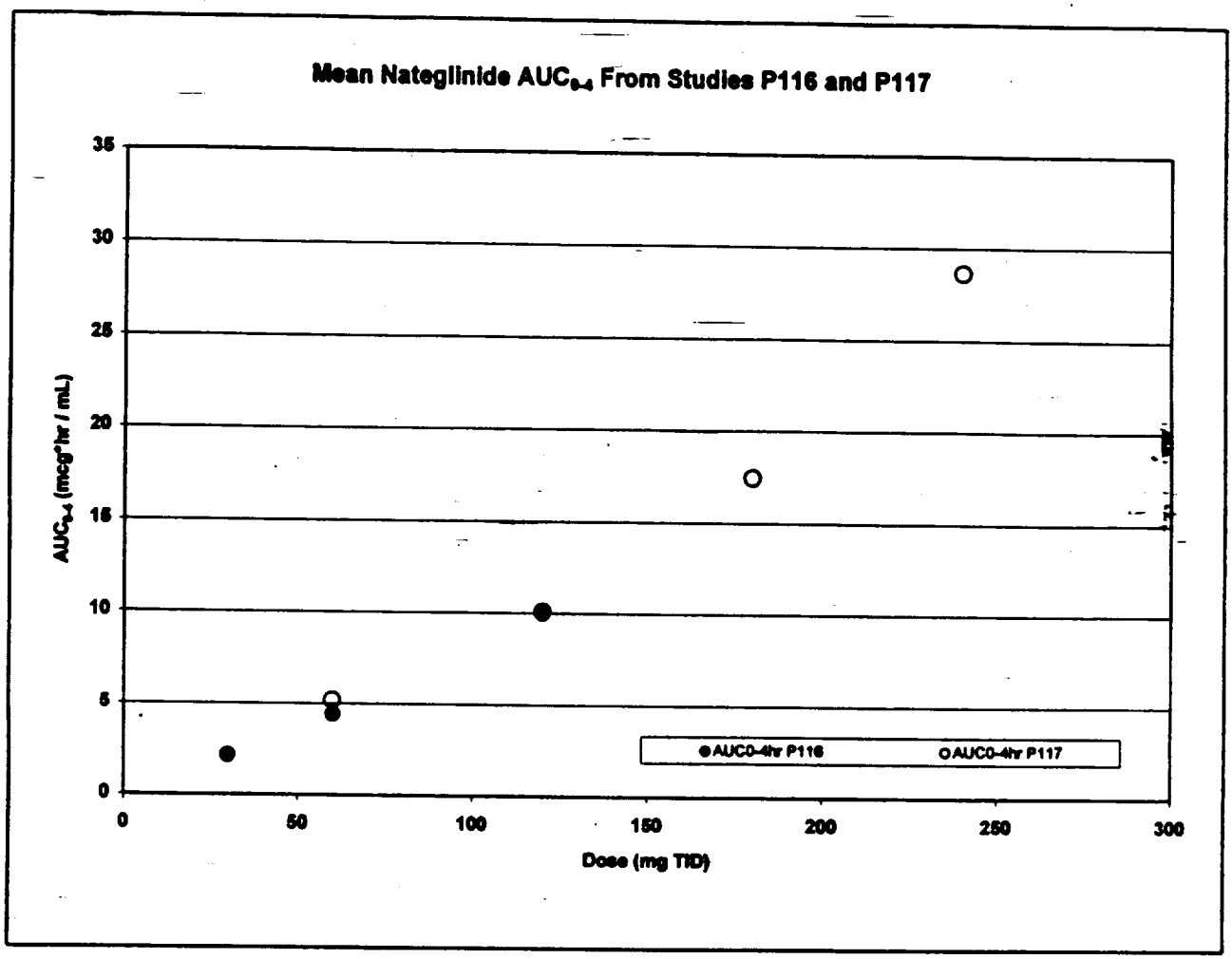
Dose Linearity

Was dose linearity established between the to-be-marketed strengths?

As shown in the following plot, the AUC_{0-4} of nateglinide is linear with dose from 30 mg to 240 mg when administered 10 minutes before a meal TID for 7 days. Two studies were used to generate the graph. Study P116 was a five-period crossover design study in which 12 type 2 DM patients were administered 1 x 30 mg, 2 x 30 mg, or 2 x 60 mg tablets, or placebo (the 120 mg dose was administered either TID or

QID). Study P117 was a four-period parallel design study in 20 type 2 DM patients administered either 1 x 60 mg, 2 x 60 mg, 3 x 60 mg, or 4 x 60 mg nateglinide tablets.

Dose linearity was also evaluated in a crossover study in 32 healthy volunteers administered either 1 x 30 mg, 1 x 60 mg, 1 x 120 mg, or 1 x 180 mg strength tablets. Linearity was described by the equations $C_{max} = (51.46)(dose)^{1.015}$ and for $AUC_{0-t} = (86.51)(dose)^{1.053}$.



Did the sponsor establish dosage form proportionality (e.g., 3 x 60 mg = 1 x 180 mg)?

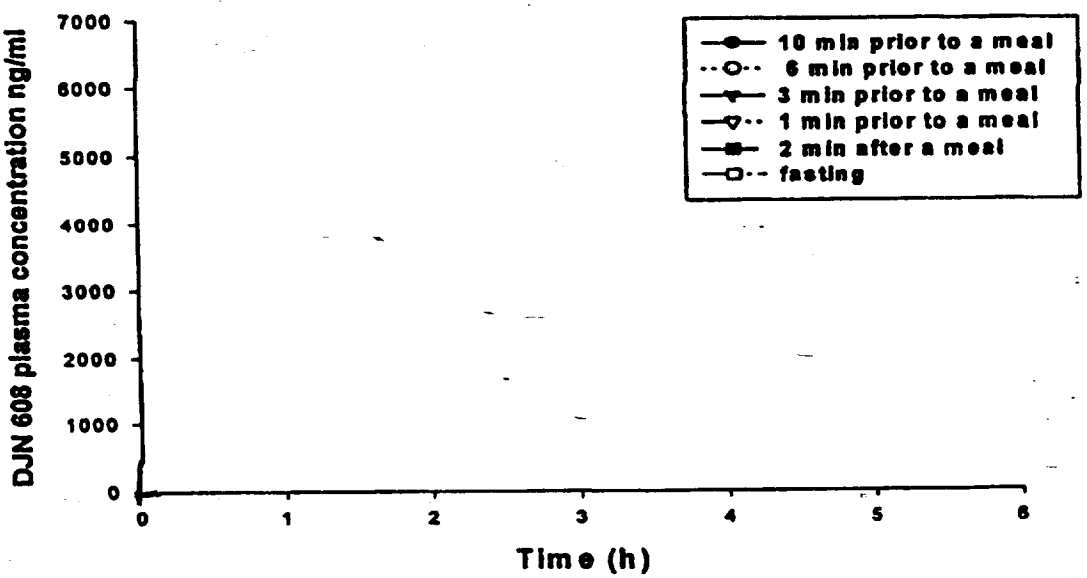
No, the sponsor did not directly establish dosage form equivalence between its products. Most of the dose escalating studies utilized multiple tablets of the same strength. However, in study W252, 30 mg, 60 mg, 120 mg, and 180 mg tablets were used to successfully demonstrate dose linearity. In the pivotal clinical trials, the 60 mg and 120 mg tablets were predominantly used. Therefore, based upon the linearity of Starlix™ PK, the sponsor indirectly demonstrated dosage form proportionality.

Food Effect

Since this product is to be taken at meal time, does the exact time of dosing in relation to the meal have any affect on the PK or PD of Starlix™?

A study was performed in type 2 DM patients to assess the optimal time of nateglinide administration in relation to a meal (fasting, -10, -6, -3, -1, and 2 minutes). The timing of the dose, in relationship to a

meal, had a notable effect on the nateglinide rate of absorption. When nateglinide is administered between 1 and 10 minutes prior to a meal, there is a slightly faster and higher rate of absorption (T_{max} = 0.64 to 1.01 hours; C_{max} = 5.663 – 6.529 µg/mL) compared to either fasting or 2 minute post-meal conditions. Pre-meal administration also corresponds with higher insulin concentrations. The time to peak insulin concentration when nateglinide was administered 2 minutes after the meal (1.89 hr) was significantly delayed when compared to the 1 minute (1.40 hr) and 6 minute (1.42 hr) pre-meal administrations ($p < 0.05$). The resultant post-prandial glucose levels were similarly affected. Therefore, based on the results of this study, it will be important for nateglinide to be administered between 1 and 10 minutes prior to meals.



Does the type of meal have any affect on Starlix™ PK?

Meal type is important. In clinical studies B202 and B251 it was recognized that when nateglinide was administered prior to a Sustacal® challenge, the PK parameters of nateglinide were extremely variable and a significant delay in T_{max} was observed. Further investigation of this phenomena was undertaken in study W369 in which an elemental liquid meal, a 70 gram glucose meal, an 800 kcal ADA breakfast, and a Sustacal® meal were compared. Results showed that the nateglinide C_{max} was significantly lower when administered with a liquid meal as compared to a solid meal. [In the phase III clinical studies, nateglinide was to be taken prior to a meal, type non-specified]. This information will be reflected the labeling.

Hepatic Insufficiency
Did hepatic insufficiency alter the PK of nateglinide?

A study (W351) was performed comparing the single-dose pharmacokinetics of nateglinide in 8 patients with biopsy-proven hepatic cirrhosis and assessed Child-Pugh scores (6 mild, 1 moderate, and 1 severe) with 8 age, sex, height, and weight-matched normal controls. Nateglinide 120 mg tablets were administered to all subjects following an overnight fast and 10 minutes prior to an 800 kcal ADA breakfast. Compared with normal subjects, those with hepatic insufficiency demonstrated a 30% increase in AUC_{0-t}, 37% increase in C_{max}, a shorter T_{max} and $t_{½}$, increased renal clearance, and reduced total clearance. None of these variables were statistically significant. However, because 6 of the 8 hepatic patients studied were typed as having mild hepatic impairment, and there were considerable, albeit non-

statistically significant, differences in systemic exposure to nateglinide, great care should be observed when Starlix™ is used in patients with chronic liver disease. Results are shown in the following table.

Healthy Subjects vs. Subjects with Liver Dysfunction: 120 mg PO Nateglinide				
Parameter	Healthy	Liver Dysfunction	90% CI	p-value
AUC_{0-t} (µg*hr/mL)	14.170 ± 2.061	18.466 ± 7.513	93 – 161	0.20
C_{max} (µg/mL)	5.617 ± 1.314	7.702 ± 4.891	70 – 205	0.54
T_{max} (hr)[1]	0.72 ± 0.53 [0.50 – 2.00]	0.59 ± 0.13 [0.50 – 0.75]	— —	— —
$t_{½}$ (hr)	2.91 ± 1.84 [1.39 – 6.03]	2.62 ± 1.42 [1.48 – 5.27]	— —	— —
Cl_{total} / F (L/hr)	8.401 ± 1.406	7.693 ± 3.012	79 – 173	0.47
Cl_{renal} (L/hr)	0.486 ± 0.137 [0.313 – 0.685]	0.546 ± 0.209 [0.234 – 0.806]	— —	— —
Mean ± SD; [range]; 1. Median				

Renal Insufficiency

Nateglinide is hepatically metabolized, with only a small percentage of the parent drug being excreted unchanged renally (< 15%), and highly protein bound (~ 98%). What effect does renal dysfunction have on the PK of nateglinide?

Forty subjects and patients with either normal or impaired renal function, either on hemodialysis or not on hemodialysis (with moderate to severe renal dysfunction as assessed by a CrCl between 15 and 50 mL/min/1.73 m^2), were administered a single oral dose of 120 mg nateglinide 10 minutes prior to an 800 kcal ADA breakfast. Subjects were demographically matched to each renal insufficiency group such that 10 subjects and 10 patients were compared, respectively. Results of this study, presented in the following two tables, clearly show differences between subjects and patients with renal dysfunction.

Patients in the hemodialysis group experienced reduced overall drug exposure, evidenced by a 25% reduction in AUC, a greatly reduced C_{max} (50%), and a 49% increase in total clearance, compared to their matched normal subject counterparts. These results suggest that nateglinide absorption is altered in hemodialysis patients. Multiple co-morbid conditions associated with total renal failure likely contribute to this observation (e.g., changes in gastric pH, gastric emptying time, intestinal edema, etc.). Also of note, is a difference in the plasma protein binding between these populations (normal: [0.9873 – 0.9892]; dialysis [0.9770 – 0.9852]). The significance of this finding is unknown since in a previous study in normal healthy subjects the bound plasma protein range was between 0.976 and 0.986.

Patients in the renal group not receiving dialysis exhibited a somewhat similar extent and rate of absorption as their normal controls, but renal clearance of nateglinide was reduced by about 75%. In this patient population, renal clearance accounted for approximately 3% of the total parent drug clearance compared with 11% in normal subjects. Given that there is a 33% reduction in half-life, and similar AUC in the renal insufficient patients, the exact clinical impact is unknown, but dosage adjustment does not seem necessary. It is of note, however, that in the ADME study 16% of the parent drug was eliminated unchanged. Free and bound fractions of nateglinide were similar between the two groups.

Healthy Subjects vs. Patients on Hemodialysis: 120 mg PO Nateglinide				
Parameter	Healthy 1	Hemodialysis	90% CI	% Difference
AUC_{0-t} (µg*hr/mL)	19.583 ± 5.873	14.668 ± 7.154	0.50 – 0.95	-25.1
C_{max} (µg/mL)	10.113 ± 4.367	4.704 ± 2.758	0.31 – 0.67	-53.5
T_{max} (hr)[1]	0.806 ± 0.325 [0.5 – 1.5]	0.950 ± 0.590 [0.5 – 2.5]	— —	17.9
$t_{½}$ (hr)	2.07 ± 0.25 [1.62 – 2.46]	2.51 ± 1.09 [1.48 – 4.55]	— —	21.2
Cl_{total} / F (L/hr)	6.504 ± 1.797	9.688 ± 5.066	—	49.0
Cl_{renal} (L/hr)	0.729 ± 0.212 [0.338 – 1.056]	— —	— —	— —
Mean ± SD; [range]; 1. Median				

Healthy Subjects vs. Patients with Moderate to Severe Renal Dysfunction: 120 mg PO Nateglinide				
Parameter	Healthy 2	Renal	90% CI	% Difference
AUC_{0-t} (µg*hr/mL)	17.494 ± 4.417	18.324 ± 6.663	0.88 – 1.18	4.74
C_{max} (µg/mL)	10.008 ± 5.948	7.394 ± 2.685	0.57 – 1.17	-26.12
T_{max} (hr)[1]	0.65 ± 0.21 [0.5 – 1.0]	0.80 ± 0.31 [0.5 – 1.5]	— —	23.08
$t_{½}$ (hr)	2.85 ± 3.27 [1.12 – 11.41]	1.91 ± 0.37 [1.54 – 2.77]	— —	-32.98
Cl_{total} / F (L/hr)	7.285 ± 2.476]	7.382 ± 3.102		1.33
Cl_{renal} (L/hr)	0.834 – 0.344 [0.394 – 1.348]	0.218 – 0.131 [0.096 – 0.460]	— —	-73.75
Mean ± SD; [range]; 1. Median				

Drug Interactions

Given that nateglinide is extensively metabolized by CYP2C9, and to a lesser extent CYP3A4, does Starlix™ interact with known substrates, inhibitors, and/or inducers of these isozymes?

In vitro studies using pooled human liver microsomes suggest that nateglinide was capable of inhibiting tolbutamide hydroxylation, a CYP2C9 substrate, with an IC_{50} of approximately 30µM – the converse was not true (IC_{50} ~500 µM). Both cyclosporine A (CYP3A4) and glyburide inhibited nateglinide hydroxylation at an IC_{50} of about 10µM. However, the concentration of glyburide necessary to produce this inhibition *in vivo* is not likely to occur clinically.

Two *in vivo* drug interaction studies in type 2 DM patients and three in normal subjects were investigated with nateglinide. The concomitant medications included in these studies were digoxin, metformin, glyburide, diclofenac, and warfarin. Based on nateglinide's known characteristics, such as high protein binding, hepatic metabolism, and *in vitro* inhibition by glyburide, the occurrence of an interaction seems highly probable with the afore mentioned agents. This turned out not to be the case. Results of these five studies are presented in the following tables.

Results from the Drug Interaction Studies

Nateglinide Kinetics (n = 12)			
Parameter	Nateglinide	Nateglinide + Glyburide	90% CI
AUC_{0-t} (ng•hr/mL)	11286 ± 3498	10734 ± 3157	(0.85 – 1.10)
C_{max} (ng/mL)	8663 ± 3075	7716 ± 2613	(0.72 – 1.16)
T_{max} (hr)	0.75	0.75	
Glyburide Kinetics (n = 12)			
Parameter	Glyburide	Glyburide + Nateglinide	90% CI
AUC_{0-24} (ng•hr/mL)	1613 ± 475	1525 ± 541	(0.82 – 1.05)
C_{max} (ng/mL)	225 ± 49	234 ± 107	(0.77 – 1.22)

T_{max} (hr)	2.50	2.25	
$t_{½}$ (hr)	7.5 ± 3.4	8.0 ± 2.8	

Nateglinide Kinetics (n = 11)			
Parameter	**Nateglinide**	**Nateglinide + Metformin**	**90% CI**
	Nateglinide 120 mg TID following the morning dose		
AUC_{0-4} (ng•hr/mL)	10276 ± 2517	10577 ± 3367	(0.92 – 1.14)
C_{max} (ng/mL)	6105 ± 1864	6705 ± 2855	(0.97 – 1.23)
T_{max} (hr)	0.96 ± 0.16	0.91 ± 0.30	
	Nateglinide 120 mg TID following the evening dose		
AUC_{0-4} (ng•hr/mL)	11820 ± 5056	11626 ± 3731	(0.79 – 1.18)
C_{max} (ng/mL)	7215 ± 4752	5766 ± 3318	(0.49 – 1.11)
T_{max} (hr)	0.82 ± 0.46	1.68 ± 1.01	
$t_{½}$ (hr) (n = 8)	1.84 ± 0.60	1.78 ± 0.47	
Metformin Kinetics (n = 12)			
Parameter	**Metformin**	**Metformin + Nateglinide**	**90% CI**
	Metformin 500 mg TID following the morning dose		
AUC_{0-4} (ng•hr/mL)	2374 ± 640	2702 ± 791	(1.06 – 1.22)
C_{max} (ng/mL)	760 ± 233	840 ± 253	(1.01 – 1.20)
T_{max} (hr)	1.92 ± 1.13	1.54 ± 0.62	
	Metformin 500 mg TID following the evening dose		
AUC_{0-4} (ng•hr/mL)	3965 ± 1419	3813 ± 1210	(0.89 – 1.03)
C_{max} (ng/mL)	1169 ± 317	1164 ± 279	(0.93 – 1.06)
T_{max} (hr)	1.38 ± 0.57	1.50 ± 0.88	
$t_{½}$ (hr) (n = 11)	4.87 ± 0.57	4.74 ± 0.46	

Nateglinide Kinetics (n = 11)			
Parameter	**Nateglinide**	**Nateglinide + Digoxin**	**90% CI**
	Nateglinide 120 mg TID following the morning dose		
AUC_{0-4} (ng•hr/mL)	12328 ± 3054	13268 ± 3478	(0.96 – 1.21)
C_{max} (ng/mL)	7865 ± 3245	7694 ± 3204	(0.73 – 1.38)
T_{max} (hr)	0.5	0.75	
	Nateglinide 120 mg TID following the evening dose		
AUC_{0-24} (ng•hr/mL)	20445 ± 5572	20900 ± 4863	(0.99 – 1.08)
C_{max} (ng/mL)	9734 ± 4200	10045 ± 2730	(0.87 – 1.40)
T_{max} (hr)	0.5	0.75	
$t_{½}$ (hr) (n = 10)	2.04 ± 0.55	1.95 ± 0.69	
Digoxin Kinetics (n = 12)			
Parameter	**Digoxin**	**Digoxin + Nateglinide**	**90% CI**
AUC_{0-120} (ng•hr/mL)	48.6 ± 11.1	51.8 ± 11.9	(0.98 – 1.16)
C_{max} (ng/mL)	4.25 ± 1.50	4.02 ± 1.63	(0.74 – 1.17)
T_{max} (hr) - median	0.75	0.75	
$t_{½}$ (hr)	42.3 ± 8.25	39.4 ± 10.5	

Nateglinide Kinetics (n = 12)			
Parameter	**Nateglinide**	**Nateglinide + Warfarin**	**90% CI**
AUC_{0-t} (ng•hr/mL)	11213 ± 2909.7	10796 ± 2136.2	(0.90 – 1.06)
C_{max} (ng/mL)	7137.5 ± 2917.5	7326.7 ± 3364.8	(0.84 – 1.18)
T_{max} (hr)	0.63	0.063	
R-Warfarin Kinetics (n = 12)			
Parameter	**Warfarin**	**Warfarin + Nateglinide**	**90% CI**
AUC_{0-inf} (ng•hr/mL)	110.52 ± 27.63	110.96 ± 31.44	(0.91 – 1.09)
C_{max} (ng/mL)	1.80 ± 0.403	1.79 ± 0.281	(0.93 – 1.07)

T_{max} (hr)	3	3	
S-Warfarin Kinetics (n = 12)			
Parameter	Warfarin	Warfarin + Nateglinide	90% CI
AUC_{0-last} (ng•hr/mL)	75.60 ± 26.67	79.58 ± 41.33	(0.92 – 1.10)
C_{max} (ng/mL)	1.80 ± 0.485	1.78 ± 0.299	(0.93 – 1.10)
T_{max} (hr)	2	2.5	

Nateglinide Kinetics (n = 18)			
	Nateglinide	Nateglinide + Diclofenac	90% CI
	Nateglinide 120 mg BID following the morning dose		
AUC_{0-4} (ng•hr/mL)	10047 ± 2353	9822 ± 2043	(0.89 – 1.10)
C_{max} (ng/mL)	6571 ± 2326	5858 ± 2061	(0.75 – 1.10)
T_{max} (hr)	1.00	1.50	
	Nateglinide 120 mg BID following the lunch dose		
AUC_{4-12} (ng•hr/mL)	15946 ± 3736	17142 ± 4966	(0.99 – 1.14)
C_{max} (ng/mL)	7530 ± 2326	7813 ± 2842	(0.89 – 1.19)
T_{max} (hr)	5.00	5.00	
	Diclofenac Sodium	Diclofenac + Nateglinide	90% CI
AUC_{0-24} (ng•hr/mL)	2504 ± 1294	2648 ± 1054	(0.92 – 1.27)
C_{max} (ng/mL)	2315 ± 1205	2273 ± 864	(0.81 – 1.30)
T_{max} (hr)	1.75	2.00	
t_{eg} (hr)	1.15 ± 0.83	1.40 ± 0.74	
$t_{½}$ (hr)	1.02 ± 0.48	1.10 ± 0.36	

Nateglinide is highly protein bound (~98%) to albumin and to a lesser extent α_1-acid glycoprotein. Does Starlix™ displace or get displaced by other highly protein bound drugs?

In vitro displacement studies with furosemide, propranolol, captopril, nicardipine, pravastatin, warfarin, phenytoin, glibenclamide, ASA, tolbutamide, and metformin showed virtually no effect on nateglinide binding. Studies in which nateglinide was the precipitant showed no significant displacement of propranolol, nicardipine, phenytoin, warfarin, glibenclamide, ASA, or tolbutamide. These results are fairly conclusive, however prudent evaluation of individual cases is warranted *in vivo*.

Labeling Comments
(Where applicable, ~~strikeout~~ text should be removed from labeling. Double <u>underlined</u> text should be added to labeling.)

Pharmacokinetics

Draft

2 pages redacted from this section of the approval package consisted of draft labeling

Drug/Food Interactions

DOSAGE AND ADMINISTRATION

Monotherapy

Dosage in renal and hepatic impairment

Comments to Firm
Dissolution
The dissolution specification of using 6 units (stage 1 testing) is not acceptable to the Agency. The Agency requires that 12 units be tested which corresponds with stage 2 testing.

The multipoint dissolution profiles from the data submitted in this application suggest that the tolerance specifications are too loose. The Agency recommends setting the dissolution tolerances at Q = — % @ 20 minutes rather than the proposed Q = — % @ 30 minutes.

Steven B. Johnson, B.S.Pharm, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

/S/ 28-NOV-2000

RD initialed by Hae-Young Ahn, Ph.D., Team Leader: 27-OCT-2000

FT initialed by Hae-Young Ahn, Ph.D., Team Leader: 27-NOV-2000

/S/

OCPB Briefing on: 02-NOV-2000

Briefing Attendees: John Hunt, John Lazor, Mehul Mehta, Saul Malozowski, Hae-Young Ahn, Steven B. Johnson, Sang Chung, Wei Qiu.

CC: NDA 21-204 (orig., 1 copy), HFD-510 (WeberJ), HFD-870 (AhnH, MalinowskiH, JohnsonST), CDR

APPENDIX - Dissolution

Starlix® 60 mg Tablets

Batch H-5012 – Phase III Formulation (Version D – Method 2)	Tablet #	10 min	20 min	30 min
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	Mean %	67	86	94
	%RSD	8.1	4.5	1.9

Batch H-05225 –FMI-2 Formulation (Version D – Method 2)	Tablet #	10 min	20 min	30 min
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	Mean %	67	85	90
	%RSD	6.6	1.1	0.8

Starlix® 120 mg Tablets

Batch H-05226 – FMI-2 Formulation (Version D – Method 2)	Tablet #	10 min	20 min	30 min
	1			
	2			
	3			
	4			
	5			
	6			
	Mean %	72	88	93
	%RSD	4.8	2.0	0.9

Starlix® 180 mg Tablets

Batch H-05001 – Phase III Formulation (Version D – Method 2)	Tablet #	10 min	20 min	30 min
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	Mean %	68	86	92
	%RSD	2.9	1.2	1.1

Batch H-05227 – FMI-2 Formulation (Version D – Method 2)	Tablet #	10 min	20 min	30 min
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	Mean %	65	82	89
	%RSD	8.9	3.1	1.5

Bioavailability Formulation Summary

Study #	Batch #	Form & Strength	Batch Size	Manuf. Date	Form. Type
0123 / W360	H-05225	60 mg Tablet		Aug-98	Market FMI-2
	H-05012	60 mg Tablet		Jan-97	Phase III
0124	H-05012	60 mg Tablet		Jan-97	Phase III
	H-05225	60 mg Tablet		Aug-98	Market FMI-2
0118 / W370	H-05226	120 mg Tablet		Aug-98	Market FMI-2
	H-05014	120 mg Tablet		Jan-97	Phase III
0125	H-05501	180 mg Tablet		Oct-96	Phase III
	H-05227	180 mg Tablet		Aug-98	Market FMI-2

Appendix – Studies by Analytical Site

Study #		Novartis/Sandoz		
P-098	X			
P-099	X			
P-100	X			
P-101	X			
P-102	X			
P-103/P104	X			
P-105	X			
P-106	X			
P-107	X			
P-108	X			
P-110		X		
P-111	X			
P-113			X	
P-114				
P-116				
P-117				
W-081		X		
W-083				
W-251				
W-253				
W351				
W352				
W353				
W354				
W355				
W357				
W358				
W359				
W360				
W361				
W362				
W363				
W365				
W366				
W367				
W369				
W370				
W371				
0124				
0125				

Appendix – Nateglinide Formulations Used in the Clinical Studies

Tablet	CSF Tablet	MF Tablet		FMI1 Tablet	FMI2 Tablet	Solution IV or Oral
P098	P110	W252	W367	W358	0118	P113
P099	P113	W351	W369		0119	P114
P100	P116	W352	0118		0123	
P101	P117	W353	0119		0124	
W081	W083	W354	0123		0125	
	W251	W355	0124			
	W252	W357	0125			
	W253	W358	B302*			
	B202	W359	B304*			
	B251	W361	B351*			
	B252	W363	B354*			
		W364	B355*			
		W365	B356*			

* no PK or PK/PD component

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pages of trade

secret and/or

confidential

commercial

information

New Drug Application Filing Memorandum

Office of Clinical Pharmacology and Biopharmaceutics

NDA:	21-204	**Priority Classification:**	1S
IND:	[redacted]	**Indication:**	Type 2 DM
Brand Name:	Starlix™	**Submission Date:**	17-DEC-99
Generic Name:	Nateglinide	**Route of Administration:**	Oral, Tablets
Strength(s):	60, 120, and 180 mg		
Sponsor:	Novartis	**UFGD:**	
Reviewer:	Steven B. Johnson, Pharm.D.	**Review Division:**	870
Team Leader:	Hae-Young Ahn, Ph.D.	**Medical Division:**	510

Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Study Synopsis	X		
Labeling	X		
ADME Study –	X		
BA Studies –			
Absolute BA	X		
Relative BA		X	
BE Studies –			
Population BE	X		
Individual BE	X		
Food-Drug Interaction Study	X		
In Vitro-In Vivo Comparison (IVIVc) Studies		X	
Reference Bioanalytical and Analytical Methods	X		
Dissolution Profiles	X		
Plasma Protein Binding Studies	X		
Metabolism Studies Using Hepatocytes, Microsomes, etc.	X		
Blood / Plasma Ratio		X	
PK and Initial Safety and Tolerability in Healthy Volunteers –			
Single Dose	X		
Multiple Dose	X		
PK and Initial Safety and Tolerability in Patient Volunteers –			
Single Dose	X		
Multiple Dose	X		
Dose Proportionality –			
Single Dose		X	
Multiple Dose	X		
PK in Population Subsets to Evaluate Intrinsic Factor Effects –			
Ethnicity	X		Japanese
Gender	X		
Pediatrics		X	
Geriatrics		X	
Renal Impairment	X		
Hepatic Impairment	X		

PK in Population Subsets to Evaluate Extrinsic Factor Effects – **In-Vivo Effects on Primary Drug** **In Vivo Effects of Primary Drug** **In-Vitro Drug Interaction**	X X X		
Population PK Studies	X		
Summary of PK / PD Studies	X		
PK / PD Studies in Volunteers	X		
PK / PD Studies in Patients	X		
Individual Datasets for all PK and PK / PD Studies in Electronic Format		X	
Genotype / Phenotype Studies		X	
Chronopharmacokinetics		X	
Literature – Number of Articles Sufficient	X		
Notes: A summary of the clinical and the sponsor's internal reports are provided in the attachment.			

This Application is filable.

Comments to be sent to Sponsor:

Please submit individual data sets in MS Excel and command files (e.g., SAS, WinNonlin, etc.) in MS Word for all PK and PK-PD studies and analyses.

/S/ 2·14·00

Steven B. Johnson, B.Pharm., Pharm.D.; FDA / CDER / OPS / OCPB / DPE-II

/S/ 2/14/00

Hae-Young Ahn, Ph.D., Team Leader; FDA / CDER / OPS / OCPB / DPE-II

CC: NDA 21-204, HFD-510 (WeberJ), HFD-870 (HuangS, AhnH, JohnsonST), CDR

References to clinical study reports

Doc.1 **P 098** (Report 7980): An ascending dose tolerance study of A-4166 in healthy volunteers with preliminary pharmacokinetic assessment

Doc.2 **P 099** (Reprot 11013) : A double-blind, placebo controlled tolerability study of A-4166 in a dose of 60 mg and 90 mg TID for one day in healthy volunteers with preliminary pharmacokinetic assessment

Doc.3 **P 100** : A double-blind, placebo controlled multiple dose tolerance study of A-4166 in healthy volunteers with preliminary pharmacokinetic assessment

Doc.4 **P 101** : Dose ranging study of a single dose of A4166 in fasting Type 2 diabetic subjects

Doc.5 **P 102** : Dose ranging study of a single dose of A4166 in Type 2 diabetic subjects to a standard meal

Doc.6 **P 103/104** : Effect of a single dose of A-4166 on intravenous glucose tolerance tests in patients with non-insulin dependent diabetes before and after diet treatment

Doc.7 **P 105** : Double blind, placebo controlled, time-lagged, dose escalating parallel study in patients with NIDDM to evaluate the pharmacokinetics, safety and tolerabilty of A-4166

Doc.8 **P 106** : A double blind, placebo controlled, randomised, crossover study to examine the pharmacokinetic and pharmacodynamic effect of A-4166 in connection with a standardised meal

Doc.9 **P 107** : The influence of meal composition on the pharmacokinetics and pharmacodynamic effect of a single oral dose of A-4166 during a meal tolerance test in healthy subjects

Doc.10 **P 108** : A double-blind, randomized, placebo controlled, crossover study to evaluate the pharmacokinetic and pharmacodynamic interaction of SDZ SDZ DJN 608 and metformin in non-insulin dependent diabetes mellitus patients

Doc.11 **P 110** : An open label, rive period, single dose, crossover study in healthy volunteers to evaluate the effect of food on the pharmacokinetics of SDZ DJN 608 and to assess the relative bioavailability of the SDZ DJN 608 tablet to the ——— tablet.

Doc.12 **P 111** : The effect of the timing of food intake on the pharmacokinetics and pharmacodynamics of A-4166 and the effect of A-4166 on gastric emptying in healthy male volunteers

Doc.13 **P 113** : A randomized, six period, double-blind, placebo-controlled, study to evaluate the safety and tolerability of single ascending intravenous doses of sdz djn 608 and to determine the absolute bioavailability of SDZ DJN 608 tablets in healthy volunteers

Doc.14 **P114** : A randomized, two period, crossover study to evaluate the absorption, distribution, metabolism and excretion of [14C]SDZ DJN 608 following oral and iv administration in healthy volunteers

Doc.15 **P 116** : A double-blind, placebo-controlled, five period, randomized, cross-over study evaluating twenty-four hour glucose and insulin profiles in NIDDM subjects treated with SDZ DJN 608

Doc.16 **P 117** : A double-blind, placebo-controlled, four period, randomized, escalating multiple dose 2 cohort study in NIDDM subjects to evaluate the safety, tolerability, pharmacodynamics and pharmacokinetics of SDZ DJN 608

Doc.17 **W 081** : A double-blind, parallel group, placebo-controlled, time-lagged study on the safty and tolerability of mulitple oral escalating doses of SDZ DJN 608 in healthy subjects

Doc.18 **W083** : A double-blind randomized, placebo-controlled, cross-over pharmacokinetic/ pharmacodynmic drug-drug interaction study with SDZ DJN 608 and glyburide in non-insulin dependent diabetes mellitus

Doc.19 **W 251** : A six-period, open-label, randomized, crossover study to evaluate the effect of the interval between a meal and drug administration on the pharmacokinetics and pharmacodynamics of SDZ DJN 608 in patients with non-insulin dependent diabetes mellitus

Doc.20 **W 252** : A two-phase, six-period, open-label, randomized, crossover study to evaluate the bioequivalence of two 60 mg SDZ DJN 608 tablet formulations and dose-linearity of the final market form tablets.

Doc.21 **W 253** : A Partially Randomized, Three-Period, Open-Label, Crossover Study to Evaluate the Pharmacokinetic and Pharmacodynamic Interaction of SDZ DJN 608 and Digoxin in Healthy Subjects

Doc.22 **W 351** : A single dose, parallel group study of the pharmacokinetics of SDZ DJN 608 in subjects with liver dysfunction (hepatic cirrhosis) compared with age, sex, height and weight matched healthy subjects.

Doc.23 **W 352** : A randomized, placebo-controlled, three-period, blinded crossover study to evaluate the pharmacokinetic and pharmacodynamic interaction of SDZ DJN 608 and troglitazone (RezulinÔ) in patients with NIDDM

Doc.24 **W 353** : A Single Dose, Open Label, Parallel Group Study to Determine the Pharmacokinetics of SDZ DJN 608 in NIDDM Subjects with Severe Renal Insufficiency Compared with Age, Sex, Height and Weight Matched Healthy Subjects.

Doc.25 **W 354** : An Open Label, Three Period, Randomised, Crossover study to Evaluate the Pharmacokinetics of SDZ DJN 608 (120 mg) and Diclofenac (75 mg) given in combination in Fasting Healthy Subjects.

Doc.26 **W 355** : An open-label study evaluating the effects of multiple doses of SDZ DJN 608 on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects.

Doc.27 **W 357** : A randomised, double blind, three period, crossover study to compare the glucose and insulin profiles of SDZ DJN 608, glibenclamide and placebo, after a single day's dosing in diet treated subjects with Type 2 diabetes mellitus.

Doc.28 **W 358** : A Two-Phase, Four-Period, Open-Label, Randomized, Crossover Study to Evaluate the Bioequivalence of Two SDZ DJN 608 Tablet Formulations.

Doc.29 **W 359** : A three-period, double-blind, crossover study to evaluate the daily glycemic profiles of NIDDM subjects after placebo, glyburide, and SDZ DJN 608 treatment.

Doc.30 **W 360 (0123)** : A two-period, open-label, randomized, crossover study to evaluate the bioequivalence of two 60 mg sdz djn 608 tablet formulations.

Doc.31 **W 361** : A Four-Phase, eight-Period, Open-Label, Randomized, Crossover Study to compare the Effects of SDZ DJN 608 with glyburide on the Beta-cell Sensitivity of healthy subjects at different clamped Plasma concentrations of Glucose.

Doc.32 **W 363** : A Randomized, Double-Blind, Placebo-Controlled, Three –Period Crossover Study to Compare the Pharmacodynamic Effects of SDZ DJN 608, Glyburide and Placebo in Type 2 Diabetic Subjects in the Event of a Missed Lunch-Time Meal and Missed Dose of SDZ DJN 608.

Doc.33 **W 365** : Randomized placebo-controlled, five-period study to determine the effects of SDZ DJN 608 on the first-phase insulin response to intravenous glucose, in comparison to glyburide, in subjects with non-insulin dependent diabetes mellitus.

Doc.34 **W 366** : A Randomized, Open-Label, Five-Period Crossover Study to Compare the Pharmacodynamic and Pharmacokinetic Effects of SDZ DJN 608, Repaglinide and Placebo in Healthy Subjects.

Doc.35 **W 367** : A Double-blind, Three Period, Placebo-Controlled, Randomized, Crossover Study to Evaluate the Effect of SDZ DJN 608 and Glyburide on Basal and Postprandial Hepatic Glucose Production and Lipolysis in Patients with NIDDM.

Doc.36 **W 369** : An Open Label, Four Period, Randomized, Crossover Study to Evaluate the Effect of Different Meals on SDZ DJN 608 Pharmacokinetics and Pharmacodynamics in Healthy Subjects.

Doc.37 **0118 (W370)** : A two-period, open-label, randomized, crossover study to evaluate the bioequivalence of two 120 mg sdz djn 608 tablet formulations.

Doc.38 **0119 (W371)** : A three-period, open-label, randomized, crossover study to evaluate the bioequivalence of three 180 mg SDZ DJN 608 tablet formulations.

Doc. 39 **0124** : A two-treatment sequence, four-period, open-label, randomized, crossover study to evaluate the bioequivalence of two 60-mg SDZ DJN 608 tablet formulations

Doc. 40 **0125** : A two-treatment sequence, four-period, open-label, randomized, crossover study to evaluate the bioequivalence of two 180-mg SDZ DJN 608 tablet formulations

References to other internal reports

Doc. 41 Population pharmacokinetics/pharmacodynamics of nateglinide

Doc.42 Metabolism of SDZ DJN 608 in human following a single oral or intravenous dose of [^{14}C] SDZ DJN 608. Novartis Report DMPK(US) 1997/004, 13-Aug-1997.

Doc. 43 In vitro metabolism of SDZ DJN 608 by human liver microsomes and cytochrome P450 identification. Novartis Report DM-3-3/15/96, 15-Mar-96.

Doc. 44 Relative cytochrome P450 isozyme involvement in the metabolism of [^{14}C]DJN608. Novartis Report DMPK(US) R99-143, 08-Sep-1999

Doc. 45 In vitro binding of [^{3}H]SDZ DJN 608 to human plasma proteins and interactions with warfarin, phenytoin, acetylsalicylic acid, tolbutamide, glibenclamide and metformin (6135-145). Novartis Report DMPK(US) 1997/086, 17-Dec-1997.

Doc. 46 *Ex vivo* protein binding of [^{14}C] SDZ DJN 608 in normal volunteers and patients with liver dysfunction. Novartis Report DMPK(US) 1998/003, 14-Jan-1998, revised 17-Feb-1998.

Doc. 47 *Ex vivo* protein binding of [^{14}C]DJN608 in normal volunteers and patients with renal failure. Novartis Report DMPK(US) R99-126, 12-Aug-1999.

Doc. 48 Phase I Study of AY4166 - Study of single oral administration to fasting healthy adult men.

Doc. 49 Phase I Study of AY4166 - Study of effect of diet in healthy adult men.

Doc. 50 Phase I Test of AY4166 - Test of repeated aministration in healthy male adults.

Doc. 51 Clinical efficacy and safety of AY4166 in NIDDm patients.

Doc. 52 Effect of AY4166 on posprandial blood glucose and pharmacokinetics in NIDDM patients