CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-204

Statistical Review(s)

Statistical Review and Evaluation

JUL 31 2000

NDA#:	21-204
Sponsor:	Novartis
Drug:	Starlix (nateglinide)
Indication:	Type 2 diabetes
Documents reviewed:	Proposed Pediatric Study Request (untitled) dated 3/30/00
Medical Reviewer:	Beth Koller, M.D. (HFD-510)

Design: Randomized, placebo-controlled, double-blind, multicenter trial to investigate the safety and efficacy of nateglinide 120mg daily for 16 weeks. Pediatric patients already receiving metformin 1000mg will be randomized to nateglinide or placebo. The double-blind portion of the trial will be preceded by a 4 week single blind-placebo run-in period.

Major entry criteria:

- Subjects will be age 10 to 16 with a diagnosis of Type 2 diabetes for at least 6 months (Sponsor is requesting a partial waiver of requirements to study Starlix in subjects with Type 2 diabetes below the age of 10.)
- Receiving metformin monotherapy for at least 3 months prior to the Week –4 Visit and receiving at least 1500mg of metformin daily for at least 4 weeks prior to the Week –4 Visit
- Mean HbA_{1c} at Weeks –4 and –2 between 7.5% and 10.0%

Efficacy variables:

- The primary efficacy variable is the change from baseline in HbA_{1c} at Week 16. Baseline HbA_{1c} is computed as the mean of the Week –2 and 0 measurements.
- Secondary variables include prandial and fasting plasma glucose, insulin, C-peptide, fasting lipid parameters (total-C, TG, LDL-C, HDL-C) and body weight.

Statistical methods: The study will test the following hypotheses using the ANCOVA

H_{01}: $\alpha_1 = \alpha_0$
H_{02}: $\alpha_2 = \alpha_0$

Where

α_0 = effect of placebo plus metformin 1000mg bid
α_1 = effect of nateglinide 120mg plus metformin 1000mg bid effect
α_2 = effect of nateglinide 120mg plus metformin 1000mg bid effect

Dunnett's procedure will be used to test the hypotheses at an experiment wise Type I error rate of 5%. 95% confidence intervals (without adjustment for multiple comparisons) will be presented for each hypothesis.

Comment: There appear to be typos throughout this section of the submission. Effects α_1 and α_2 are identical, therefore hypotheses H_{01} and H_{02} are identical as well. Hence there is only one primary hypothesis (as there should be with just two treatment groups) and no multiple comparison issue. Details of the ANCOVA including what terms should be in the model are not presented.

Analysis population: The primary analysis population will be the ITT population. The same analysis will be conducted using completers to assess the effect of dropouts on the results. An LOCF approach will be used for patients who do not complete the Week 16 assessment. "Efficacy assessments which occur more than 7 days after the date of examination of the Study Completion CRF and the date of last drug taken by the subject will be excluded from all efficacy analyses."

Sample size: Based on a 0.7% effect size with standard deviation of 1.25%, a Type I error rate of 5% (2-sided), and power of 80%, 52 patients per group are required. Assuming a dropout rate of 25%, the sponsor expects to randomize 70 patients per group. Each center will aim "to randomize a minimum of one patient".

Comment: Each center should attempt to randomize *more than one patient per treatment arm* so that treatment differences can be assessed across centers as part of a secondary analysis.

Suggested Language for 'Statistical Information' Section of the Written Request

Change from baseline in HbA_{1c} at sixteen weeks will be compared between treatment groups using ANCOVA adjusted for baseline HbA_{1c}. The primary analysis population will be the intent-to-treat (ITT) population consisting of all randomized subjects with an observation at baseline and at least one observation after randomization. For withdrawals or missing data, the last value recorded during treatment will be used in the ITT analysis.

/S/

J. Todd Sahlroot, Ph.D.
Team Leader
Division of Biometrics 2

cc: Arch NDA 21-204
HFD-510/BKoller
HFD-510/JWeber
HFD-715/Division file, TSahlroot

This review contains 2 pages

Statistical Review and Evaluation
(Carcinogenicity Studies)

Date:
JUN 2 7 2000

NDA No.: 21-204

Applicant: Novartis

Name of Drug: Starlix (nateglinide) Tablets

Reviewing Pharmacologist: Herman Rhee, Ph.D., HFD-510

Statistical Reviewer: Karl K. Lin, Ph.D., HFD-715

Summary of Review

After adjusting the effect of multiple testings, the positive trends in tumor incidence in pancreatic islet cell adenoma alone, and both adenoma and carcinoma combined in females of the first rat study are not statistically significant regardless reported as significant by the sponsor.

The sponsor's conclusion of significant positive trends in incidence rate of the two tumor types may be due to its failure to make the adjustment for the effect of multiple testings in analysis of carcinogenicity study data.

1. Introduction

There are three long-term carcinogenicity studies included in this submission. Two studies were conducted in Sprague-Dawley (Crl; CD(SD)BR) rats and one study in B6C3F1 mice. The purpose of the carcinogenicity studies was to evaluate the carcinogenic potential of the drug when tested animals received daily treatment with the drug for two years. Dr. Herman Rhee of HFD-580, the reviewing pharmacologist of this submission, has asked the Division of Biometrics II to perform a statistical review and evaluation on the carcinogenicity studies.

According to Dr. Rhee, the second rat study that used a high dose 20 times higher than that in the first rat study and the mouse study are clearly negative and there is no major statistical issue in the interpretation of the results of the two studies. However, Dr. Rhee has questions regarding the interpretation of the statistical analysis results of the data of pancreatic islet cell adenoma and carcinoma in females of the first rat study and the sponsor's use of historical control data in its conclusion of the negative carcinogenic effect of the drug in that study. This reviewer performed some independent analysis using the pancreatic islet tumor data of the first rat study and the historical control data reported by Dr. Rhee.

2. Reviewer's Analysis of Pancreatic Tumor Data of Female Rats

The incidence rates of pancreatic islet cell tumors (adenoma and carcinoma) of females of the first rat study reported by Dr. Rhee are given in Table 1 below.

Table 1

Pancreatic Islet Cell Tumors in Females in the First Rat Study

Tumor Type	Control	625 ppm	1250 ppm	2500 ppm
# of Animals Examined	56	56	56	56
Adenoma	2	2	2	6
Carcinoma	0	1	0	1
Total Tumor Bearing Animals*	2	3	2	7

*Assuming that each tumor bearing animal has either adenoma or carcinoma but not both.

The historical control data of the above tumor types from 10 other studies submitted by the sponsor are given in Table 2 below.

Table 2

Historical Control Data of Pancreatic Islet Cell Tumors in Female Rats

Study #	9006	9008	9009	9010	9011	9012	9105	9106	9107	9108
# of Animals Examined	59	50	49	55	59	49	50	50	60	60
Adenoma	3	1	2	1	1	1	0	5	2	0
Carcinoma	1	0	1	0	0	0	0	1	1	0
Total*	4	1	3	1	1	1	0	6	3	0
% (Total/# of Animals Examined	7	2	6	2	2	2	0	12	5	0

*Assuming that each tumor bearing animal has either adenoma or carcinoma but not both.

Using the statistical procedures described in the IARC paper by Peto, et al. (1980), the sponsor reported that the positive trend in pancreatic islet cell tumor incidence rate (adenoma and carcinoma combined) is statistically significant (p = 0.039) but the differences between pairs of the four treatment groups are not. The sponsor also pointed out that the pancreatic islet cell tumor incidence rate of the high dose group (7/56 = 12.5%) of the first rat study was just a little bit outside the historical control range, and therefore the significant trend can be ignored.

Since the survival rates of the treatment groups (both tests for heterogeneity and linear trend) of the females in this rat study are not statistically significant, survival-unadjusted procedures were used to test the positive trend and difference in tumor incidence rate for adenoma alone and adenoma and carcinoma combined. The test results are presented in Table 3 (results of trend tests) and Table 4 (results of pairwise comparison tests). The detailed outputs of the statistical tests are included in the appendix for reference. The reviewer's p-value (0.0545) from the survival-unadjusted trend test for the positive trend in the incidence rate of pancreatic islet cell adenoma and carcinoma combined is little bit larger than the survival-adjusted p-value (0.039) reported by the sponsor.

Table 3

Results (P-Values) of Trend Tests

Tumor Types	P-Value
Pancreatic Islet Cell Adenoma	0.0729
Pancreatic Islet Cell Adenoma + Carcinoma	0.0545

Table 4

Results (P-Values) of Pairwise (Control vs High) Comparison Tests

Tumor Types	P-Value
Pancreatic Islet Cell Adenoma	0.1355
Pancreatic Islet Cell Adenoma + Carcinoma	0.0809

To control the overall false positive rate to around 10%, the following methods (or decision rules) of adjustment for the effect of multiple tests presented in Table 5 (on next page) are used. These methods are also recommended in the Agency's draft guidance for industry document.

The spontaneous incidence rates of pancreatic islet cell adenoma, and adenoma + carcinoma of the concurrent control are both 3.57% (2/56). The above spontaneous incidence rates based on the historical control data of other ten studies submitted by the sponsor are 2.96% (16/541), and 3.70% (20/541), respectively. Since the spontaneous incidence rates of the above two tumor types based either on the concurrent control or the submitted historical control data are greater than 1%, they are classified as common tumor types.

Based on the decision rules given in Table 5, the positive trends, and differences (control versus high) in incidence rate of the above two tumor types will be considered as statistically significant only if the p-values from the exact tests are less than 0.005 (for trend test), and 0.01 (for control-high comparison test), respectively. Since the p-values from the reviewer's trend tests (0.0729 for adenoma alone and 0.0545 for adenoma and carcinoma combined) are greater than 0.005, the positive trends in incidence rate of the above two tumor types are not statistically significant regardless as reported as significant by the sponsor. The sponsor's conclusion of significant positive trends in incidence rate of the two tumor types may be due to its failure to make the adjustment for the effect of multiple testings in analysis of carcinogenicity study data. The reviewer's negative results of the survival-unadjusted pairwise comparison tests between the control and the high dose groups ($p = 0.1355$ for adenoma alone and 0.0809 for adenoma and carcinoma combined) are consistent with those of the sponsor.

Table 5

Statistical Decision Rules for Controlling the Overall False Positive Rates Associated with Tests for Positive Trend or with Control-High Pairwise Comparisons in Tumor Incidences to Around 10% in Carcinogenicity Studies of Pharmaceuticals.

	Tests for Positive Trend	Control-High Pairwise Comparisons
Standard Two-Year Studies with 2 Species and 2 Sexes	Common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively.	Common and rare tumors are tested at 0.01 and 0.05 significance levels, respectively.
Alternative ICH Studies (One Two-Year Study in One Species and One Short or Medium-Term Study, 2 Sexes)	Common and rare tumors are tested at 0.01 and 0.05 significance levels, respectively.	Under development in CDER/FDA and not yet available.

/S/

Karl K. Lin, Ph.D.
Expert Mathematical Statistician
(Applications in Pharmacology and Toxicology)

Concur: /S/ 6-27-01

S. Edward Nevius, Ph.D.
Director, Division of Biometrics II

cc: Original/NDA 21-204 File
HFD-580/ H Rhee, J El Hage
HFD-715/Chron
HFD-715/E Nevius, K Lin

Appendix

Computer Outputs of the Trend and Pairwise Comparison Tests of Tumor Incidence Rates of Pancreatic Islet Cell Adenoma and Carcinoma in Female Rats

```
ADENOMA + CARCINOMA

TREND TEST


StatXact-3 Output
Date: 6/15/2000
Time: 16:0:50


>>> TC TR/EX

Datafile: <new>

COCHRAN-ARMITAGE TREND TEST
[  Sum of scores from population <row1      > ]

        Min          Max          Mean      Std-dev     Observed   Standardized
                                  21.00        4.060        28.00          1.724

Asymptotic Inference:
    One-sided p-value: Pr {   Test Statistic .GE. Observed }  =      0.0423
    Two-sided p-value: 2 * One-sided                          =      0.0846

Exact Inference:
    One-sided p-value: Pr {   Test Statistic .GE. Observed }  =      0.0423
                       Pr {   Test Statistic .EQ. Observed }  =      0.0228
    Two-sided p-value: Pr { | Test Statistic - Mean |
                          .GE. | Observed - Mean |            =      0.1091
    Two-sided p-value: 2*One-Sided                            =      0.1091

Elapsed Time is 0:0:0.05
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ADENOMA ONLY

TREND TESTS


>>> TC TR/EX

Datafile: <new>

COCHRAN-ARMITAGE TREND TEST
[  Sum of scores from population <row1      > ]

        Min          Max          Mean      Std-dev     Observed   Standardized
                                  18.00        3.776        24.00          1.589

Asymptotic Inference:
    One-sided p-value: Pr {   Test Statistic .GE. Observed }  =      0.0560
    Two-sided p-value: 2 * One-sided                          =      0.1121

Exact Inference:
    One-sided p-value: Pr {   Test Statistic .GE. Observed }  =      0.0560
                       Pr {   Test Statistic .EQ. Observed }  =      0.0307
    Two-sided p-value: Pr { | Test Statistic - Mean |
                          .GE. | Observed - Mean |            =      0.1458
    Two-sided p-value: 2*One-Sided                            =      0.1458
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Elapsed Time is 0:0:0.05

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ADENOMA ALONE

CONTROL-HIGH PAIRWISE COMPARISON


>>> TB FI/EX

Datafile: <new>

FISHER'S EXACT TEST

Statistic based on the observed 2 by 2 table(x) :
     P(X)  = Hypergeometric Prob. of the table =      0.1052
     FI(X) = Fisher statistic                  =       2.048

Asymptotic p-value: (based on Chi-Square distribution with 1 df )
     Two-sided:Pr{FI(X) .GE.        2.048} =      0.1524
     One-sided:0.5 * Two-sided             =      0.0762

Exact p-value and point probabilities :
 Two-sided:Pr{FI(X) .GE.        2.048}= Pr{P(X) .LE.       0.1052}=      0.2709
           Pr{FI(X) .EQ.        2.048}= Pr{P(X) .EQ.       0.1052}=      0.2103
 One-sided:Let y be the value in Row 1 and Column 1
                                 mean(Y) =       4.000 std(Y) =       1.369

           Pr { Y .GE. 2 } =      0.1355
           Pr { Y .EQ. 2 } =      0.1052

Elapsed Time is 0:0:0.00

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ADENOMA + CARCINOMA

CONTROL-HIGH PAIRWISE COMPARISON


>>> TB FI/EX

Datafile: <new>

FISHER'S EXACT TEST

Statistic based on the observed 2 by 2 table(x) :
     P(X)  = Hypergeometric Prob. of the table =      0.0650
     FI(X) = Fisher statistic                  =       2.902

Asymptotic p-value: (based on Chi-Square distribution with 1 df )
     Two-sided:Pr{FI(X) .GE.        2.902} =      0.0885
     One-sided:0.5 * Two-sided             =      0.0442

Exact p-value and point probabilities :
 Two-sided:Pr{FI(X) .GE.        2.902}= Pr{P(X) .LE.       0.0650}=      0.1617
           Pr{FI(X) .EQ.        2.902}= Pr{P(X) .EQ.       0.0650}=      0.1300
 One-sided:Let y be the value in Row 1 and Column 1
                                 =9 mean(Y) =       4.500 std(Y) =       1.445

           Pr { Y .GE. 2 } =      0.0808
           Pr { Y .EQ. 2 } =      0.0650

Elapsed Time is 0:0:0.00
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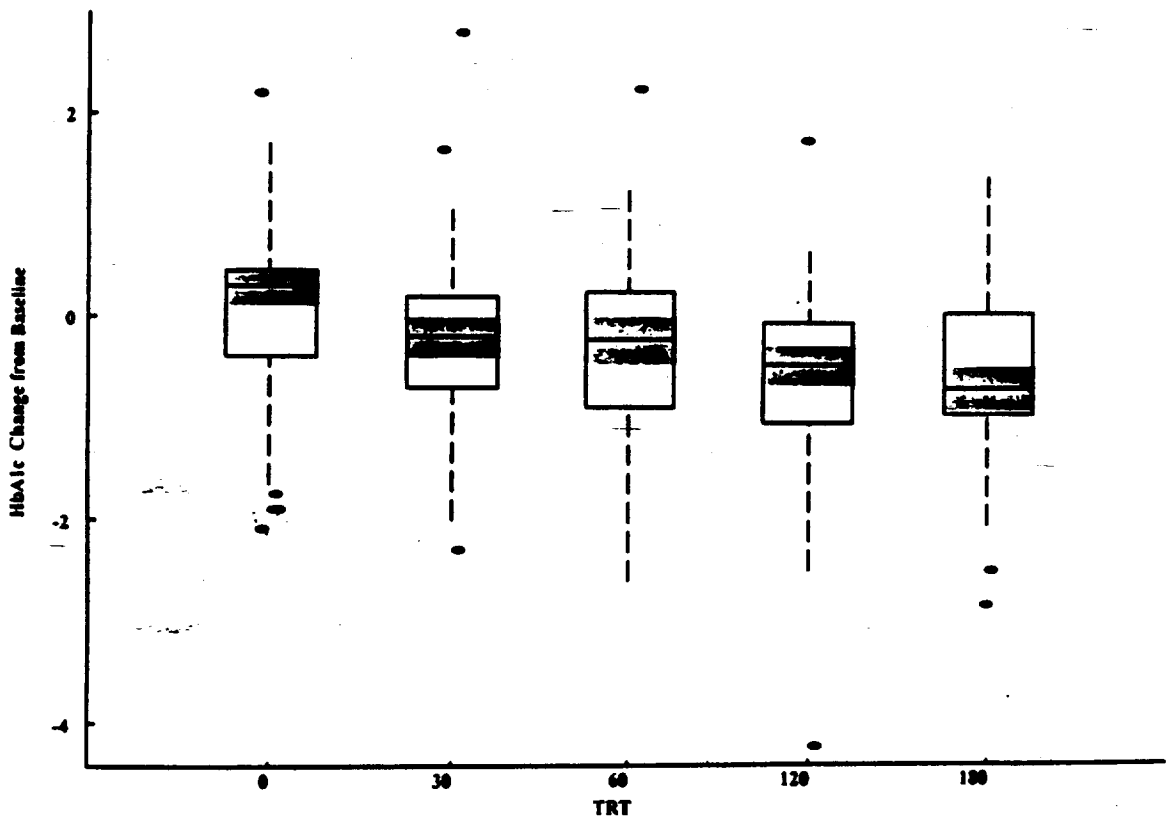
Table 6. Study B202 HbA1c Results

	Placebo Mean (SD)	NAT 30 Mean (SD)	NAT 60 Mean (SD)	NAT 120 Mean (SD)	NAT 180 Mean (SD)
Completers	(n=54)	(n=46)	(n=53)	(n=59)	(n=55)
Baseline	8.4 (1.0)	8.4 (1.2)	8.4 (1.1)	8.2 (0.8)	8.4 (1.0)
Week 12	-0.04 (0.88)	-0.23 (0.91)	-0.37 (0.97)	-0.59 (0.91)	-0.59 (0.83)
ITT	(n=58)	(n=50)	(n=58)	(n=62)	(n=57)
Baseline	8.5 (1.0)	8.4 (1.1)	8.3 (1.1)	8.2 (0.9)	8.5 (1.1)
Week 12 LOCF	+0.03 (0.91)	-0.20 (0.90)	-0.37 (0.92)	-0.60 (0.89)	-0.54 (0.86)
Least Squares Mean	-0.06	-0.28	-0.49	-0.71	-0.60
Unadjusted p-value for comparison to placebo[1]		.18	.01	.0001	.001

The three highest doses (60, 120 and 180) all show a significant change from baseline compared to placebo (note that adjustments to the p-values for multiple comparisons would still render these comparisons significant). The means suggest that the two highest doses (120 and 180) are comparable, however an examination of the distribution of the data (Figure 2 boxplots) shows a shift in the medians going from 120 mg to 180 mg. See page 24 for a more thorough examination of the dose response relationship of nateglinide.

Figure 2. Study B202 Boxplots of HbA1c change from baseline at Week 12 LOCF by dose



1 P-values are results of pairwise comparisons from ANCOVA with treatment and country as main effects and with baseline HbA1c as covariate.

Fasting Plasma Glucose (FPG)

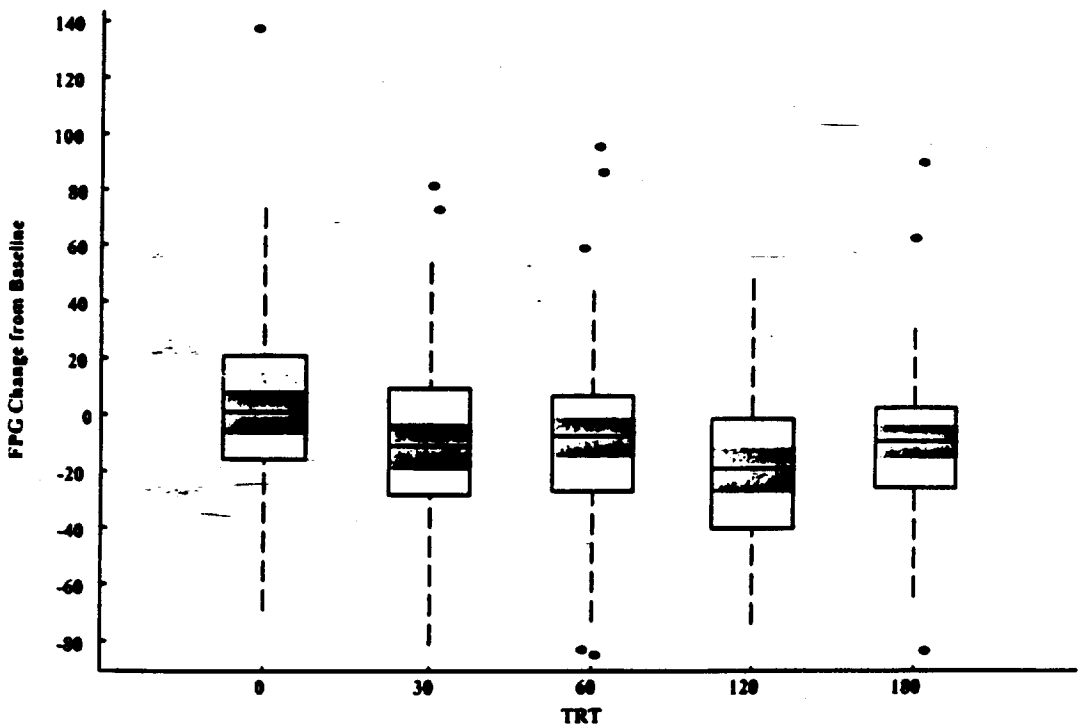
In this study, fasting plasma glucose was a primary efficacy variable measured at Weeks -4, -2, 0, 2, 4, 8 and 12. Week 12 was considered the primary endpoint. The FPG Week 12 results (Table 7) show only the 120 dose significantly different from placebo after adjustment for multiple comparisons (the results for 60 are borderline significant). The sizeable difference between the 180 mg dose means of -11.1 for completers and –8.0 for ITT is due to large FPG increases at early weeks for the early dropouts (the highest increase was +64).

Table 7. Study B202 FPG Results

	Placebo Mean (SD)	NAT 30 Mean (SD)	NAT 60 Mean (SD)	NAT 120 Mean (SD)	NAT 180 Mean (SD)
Completers	(n=52)	(n=46)	(n=51)	(n=60)	(n=53)
Baseline	185 (37)	191 (42)	184 (40)	190 (34)	187 (37)
Week 12	-0.02 (28)	-9.5 (35)	-9.9 (37)	-15.8 (28)	-11.1 (26)
ITT	(n=59)	(n=51)	(n=58)	(n=62)	(n=57)
Baseline	187 (38)	191 (41)	183 (39)	190 (34)	188 (1.1)
Week 12 LOCF	+3.8 (33)	-8.6 (34)	-9.0 (35)	-16.6 (28)	-8.6 (28)
Least Squares Mean	+3.5	-7.9	-9.6	-15.4	-8.0
Unadjusted p-value for comparison to placebo[1]		.06	.02	.001	.05

The distributions for the FPG endpoint results (Figure 3) further illustrate the significant effects for the 120 dose.

Figure 3. Study B202 Boxplots of FPG change from baseline at Week 12 LOCF by dose



1 P-values are results of pairwise comparisons from ANCOVA with treatment and country as main effects and with baseline FPG as covariate.

Study B302 (conducted 3/97 to 1/99)

Study B302 is a double-blind, multicenter, placebo controlled trial designed to assess the efficacy and safety of 3 doses of nateglinide compared to placebo. Following a single-blind placebo period of 4 weeks (Weeks –4 to 0 (baseline)), patients were randomized to nateglinide 60, 120 or 180 mg three times a day (10 minutes before each meal) or placebo and treated for 24 weeks.

The primary efficacy endpoint in this study is change from baseline of HbA1c at Week 24. HbA1c was measured at Weeks -4, -2, 0, 8, 12, 16 and 24. Baseline was computed as the average of Weeks -2 and 0.

Inclusion/Exclusion Criteria

Patients could enter the 4-week placebo run-in if they fulfilled the following criteria (this is a partial listing of all criteria):

1. Aged ≥30 years
2. Diagnosis of NIDDM
3. Diet therapy for at least one month prior to run-in
4. No history of chronic insulin therapy or therapy within 1 month with sulphonylureas, biguanides α-glucosidase inhibitors and thiazolidindiones.

Following the 4-week placebo run-in, patients were randomized to treatment if they fulfilled the following criteria (this is a partial listing of all criteria):

1. No FPG>15 mmol/l (>275 mg/dl) between Week -4 and Week -2
2. 6.8%≤HbA1c≤11% based on mean of Week -4 and -2

Patient Disposition

A total of 1,238 patients were screened at 64 centers in North America (37 centers) and Europe (24 centers); 697 patients were randomized to treatment (Table 8). About 80% of the patients completed the study; the largest dropout rate occurred in the placebo group (27%). Only one randomized patient was excluded from the ITT population due to a lack of post-baseline data.

Table 8. Study B302 Patient Disposition

	Placebo	NAT 60	NAT 120	NAT 180
Randomized	176 (100%)	174 (100%)	172 (100%)	175 (100%)
Week 8	148 (84%)	159 (91%)	158 (92%)	156 (89%)
Week 12	137 (78%)	152 (87%)	150 (87%)	149 (85%)
Week 16	132 (75%)	150 (86%)	146 (85%)	149 (85%)
Week 24	128 (73%)	147 (85%)	143 (83%)	145 (83%)
ITT	174 (99%)	171 (98%)	168 (98%)	172 (98%)

The reasons for dropout are shown in Table 9 below. The pattern of dropouts due to treatment failure suggest a dose response relationship; dropouts for other reasons appear to be independent of treatment group with similar patterns seen for all groups.

Table 9. Study B302 Reasons for discontinuation

	Placebo (n=176)	NAT 60 (n=174)	NAT 120 (n=172)	NAT 180 (n=175)
ADE	13 (7%)	6 (3%)	7 (4%)	8 (5%)
Protocol violation	2 (1%)	1 (1%)	0	4 (2%)
Consent withdrawn	12 (7%)	6 (3%)	7 (4%)	10 (6%)
Death	0	0	1 (1%)	0
Treatment Failure	18 (10%)	12 (7%)	7 (4%)	3 (2%)
Lost-to-follow-up	3 (2%)	2 (1%)	7 (4%)	5 (3%)

Reviewer's Comments: *A dropout rate of about 20% suggests that the efficacy results should be examined for the effects of dropouts on the analyses. A comparison of results of Completers to LOCF results should suffice.*

Patient Demographics

The treatment groups were comparable at baseline regarding baseline demographics (Table 10). The majority of the patients were male and Caucasian. Patients ranged in age from 31 to 82 years with a mean of about 58; about 30% of the patients were 65 years or older. The majority of the patients were naive to diabetic treatment.

Table 10. Study B302 Baseline demographics

	Placebo (n=176)	NAT 60 (n=174)	NAT 120 (n=172)	NAT 180 (n=175)
Age (years)				
Mean (SD)	58 (11)	58 (11)	57 (11)	59 (10)
Range	31-79	34-83	31-82	31-79
Race: Caucasian	88%	88%	86%	89%
Gender: M/F	58%/42%	61%/39%	59%/41%	57%/43%
BMI				
Mean (SD)	30 (4)	29 (4)	30 (4)	29 (4)
Years of Diabetes				
Mean (SD)	4 (4)	5 (6)	5 (6)	5 (6)
Median	2.5	2.9	3.0	3.0
Range				
% Naive	79%	75%	78%	79%
% Previously treated	21%	25%	22%	21%

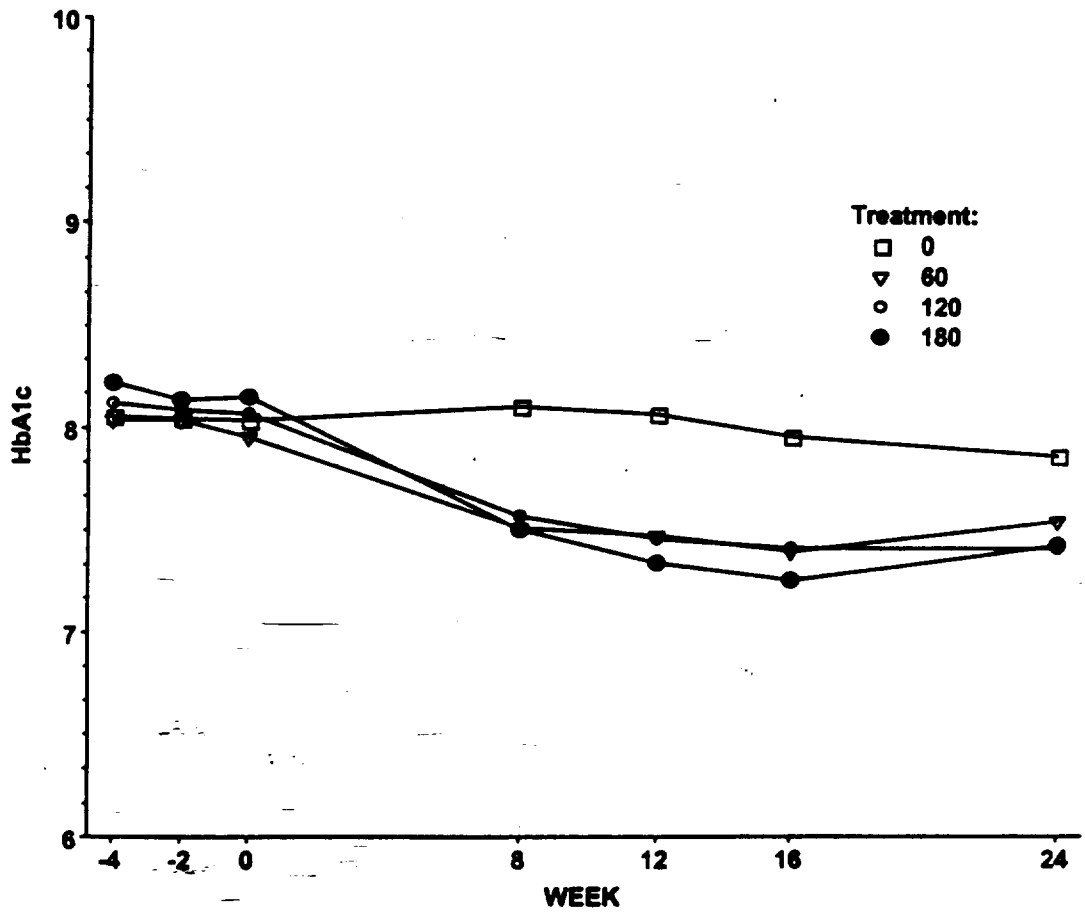
The most common medical conditions at baseline were hypertension (40%), neuropathy (16%) and hyperlipaemia (14%).

Efficacy Results

HbA1c

HbA1c, the primary efficacy variable, was measured at Weeks -4, -2, 0, 8, 12 and 24. The mean results at each timepoint are depicted in Figure 4 below. Essentially no change in HbA1c is seen for the placebo group while all doses of nateglinide showed a decrease by Week 8 that appears to be sustained for the 16 weeks of therapy. By Week 24 the mean HbA1c is higher than at Week 16 for all nateglinide groups with a median increase of 0.1 in all groups. So more than 50% of the patients in all groups had an increase in HbA1c from Week 16 to Week 24.

Figure 4. Study B302 Mean HbA1c by week on study and by treatment group for observed cases.



The primary endpoint in this study is Week 24 LOCF. Both the ITT and completer results for Week 24 are presented in Table 11 on the following page. The change from baseline of HbA1c for each dose of nateglinide was significantly different from the results for placebo. The means suggest a dose response relationship exists (for further discussion of dose response, see page 24).

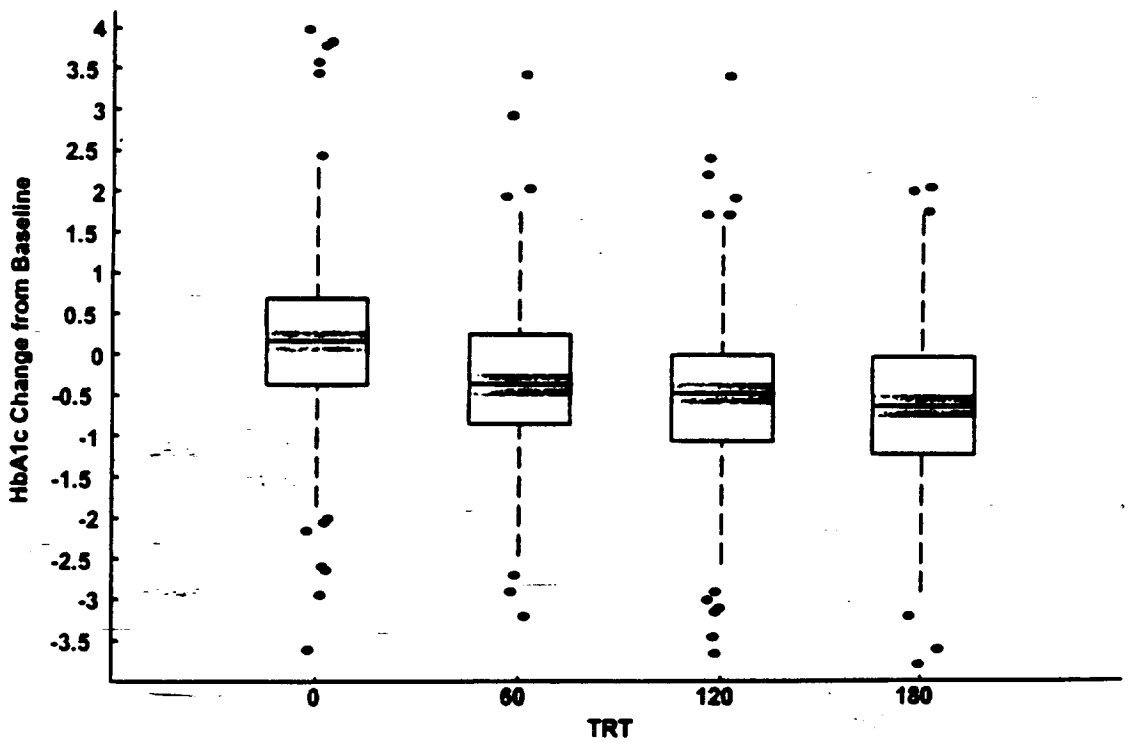
The results at Week 12 are similar to the results observed at Week 12 in Study B202 (see Table 6 and Table 11 below). A comparison of the completer results at Week 12 and Week 24 show a decline in effect as was illustrated in Figure 4.

Table 11. Study B302 HbA1c Results

	Placebo Mean (SD)	NAT 60 Mean (SD)	NAT 120 Mean (SD)	NAT 180 Mean (SD)
Completers				
Baseline	7.9 (1.0)	7.9 (1.0)	8.1 (1.0)	8.1 (1.0)
Week 12	+0.10 (0.85)	-0.45 (0.83)	-0.60 (0.97)	-0.82 (0.85)
	(n=145)	(n=158)	(n=155)	(n=156)
Week 24	+0.02 (1.1)	-0.33 (1.1)	-0.62 (1.0)	-0.69 (1.1)
	(n=128)	(n=149)	(n=144)	(n=146)
ITT	(n=168)	(n=167)	(n=168)	(n=167)
Baseline	8.0 (1.0)	7.9 (1.0)	8.1 (1.1)	8.1 (1.1)
Week 24 LOCF	+0.18 (1.1)	-0.32 (1.1)	-0.49 (1.1)	-0.64 (1.1)
Least Squares Mean	+0.13	-0.37	-0.52	-0.67
Unadjusted p-value for comparison to placebo[1]		.0001	.0001	.0001

The boxplot distributions (Figure 5) for change from baseline for HbA1c at Week 24 LOCF further illustrate the shift in response as dose increases particularly from 60 to 120.

Figure 5. Study B302 Boxplots of HbA1c change from baseline at Week 24 LOCF by dose



1 P-values are from pairwise comparisons from ANCOVA with treatment and country as main effects and with baseline HbA1c as covariate.

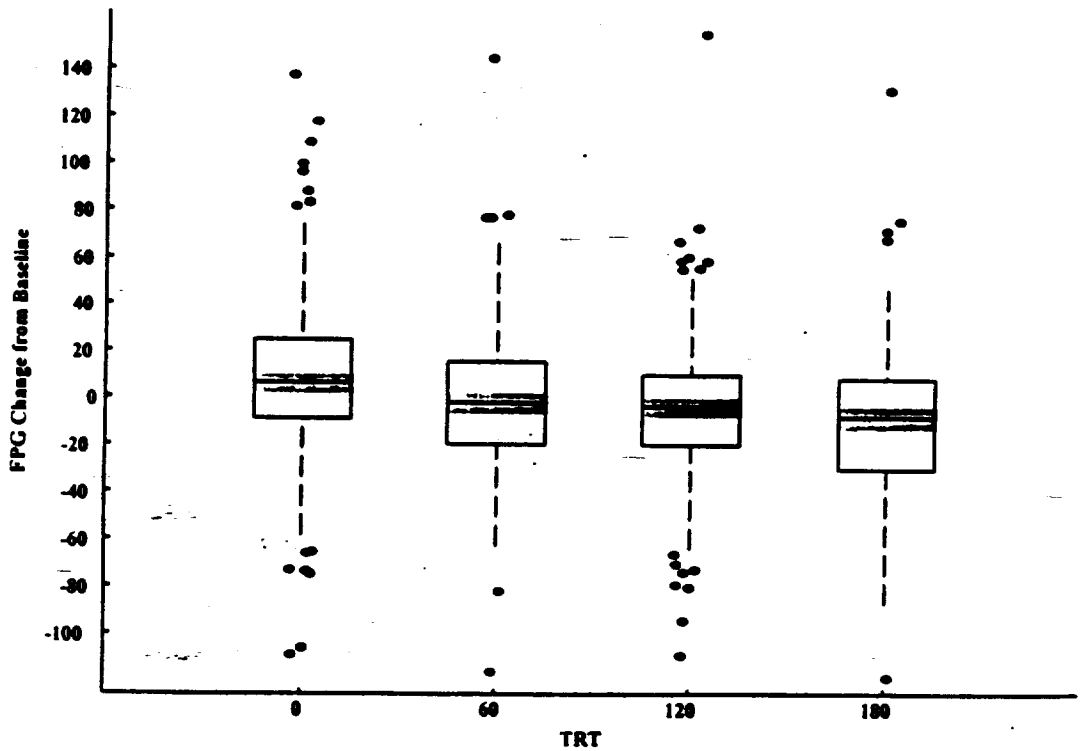
FPG

In this study, FPG was named as a secondary endpoint. The results for completers and the ITT population (Table 12) showed statistically significant changes from baseline compared to placebo for each dose of nateglinide. Both the means and the distributions in Figure 6 indicate the presence of a dose response relationship.

Table 12. Study B302 FPG Results

	Placebo Mean (SD)	NAT 60 Mean (SD)	NAT 120 Mean (SD)	NAT 180 Mean (SD)
Completers				
Baseline	164 (36)	158 (34)	165 (39)	166 (38)
Week 12	+5.0 (34)	+1.1 (33)	-5.2 (31)	-8.4 (31)
	(n=128)	(n=143)	(n=143)	(n=146)
Week 24	+4.0 (30)	-7.1 (27)	-9.6 (34)	-17.7 (27)
	(n=143)	(n=158)	(n=154)	(n=153)
ITT	(n=172)	(n=171)	(n=169)	(n=170)
Baseline	168 (39)	161 (36)	167 (40)	167 (38)
Week 24 LOCF	+9.1 (37)	+0.4 (33)	-4.5 (33)	-8.9 (32)
Least Squares Mean	+13.6	+3.5	-0.003	-4.2
Unadjusted p-value for comparison to placebo[1]		.004	.0001	.0001

Figure 6. Study B202 Boxplots of FPG change from baseline at Week 24 LOCF by dose

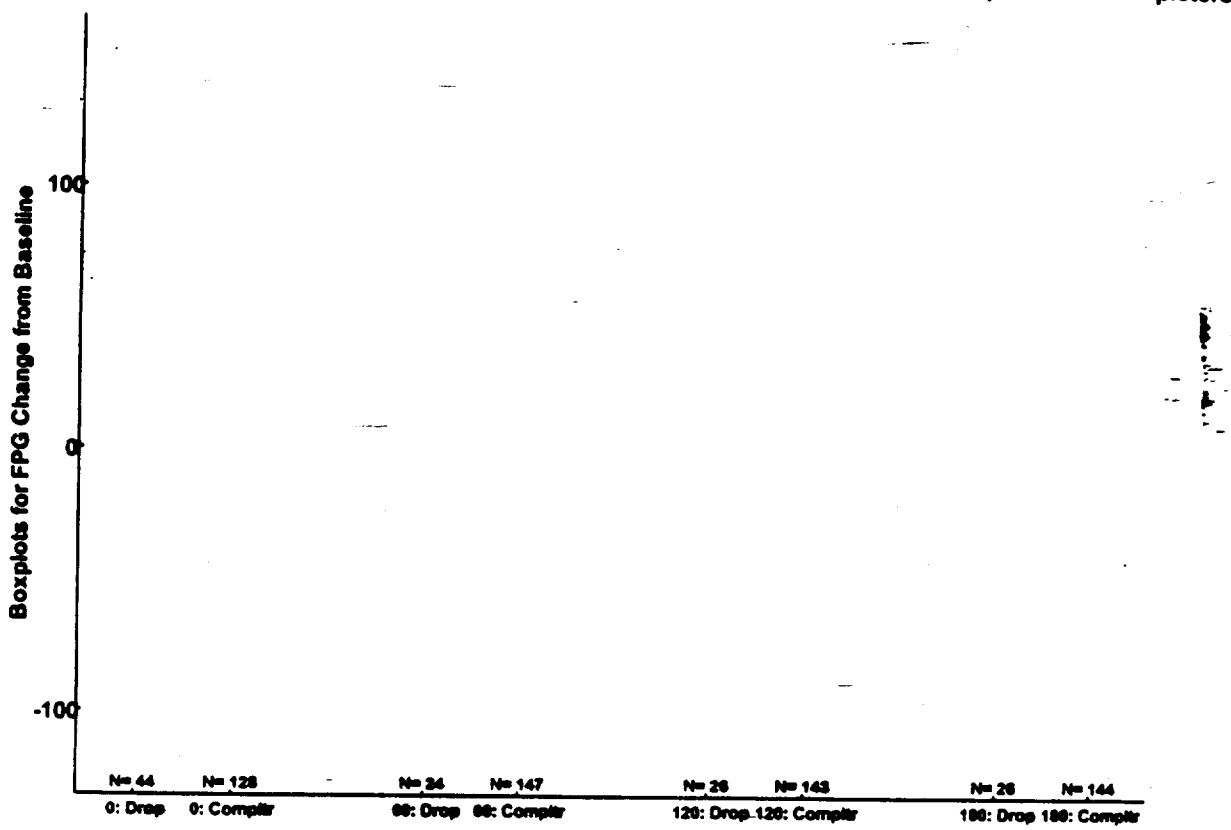


The difference between the estimates for the completers and the ITT population is striking

1 P-values are from pairwise comparisons from ANCOVA with treatment and country as main effects and with baseline FPG as covariate. The test for homogeneity of slopes was significant indicating nonparallel lines; the results are nevertheless robust with significant treatment effects seen when including the interaction term. In addition the lines were seen to cross at very low values of FPG (about 100) where there is very little data.

and warrants further examination. Figure 7 shows the change from baseline FPG for the last observation on study for dropouts and completers. The impact of carrying forward the dropout data is evident particularly for placebo; LOCF estimates for the ITT population will be smaller than completer estimates by the inclusion of the dropout data as we saw in Table 12. These results are consistent with the discontinuation data which showed that for placebo and the 60 mg dose the major reason for dropout was treatment failure. So the LOCF results best represent the data in this study.

Figure 7. Study B302 Boxplots of FPG change from baseline at last observation for dropouts and completers



Study B304 (conducted 2/98 to 6/99)

Study B304 is a double-blind, multicenter, glyburide-controlled trial designed to assess the efficacy and safety of nateglinide to glibenclamide. Following a single-blind 4-week period (Weeks –4 to 0) of glibenclamide 10 mg/day, patients were randomized to nateglinide 60 or 120 mg three times a day (10 minutes before each meal) or glibenclamide 10 mg/day and treated for 24 weeks. Matching placebos were used to maintain the blind.

The primary efficacy endpoint in this study is change from baseline of HbA1c at Week 24. HbA1c was measured at Weeks –4, -2, 0, 8, 12, 16 and 24. Baseline was computed as the average of Weeks –2 and 0.

The trial was powered with 170 patients in each group to find a 0.5% difference in HbA1c between glibenclamide and each nateglinide dose.

Inclusion/Exclusion Criteria

Patients could enter the 4-week glibenclamide run-in if they fulfilled the following criteria (this is a partial listing of all criteria):

1. Aged ≥30 years
2. History of NIDDM
3. **Sulfonylurea therapy for at least 12 weeks prior to run-in**
4. No history of chronic insulin therapy or therapy within 3 months with biguanides (metformin), α-glucosidase inhibitors and thiazolidindiones.

Following the 4-week glibenclamide run-in, patients were randomized to treatment if they fulfilled the following criteria (this is a partial listing of all criteria):

1. No FPG>15 mmol/l (>275 mg/dl) between Week –4 and Week -2
2. 6.5%≤HbA1c≤10% based on mean of Week –4 and -2

Patient Disposition

A total of 841 patients were screened at 70 centers in North America (20 centers), Australia (8 centers), South Africa (5 centers) and Europe (37 centers); 563 patients were randomized to treatment (Table 13) following the run-in treatment with glibenclamide. Only about half of the nateglinide-treated patients completed 24 weeks of treatment compared to 82% in the glibenclamide group.

Table 13. Study B304 Patient Disposition

	Glibenclamide	NAT 60	NAT 120
Randomized	185 (100%)	191 (100%)	187 (100%)
Week 8	171 (92%)	134 (70%)	142 (76%)
Week 12	163 (88%)	103 (54%)	120 (64%)
Week 16	158 (85%)	93 (49%)	108 (58%)
Week 24	152 (82%)	84 (44%)	101 (54%)
ITT	185 (100%)	184 (96%)	183 (98%)

The primary reason for discontinuation (Table 14) in all groups was treatment failure, the failure rates (about 30%) in the nateglinide groups was about 4 times the rate in the glibenclamide group (7%). Treatment failure was defined as an FPG>270 mg/dl. Dropouts due to treatment failure were seen throughout the trial with most observed during the first 12 weeks. The majority of dropouts due to ADE or consent withdrawn occurred during the first 8 weeks of therapy.

Table 14. Study B304 Reasons for discontinuation

	Glibenclamide (n=185)	NAT 60 (n=191)	NAT 120 (n=187)
ADE	6 (3%)	22 (12%)	15 (8%)
Protocol violation	4 (2%)	3 (2%)	1 (1%)
Consent withdrawn	5 (3%)	15 (8%)	15 (8%)
Death	3 (2%)	0	1 (1%)
Treatment Failure	13 (7%)	62 (33%)	48 (26%)
Other	2 (1%)	5 (3%)	6 (3%)

Patient Demographics

The treatment groups were comparable at baseline regarding baseline demographics (Table 15). The majority of the patients were male and Caucasian. Patients ranged in age from 29 to 85 years with a mean of about 61; about 37% of the patients were 65 years or older. All patients had been previously treated with sulfonylureas as dictated by the protocol.

Table 15. Study B304 Baseline demographics

	Glibenclamide (n=185)	NAT 60 (n=191)	NAT 120 (n=187)
Age (years)			
Mean (SD)	62 (11)	61 (10)	61 (10)
Range	37-83	33-85	29-84
Race: Caucasian	89%	92%	86%
Gender: M/F	62%/38%	63%/37%	64%/36%
BMI			
Mean (SD)	28 (4)	29 (4)	28 (4)
Years of Diabetes			
Mean (SD)	7 (6)	8 (7)	8 (7)
Median	5.3	6.3	6.3
Range			

The treatment groups were also comparable with regard to medication compliance; more than 80% of the patients in each group took 80% or more of their prescribed medication.

Efficacy Results

HbA1c

There were **statistically significant increases** from baseline in HbA1c for both nateglinide doses compared to glibenclamide ($p<.001$, sponsor's analyses). Increases were seen in both the ITT population and the completer populations (Table 16).

Table 16. Study B304 HbA1c Results

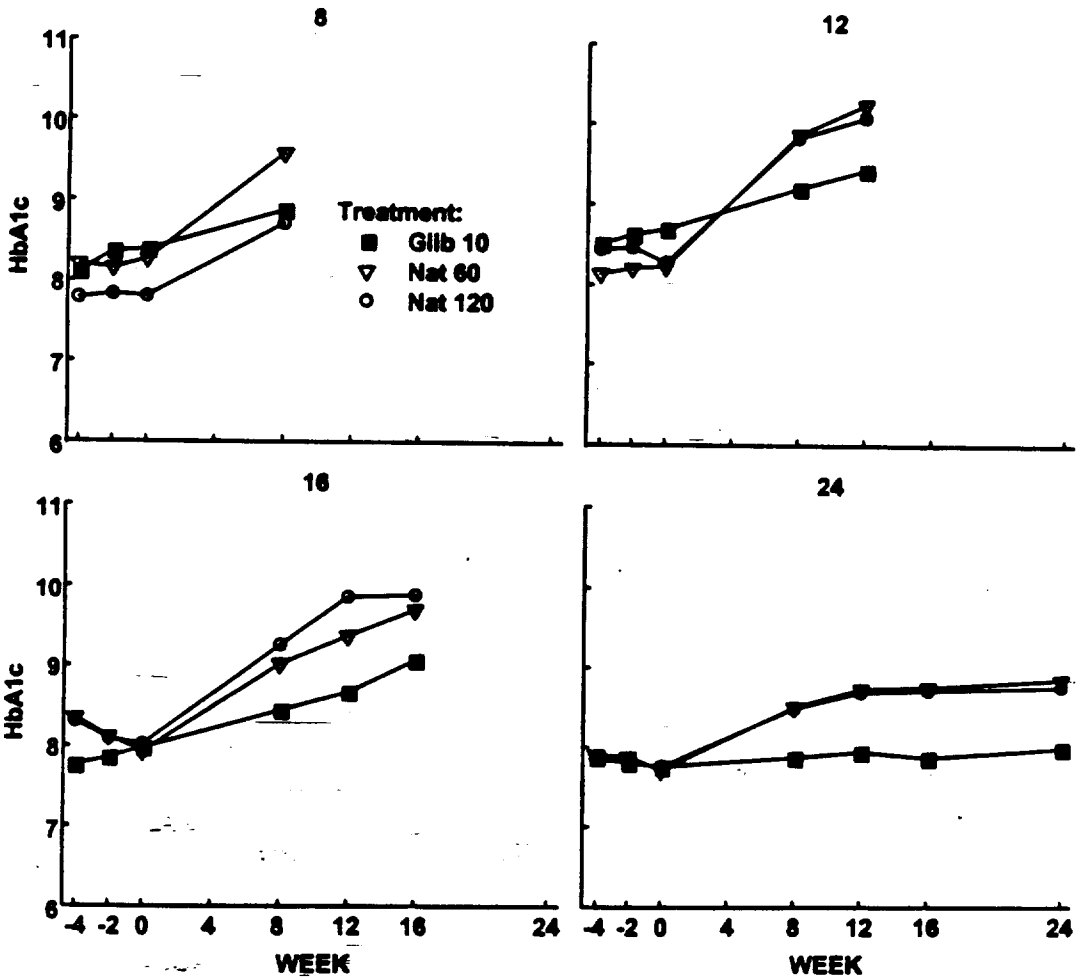
	Glibenclamide Mean (SD)	NAT 60 Mean (SD)	NAT 120 Mean (SD)
Completers			
Baseline	7.8 (0.9)	7.9 (1.0)	7.9 (0.9)
Week 12	+0.21 (0.81) (n=168)	+1.2 (1.1) (n=131)	+1.1 (1.0) (n=140)
Week 24	+0.21 (0.89) (n=155)	+1.1 (1.2) (n=89)	+1.1 (1.1) (n=106)
ITT	(n=183)	(n=178)	(n=179)
Baseline	7.8 (0.9)	8.0 (1.0)	7.9 (0.9)
Week 24 LOCF	+0.28 (0.92)	+1.3 (1.2)	+1.1 (1.1)

The majority of patients in all three treatment groups showed an increase in HbA1c at endpoint (63% for glibenclamide, 88% for 60 mg and 86% for 120 mg).

Analyses of subgroups revealed responses consistent with these overall results, there were no subgroups (based on age, weight, bmi, baseline HbA1c, baseline FPG, gender, race or duration of diabetes) which showed a decrease in HbA1c.

To examine the dropout data and the completer data, this reviewer plotted data for four cohorts; patients who completed only 8 weeks of therapy, only 12 weeks, only 16 weeks and patients who completed the full 24 weeks (Figure 8). The patients who dropout in all treatment groups show an increase in HbA1c at 8 weeks and continue to deteriorate if they remain on study (this is not surprising considering that the major reason for dropout was treatment failure). For patients who are able to complete the study, essentially no change is seen in the glibenclamide group while nateglinide patients show an increase at 8 weeks and sustain the increase for the duration of the trial (generally do not worsen).

Figure 8. Mean HbA1c by last week completed on study



The data from this study clearly shows that patients who are poor responders[1] to sulfonylurea treatment lose additional glycemic control when switched to nateglinide.

1 The definition of "poor responders" here includes some patients who could be characterized as partial responders in that their HbA1c levels at baseline were between 6.5% and 7%.

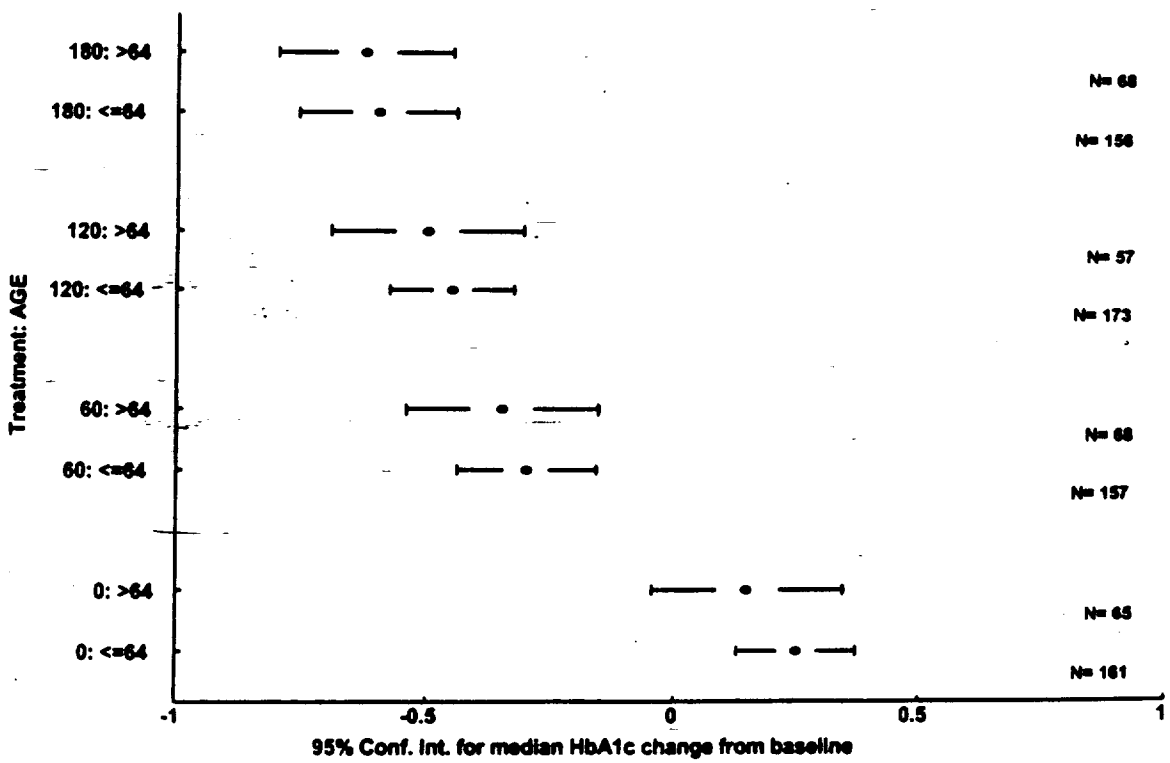
Subgroup Results for Fixed Doses of Nateglinide

To assess the consistency of the treatment effect across subgroups, this reviewer tested the interaction of the subgroup factor with treatment in an ANOVA model and examined the descriptive results for HbA1c change from baseline at endpoint (medians and 95% confidence intervals in Figures 9-15) by treatment group and subgroup. For these analyses, the data from Studies B202 and B302 were combined. Even though the endpoint data was taken from different timepoints (Week 12 in Study B202 and Week 24 in Study B302), the data from Study B302 suggests no improvement in response from Week 12 to Week 24(see Figure 4 and Table 11.). So Week 12 LOCF data is very similar to Week 24 LOCF data. Nevertheless, this reviewer did check the homogeneity of the subgroup results depicted here by looking at all results by study and saw no notable differences between the studies. The 30 mg dose was not included in this assessment since it was found to be non-efficacious.

Subgroups were defined by age, sex, duration of disease, baseline HbA1c, baseline FPG, previous treatment for diabetes and baseline BMI. The only statistically significant (i.e. p<.15) test for interaction was BMI (≤30, >30) with p=.11. The interaction for duration of diabetes was close to statistical significance with a p-value of .17.

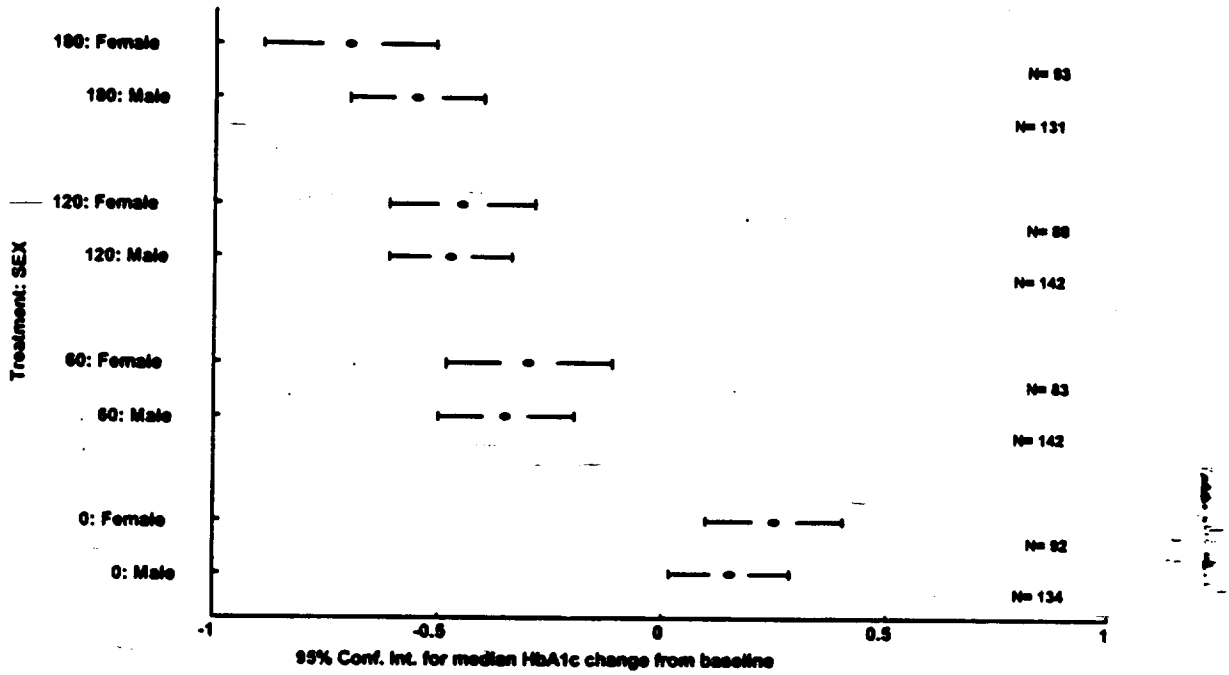
Patients in Studies B202 and B302 ranged in age from 31 to 83 years (median of 58). About 30% of the patients were 65 or older. The results for the elderly population (65 or older) were consistent with the results seen for patients under 65 (Figure 9). Further examination using different age cutpoints revealed a more pronounced dose response for older patients (see following section in this review on dose-response).

Figure 9. Median HbA1c change from baseline and 95% confidence intervals (CI) by treatment and age (<65 years, ≥65 years)



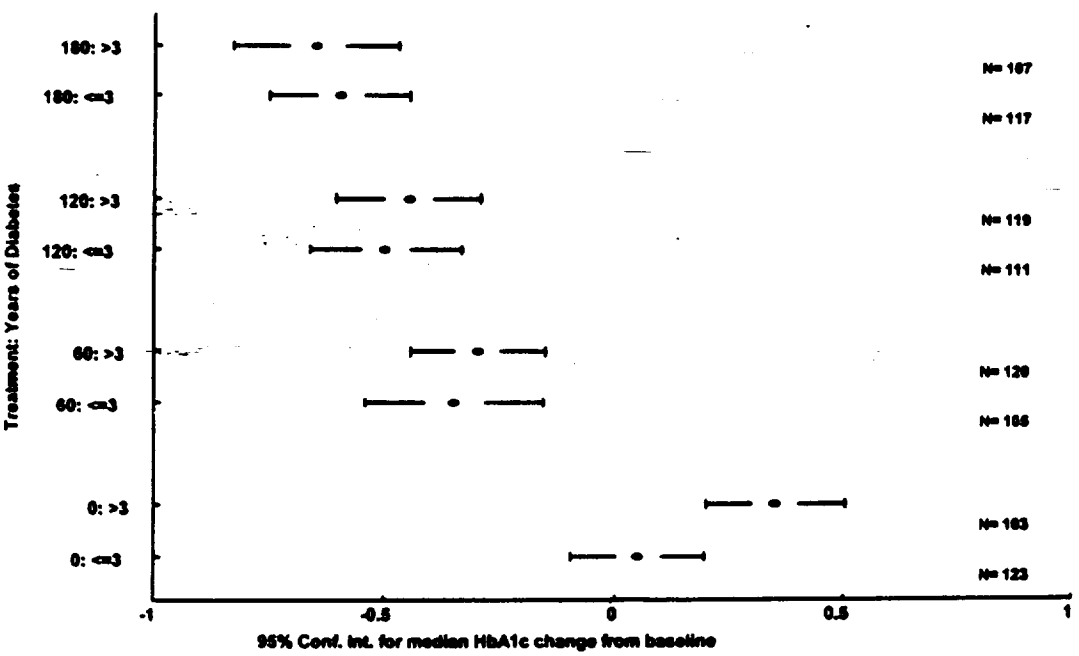
There were more males (61%) than females (39%) in Studies B202 and B302. The baseline demographics for the two groups were similar as were the HbA1c results (Figure 10).

Figure 10. Median HbA1c change from baseline and 95% CI by treatment and sex.



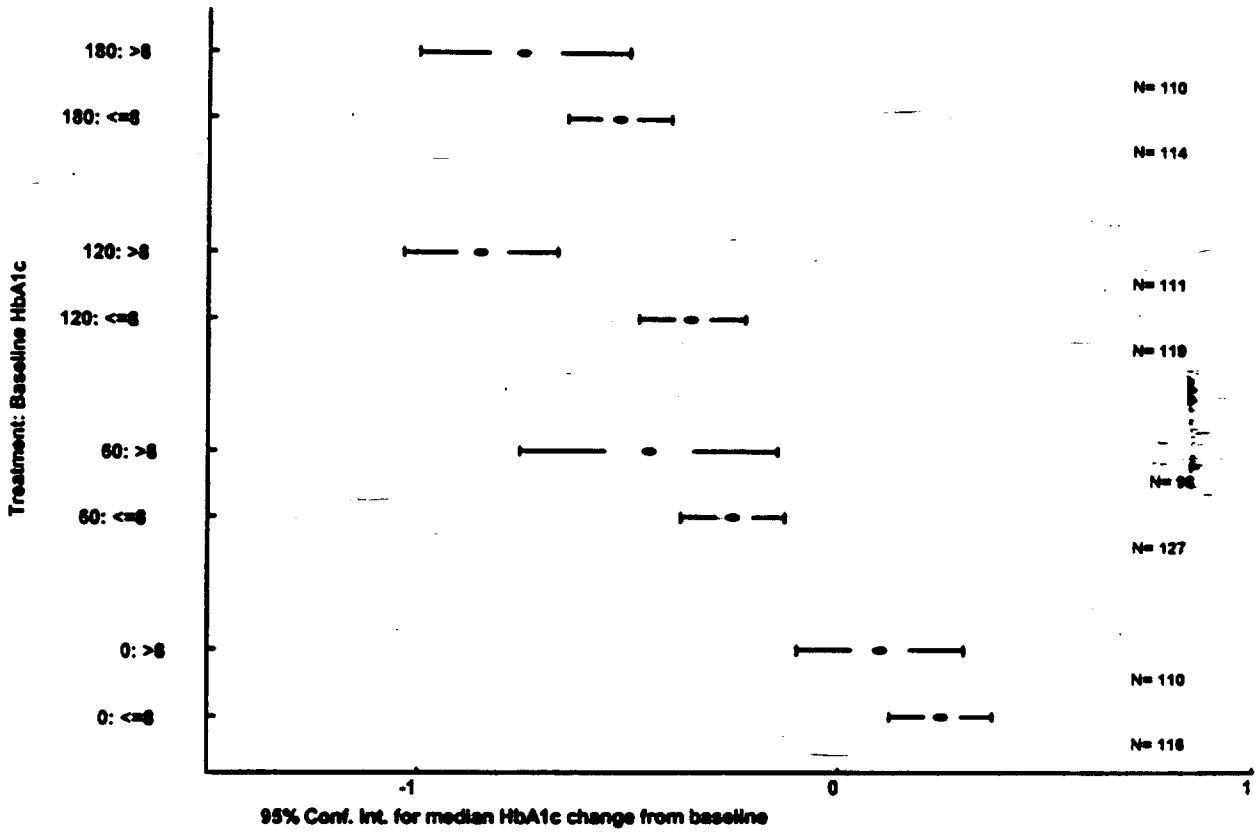
The median length of time since diagnosis of diabetes was about 3 years (range from .2 to 52). A significant worsening is seen in the placebo patients with diabetes>3 years and the treatment effect is larger in this subgroup (Figure 11).

Figure 11. Median HbA1c change from baseline + 95% CI by treatment and duration of diabetes



To assess the relationship between baseline HbA1c and change from baseline HbA1c at endpoint, this reviewer examined the results using baseline HbA1c of 8 as a cutpoint (Figure 12).. In the 120 mg group, a larger effect is seen for patients with baseline HbA1c greater than the median of 8; using a cutpoint of 8.5 also revealed the same results. Overall though no strong relationship between baseline and response was seen.

Figure 12. Median HbA1c change from baseline + 95% CI by treatment and by baseline HbA1c median



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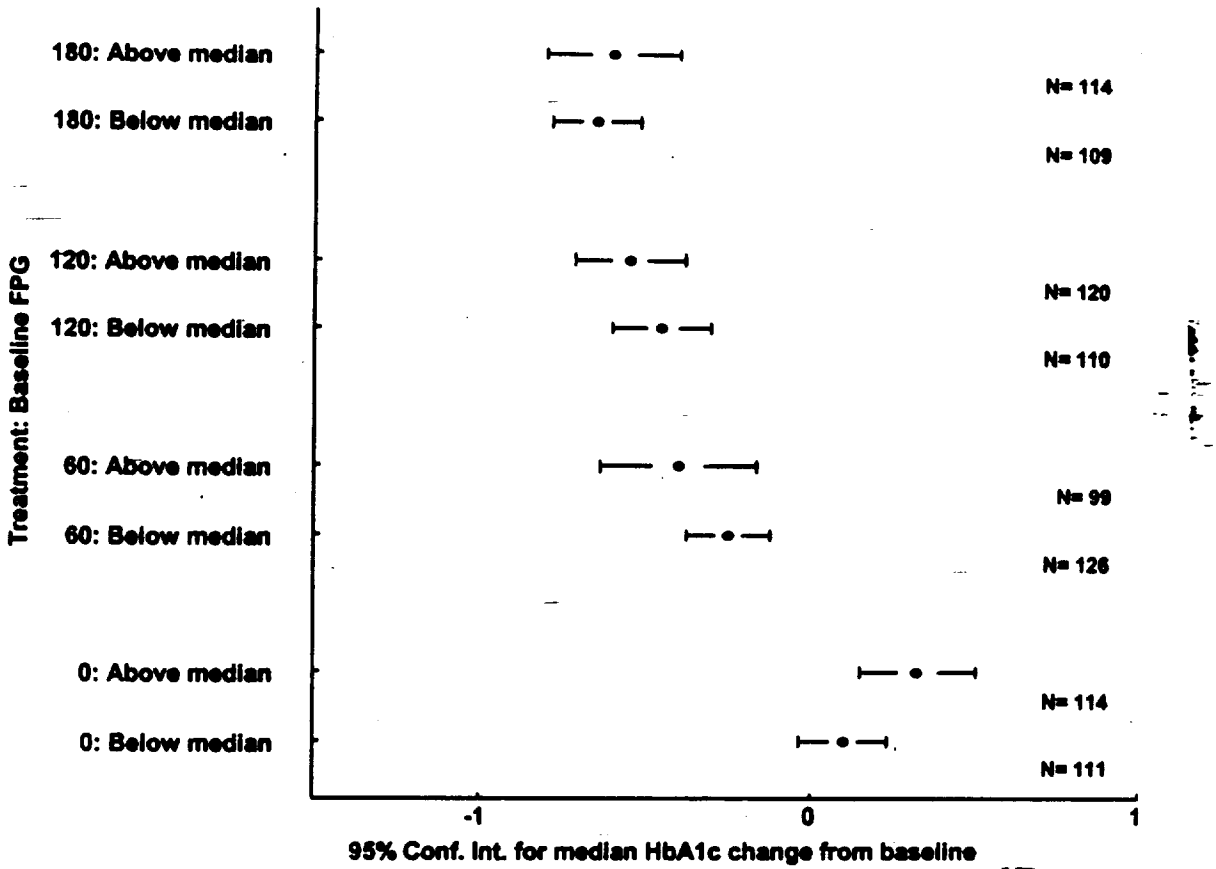
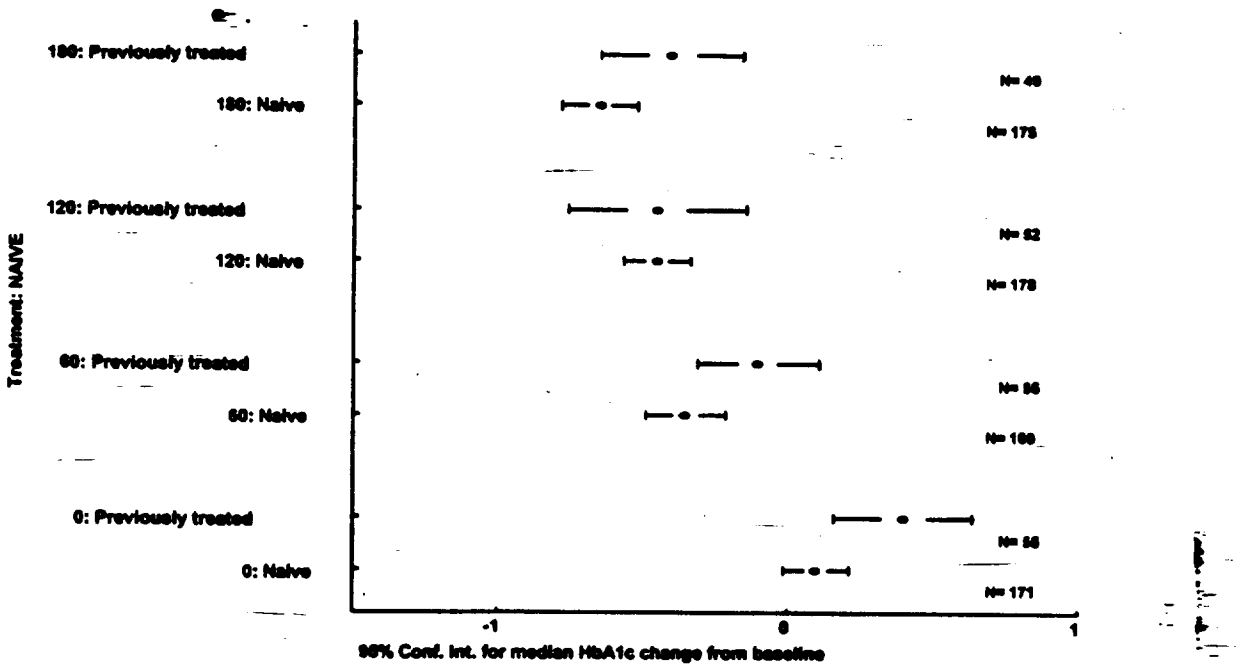
The medical reviewer suggested looking at subgroups based on FPG<126, 126-139 and >139. Most patients (>80%) are in the >139 group leaving too few patients in the lower groups for assessment. A slightly larger treatment effect is seen for patients with baseline FPG greater than 166 (the median); this difference, however, is not significant and does not indicate any subgroup differences due to differences in baseline FPG.

Figure 13. Median HbA1c change from baseline + 95% CI by treatment and by baseline FPG median of 166



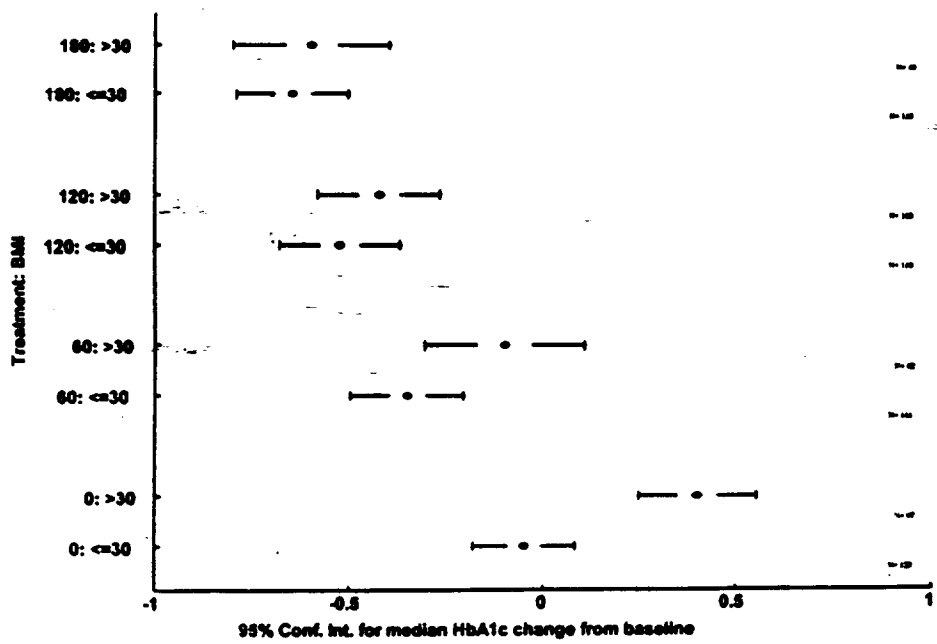
The majority of the patients in Studies B202 and B302 were patients (76%) naive to treatment for diabetes so the results on previously treated patients is limited. As expected, the placebo controls show an increase in HbA1c with a greater shift seen for previously treated patients compared to naive patients (Figure 14 on following page). A comparison of each dose to placebo by subgroup indicate consistent treatment effects for the 60 and 180 doses while for the 120 dose a slightly larger effect is seen for previously treated than naive patients.

Figure 14. Median HbA1c change from baseline + 95% CI by treatment and prior diabetes treatment (naive versus previously treated)



The significant treatment by BMI (≤30 versus >30) interaction is illustrated in Figure 15. The effects for the 120 and 180 doses in heavier patients is clearer larger than for patients with BMI<30; the subgroup difference for the 60 mg dose is not notable.

Figure 15. Median HbA1c change from baseline + 95% CI by treatment and BMI (≤30 versus >30)



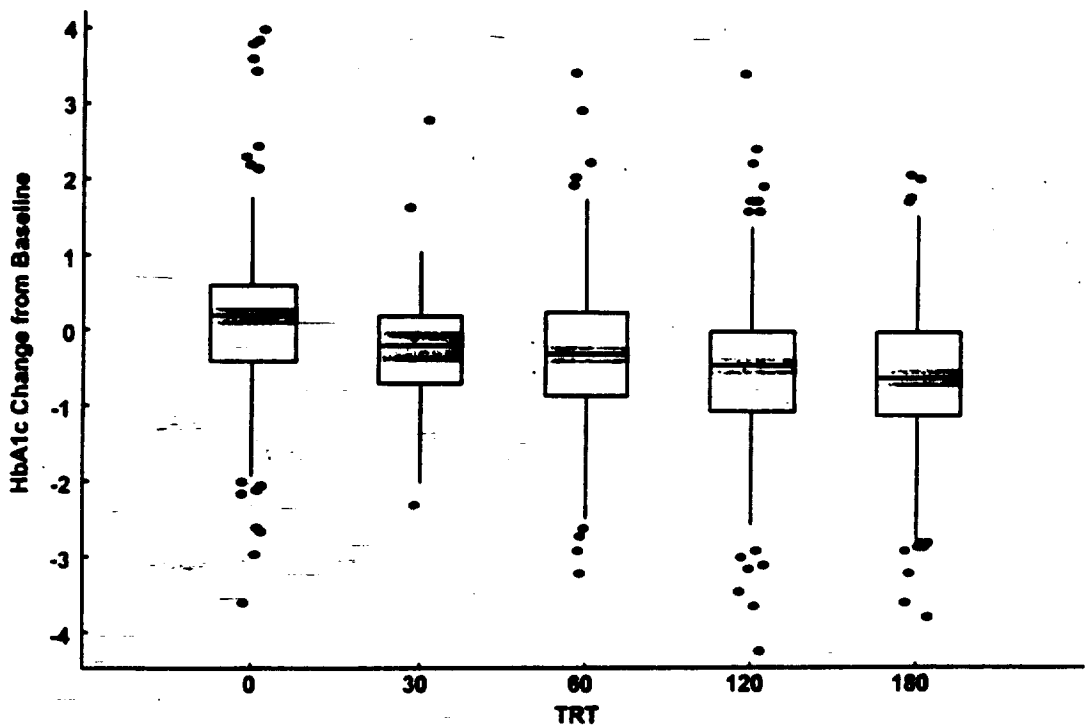
In summary, both results for tests of interaction and examination of descriptive statistics for subgroups show that nateglinide is consistently effective across a number of subgroups. There is a suggestion that there is benefit to using higher doses (120-180mg) in patients with duration of disease greater than 3 years and for patients with BMI greater than 30[1]. (See the following section of this review regarding dose response.)

Dose Response Assessment

To characterize the dose response relationship of nateglinide, this reviewer created graphs and performed statistical analyses to test for linear and quadratic effects. For these analyses the HbA1c change from baseline LOCF data of Studies B202 and B302 were combined as for the subgroup analyses.

Figure 16 shows the distribution of HbA1c change from baseline for placebo and for each dose of nateglinide; the lowest dose of 30 mg was not significantly different from placebo while each of the three higher doses (60, 120 and 180) were at p<.0001.

Figure 16. Boxplots of HbA1c change from baseline by treatment group for Studies B202 and B302 combined.

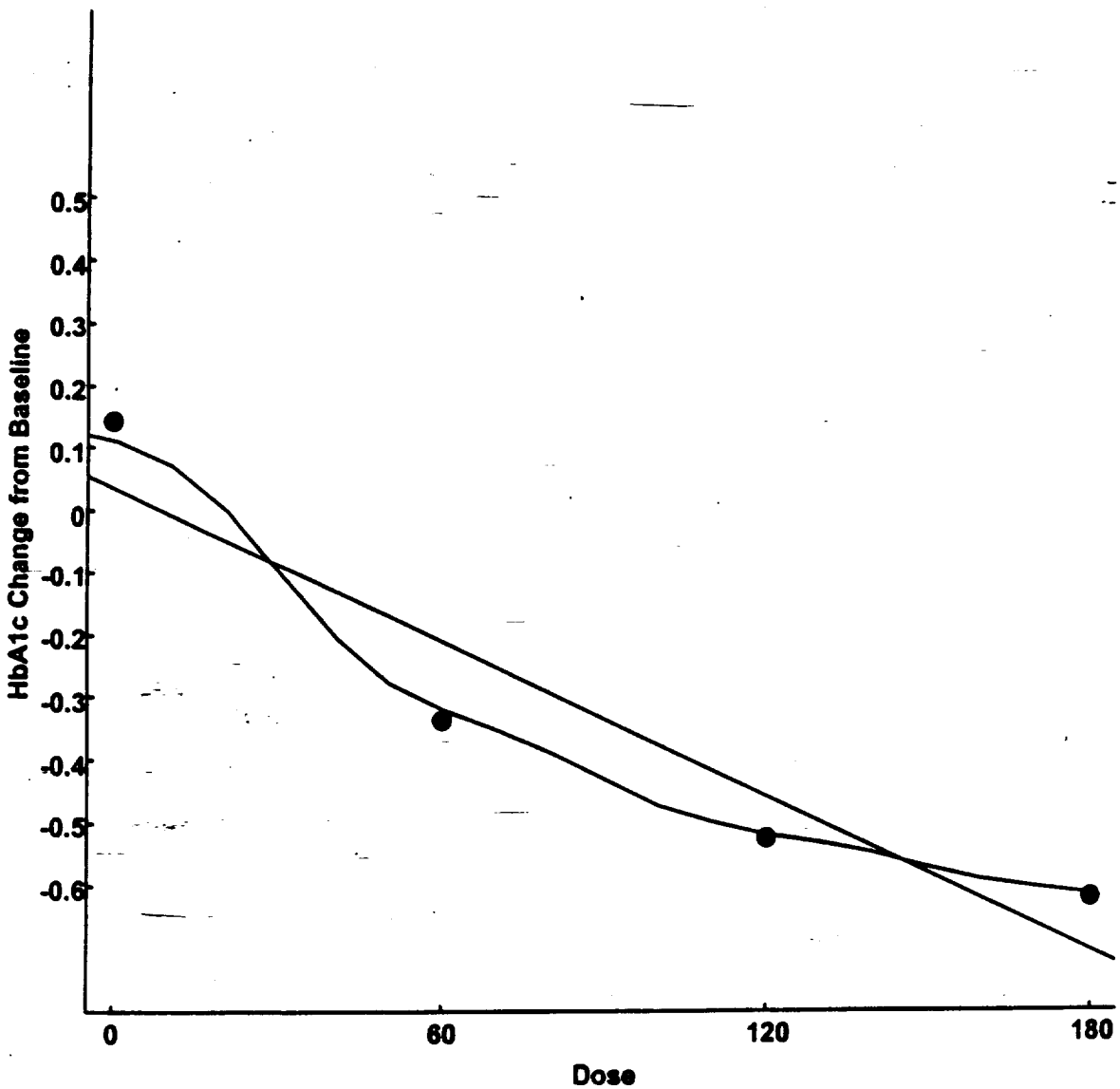


1 The cutpoints of 3 for duration of disease and 30 for BMI are both close to the medians for those measures and were chosen primarily for that reason. Additional analyses were performed to check the robustness of the results for various cutpoints and those results were consistent with the results shown here.

To examine the relationship among the three higher doses (60, 120, and 180), this reviewer tested for linear and quadratic effects in an ANOVA model and found the addition of a quadratic term improved the model minimally though the effect was highly significant. Tests for linearity were statistically significant indicating improved response with increasing dose.

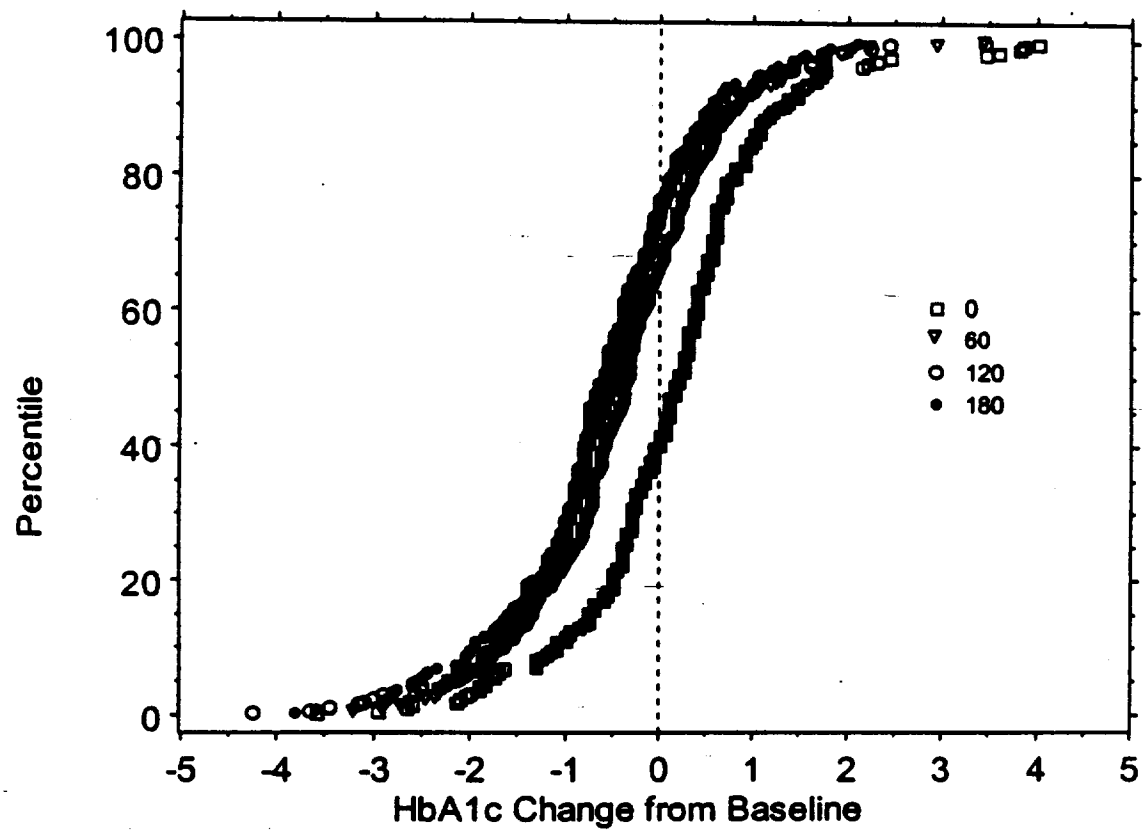
A plot of the mean responses by dose (Figure 17) with two fitted lines (smoothed and linear) illustrates that the dose response appears to be quadratic. A plateauing of effect at the two higher doses is observed.

Figure 17. Plot of mean HbA1c change from baseline by dose with linear and smoothed fit lines



To further explore the relationship among the doses, this reviewer created a cumulative distribution plot. This plot (Figure 18) shows a clear demarcation between placebo and the three doses (60, 120 and 180). Also the 60 mg dose is easily distinguishable from the two higher doses while the patient responses for the 120 and 180 doses overlap. The latter is consistent with the plateauing of the effect we saw in Figure 17.

Figure 18. Cumulative distribution plot of HbA1c change from baseline at endpoint



From Figure 18 and Table 17 below, we see that about half the patients in the higher dose groups (120 and 180) had a decrease in HbA1c of 0.5% or greater; about 10% less had such a decrease in the 60 mg dose group.

Table 17. Percentage of patients for each dose by HbA1c change from baseline categories

HbA1c Change from baseline	Placebo	NAT 60	NAT 120	NAT 180
≥0	60%	36%	26%	28%
<0 to -0.5%	21%	24%	26%	18%
-0.5% to -1.0%	7%	20%	22%	27%
< -1.0%	12%	21%	26%	27%

Examination of the dose data suggests to this reviewer that the 120 and 180 dose are comparable and that both these doses offer some benefit over the 60 dose; however, there may be some groups of patients who show a benefit taking the 180 dose compared to the 120 dose. Looking at all the same subgroups described earlier, this reviewer found that older patients (Figure 19), patients with diabetes for more than 3 years (Figure 20) and patients with BMI>30 (not illustrated here but similar to figures below) appear to benefit from the higher dose of 180. The latter illustrates that groups of patients may benefit from doses that do not necessarily show an appreciable benefit over a lower dose and forms a basis for approving these doses (assuming the highest dose is found to be safe).

Figure 19. Plot of mean HbA1c change from baseline by dose and median age (<58 and >58) with linear and smoothed fit lines.

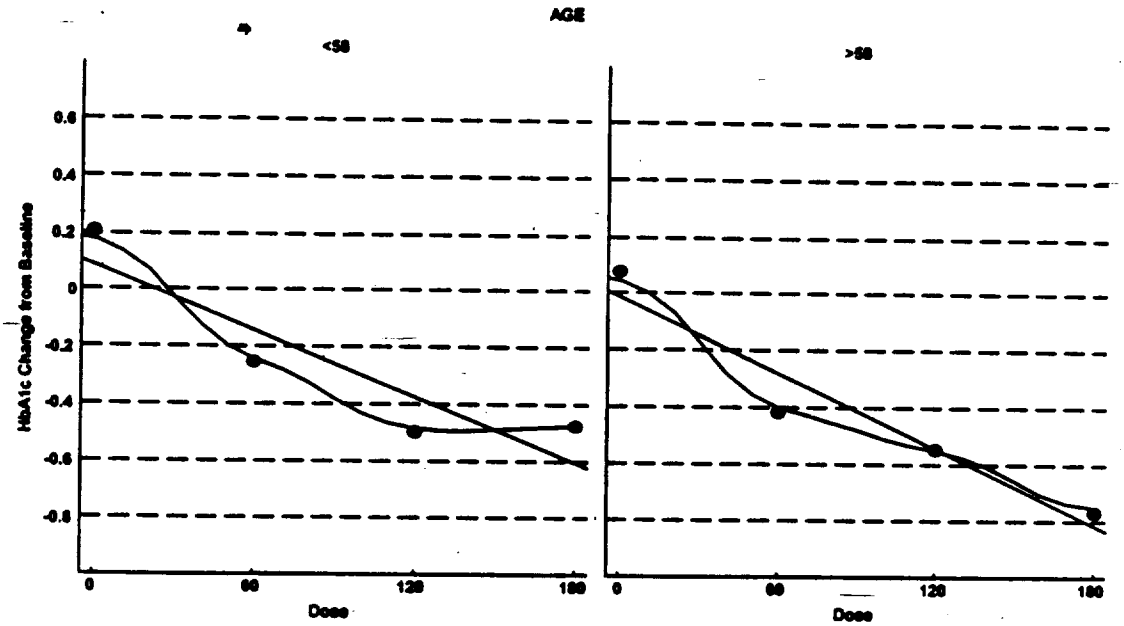
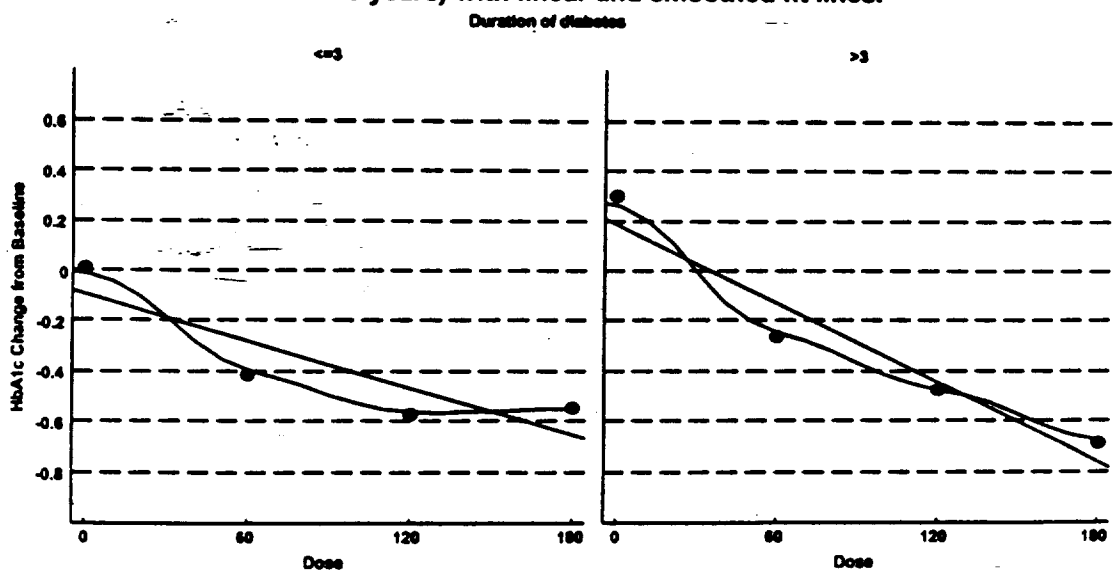


Figure 20. Plot of mean HbA1c change from baseline by dose and duration of diabetes (<=3 and >3 years) with linear and smoothed fit lines.



Lipids

The results for the lipid parameters are shown for each study rather than combined due to the differences in baselines (Table 18). No dose response relationships are seen and the changes are small and inconsistent. The only notable changes are seen for triglycerides at the 180 dose (a median decrease of about 9%).

Table 18. Mean (SD) lipid baseline (mg/dL) and percent change from baseline at endpoint (Week 12 LOCF for Study B202 and Week 24 LOCF for study B302) by dose and study

	Placebo	NAT 30	NAT 60	NAT 120	NAT 180
Total Cholesterol					
Study B202					
Baseline	216 (51)	214 (41)	215 (46)	220 (45)	223 (33)
% change	0.4% (10)	+2.3% (10)	+2.4% (11)	+1.3% (10)	-0.5% (11)
Study B302					
Baseline	254 (45)	NA	251 (45)	249 (40)	256 (44)
% change	-0.2% (10)		+0.8% (9)	+2.0% (10)	+1.3% (9)
LDL					
Study B202					
Baseline	136 (45)	139 (38)	133 (42)	134 (37)	140 (36)
% change	+1.7% (17)	+2.2% (16)	+7.1% (23)	+3.3% (17)	+4% (17)
Study B302					
Baseline	170 (41)	NA	169 (42)	167 (38)	172 (44)
% change	-1.0% (13)		+0.2% (14)	+2.2% (17)	+2.4% (15)
HDL					
Study B202					
Baseline	43 (12)	44 (11)	41 (13)	46 (16)	46 (14)
% change	-3% (16)	+4.1% (21)	+3.6% (22)	+1.1% (17)	+1.3% (23)
Study B302					
Baseline	42 (17)	NA	40 (13)	42 (14)	43 (17)
% change	+8.6% (31)		+8.9% (24)	+4.7% (23)	+7.6% (24)
Triglyceride					
Study B202					
Baseline	190 (106)	171 (96)	218 (150)	217 (139)	201 (126)
% change	+3.2% (34)	+9% (43)	-1.2% (32)	+1.6% (43)	-8.8% (28)
Median %ch	-1.3%	0%	-6.3%	-3.1%	-7.9%
Study B302					
Baseline	202 (174)	NA	198 (159)	175 (93)	188 (126)
% change	+5.5% (45)		+5.7% (48)	+9.3% (45)	+1.8% (39)
Median %ch	-3.5%		0%	+2.1%	-9.1%

Weight Gain

Statistically significant weight gains ($p \leq .0001$) were seen for the three higher doses in both fixed dose studies (Table 19).

Table 19. Mean (SD) baseline and change from baseline weight (kg) at endpoint (Week 12 LOCF for Study B202 and Week 24 LOCF for Study B302) by dose and study

	Placebo	NAT 30	NAT 60	NAT 120	NAT 180
Study B202					
Baseline	82 (12)	85 (13)	84 (12)	85 (13)	84 (12)
Change	-0.4 (1)	-0.3 (2)	+0.8 (2)	+0.7 (2)	+0.6 (1)
Study B302					
Baseline	86 (14)		84 (14)	87 (14)	83 (13)
Change	-0.7 (2)	NA	+0.3 (2)	+0.9 (3)	+0.7 (3)

Looking further at Study B302 (the longer study), we see that about 40-50% of nateglinide patients had at least a 1 kg weight gain compared to 24% of placebo patients (Table 20). The relationship between dose and weight gain is similar to what was seen for dose and HbA1c with larger changes seen for the higher doses but similar responses for the 120 and 180 doses.

Table 20. Percentage of patients with weight gain at Week 24 LOCF in Study B302

	Placebo	NAT 60	NAT 120	NAT 180
Weight Gain (kg)				
≥ 1	24%	39%	48%	47%
≥ 2	13%	20%	32%	30%
≥ 3	6%	11%	18%	17%

Interestingly, though, no correlation between HbA1c (or FPG) change and weight gain was seen ($R < .24$ for all groups). Also the small correlation was positive indicating larger weight gains with increases in HbA1c (see Appendix 3); so a gain in weight is not correlated with a benefit (gain in glycemic control). (Note this is quite different from what was observed for rosiglitazone where a gain in weight was correlated with a decrease in HbA1c.)

Reviewer's Comments on Fixed Dose Studies

1. The fixed dose studies of B202 and B302 showed independently that doses of 60 mg and higher significantly reduce HbA1c compared to placebo. The mean change from baseline adjusting for baseline (LOCF) is shown below. Also shown here for comparison are results from Study B351 which is reviewed in the following section of this review. (Page 26 gives further details regarding the magnitude of response.)

Study	Placebo	Nat 60 mg	Nat 120 mg	Nat 180 mg
B202 Week 12	-0.06	-0.5	-0.7	-0.6
B302 Week 24	+0.1	-0.4	-0.5	-0.7
B351 Week 24	+0.4	NA	-0.5	NA

2. In Study B302, the maximum change in HbA1c is achieved by Week 16. More than half the nateglinide patients show an increase in HbA1c from Week 16 to Week 24 (see Figure 4 on page 12).

3. Study B304 showed that patients who do not respond to sulfonylurea treatment (HbA1c≥6.5% after a minimum of 16 weeks of therapy with a sulfonylurea) also do not respond to nateglinide treatment (60 or 120 mg). About 87% of nateglinide-treated patients versus 63% of glibenclamide-treated patients in Study B304 had an increase in HbA1c at endpoint (see Figure 8 on page 18). Switching patients inadequately treated with sulfonylureas to nateglinide results in a significant loss in glycemic control.

4. Treatment effects for subgroups based on age and gender were consistent. About 90% of the patients in these studies were Caucasian so there were too few patients to assess effects by race.

5. Dose response analyses revealed a significant linear trend suggesting a greater response at higher doses. Overall the greatest improvement in effect is seen when going from 60 mg to 120 mg (see Figures 17 and 18 on page 25 and 26). Subgroup analyses revealed that patients older than 58 or with diabetes for more than 3 years or with BMI>30[1] benefited from the 180 mg dose (see page 27).

6. No notable changes in lipids were observed.

7. Significant gains in weight were seen for nateglinide 60, 120 and 180 compared to placebo in both fixed dose studies. About half the patients treated with nateglinide 120 and 180 had a gain of 1 kg or greater at Week 24; about one-third had a gain of 2 kg or greater. Interestingly, these weight gains were not correlated with decreases in HbA1c.

8. Both naïve (about 75%) and previously treated patients were studied in the fixed dose studies. A comparison of these subgroups for the 120 mg nateglinide dose against placebo for the fixed dose studies and Study B351 is shown in a graph in Appendix 1. One subgroup does not consistently show a larger effect over the other. The graph in Appendix 2 further illustrates via the nearly parallel lines the comparability of the results for these subgroups.

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1 Changing the cutpoints for age, duration of disease and BMI consistently showed that older patients, heavier patients or patients with diabetes longer had an improved response with an increase in dose to 180 mg. The results, then, are not cutpoint dependent.

Combination Studies

The sponsor has submitted the results of 4 combination studies; three with metformin and one with glyburide (Table 21). Three (Studies B251, B252 and B354) of the four combination studies, more precisely, should be called add-on studies since in each of these studies nateglinide or placebo was added after run-in treatment with the active control. So in those three studies, one is assessing the effect of adding nateglinide to a regimen of glyburide or metformin for patients shown to be inadequately treated on the active control. The fourth study, Study B351, is designed to study the effectiveness of metformin plus nateglinide compared to placebo and each component. In Study B351, both naive and non-naive patients are treated with diet alone during run-in.

For Studies B251 and B252, this reviewer only gives a brief presentation of the efficacy results (mostly through graphics) since the results for both studies provide no statistical evidence in favor of combination therapy over monotherapy. Note also that the sponsor as well concludes that no improvement in glycemic control was shown by the addition of nateglinide in these studies. The combination studies with metformin (B351 and B354) are more thoroughly examined by this reviewer.

Table 21. Clinical trials designed to assess combination therapy

Study Number	Design	NIDDM Patient Population	Treatment Arms (N)	Duration of Treatment
B251	Combination with glyburide	Previously treated with glyburide	PLA + GLY 10 (56) NAT 60 + GLY 10 (56) NAT 120 + GLY 10 (56)	12 weeks
B252	Combination with metformin	Previously treated with sulfonylureas+metformin	MET 500 mg 3X (42) NAT 60 + MET 500 (41) NAT 120 + MET 500 (40)	12 weeks
B351	Combination with metformin	Inadequately treated with diet alone	PLA (172) NAT 120 mg 3X (179) MET 500 mg 3X (178) NAT 120 + MET 500 (172)	24 weeks
B354	Combination with metformin	Inadequately treated with metformin +diet	MET 1000 mg BID (152) NAT 60 + MET 1000 (155) NAT 120 + MET 1000 (160)	24 weeks

Study B251 (conducted 2/96 to 4/97)

Study B251 is a double-blind, multicenter trial designed to assess the efficacy and safety of nateglinide plus glyburide compared to glyburide alone. Following an 8-week run-in period (Weeks –8 to 0) of glyburide (10 mg once a day), patients satisfying entry criteria were randomized stratifying on baseline HbA1c (6.8-8 and >8-11) to one of the following treatment groups:

glyburide 10 mg
nateglinide 60 mg plus glyburide 10 mg
nateglinide 120 mg plus glyburide 10 mg

Matching placebos were used to maintain the nateglinide blind. Patients were treated for 12 weeks.

The primary efficacy endpoints in this study are change from baseline for HbA1c and FPG at Week 12. HbA1c was measured at Weeks -8, -2, 0, 4, 8, and 12 and FPG was measured at Weeks -4, -2, 0, 1, 2, 4, 8, and 12. Baseline was computed as the average of Weeks –2 and 0.

The trial was powered with 56 patients in each group to find a 1% difference in HbA1c between glyburide and each combination.

Inclusion/Exclusion Criteria

Patients could enter the 8-week glyburide run-in if they fulfilled the following criteria (this is a partial listing of all criteria):

1. Aged 30-75 years
2. Diagnosis of NIDDM
3. Glyburide (≥10 mg daily) or glipizide (≥15 mg daily) therapy for at least 4 weeks prior to run-in

Following the 8-week run-in, patients were randomized to treatment if they fulfilled the following criteria (this is a partial listing of all criteria):

1. Mean FPG≥7.8 mmol/l (≥140 mg/dl) between Week -8 and Week -2
2. 6.8%≤HbA1c≤11% at Week –4 and Week -2
3. 80% compliant on glyburide during the run-in
4. No FPG>275 between Week –8 and Week –2 during run-in

Patient Disposition

A total of 348 patients were screened at 14 centers in the United States and Canada; 172 patients were randomized to treatment (Table 22) following the run-in treatment with glyburide.

There were twice as many dropouts in each of the combination groups (about 20%) as the glyburide group (10%).

Table 22. Study B251 Patient Disposition

	Glyburide 10mg	NAT 60 + GLY	NAT 120 + GLY
Randomized	58 (100%)	58 (100%)	56 (100%)
Week 8	52 (90%)	50 (86%)	47 (84%)
Week 12	52 (90%)	48 (83%)	45 (80%)
ITT	58 (100%)	58 (100%)	56 (100%)

ITT refers to patients having at least one observation post-baseline for HBA1c OR FPG.

In the high dose (120mg) combination group, the major reason for dropout was ADE (11%)

while in the low dose (60mg) combination group, the major reason was withdrawal of consent (7%) (Table 23).

Table 23. Study B251 Reasons for discontinuation

	Glyburide 10mg (n=58)	NAT 60 + GLY (n=58)	NAT 120 + GLY (n=56)
ADE	2 (3%)	2 (3%)	6 (11%)
Protocol violation	0	2 (3%)	2 (4%)
Consent withdrawn	3 (5%)	4 (7%)	1 (2%)
Death	0	0	0
Lost-to-follow-up	1 (2%)	1 (2%)	2 (4%)
Other	0	1 (2%)	0

Patient Demographics

Some differences among the treatment groups are evident for race, gender and years of diabetes; however, these differences are not statistically significant (Table 24). The majority of the patients were male and Caucasian as in the other studies in this application. This study enrolled a significant number of patients classified as Other for race; presumably these patients were of Hispanic origin since about half the centers were located in southwestern United States. Patients ranged in age from 33 to 74 years with a mean of about 57 years; about 16% of the patients were 65 years or older. All patients had been previously treated with glyburide (at least for 4 weeks prior to randomization) according to the protocol.

Table 24. Study B251 Baseline demographics

	Glyburide 10mg (n=58)	NAT 60 + GLY (n=58)	NAT 120 + GLY (n=56)
Age (years)			
Mean (SD)	56 (9)	57 (7)	57 (8)
Range	33-72	39-74	37-72
Race: Caucasian	72%	62%	63%
Black	5%	5%	5%
Asian	5%	10%	7%
Other	17%	22%	25%
Gender: M/F	64%/36%	83%/17%	71%/29%
BMI			
Mean (SD)	29 (4)	29 (4)	29 (4)
Years of Diabetes			
Mean (SD)	6.5 (5)	8.5 (6)	8.8 (7)
Range			

Efficacy Results

The results for both HbA1c and FPG showed no significant difference between each combination and glyburide alone indicating no improvement in response due to the addition of nateglinide (Figures 21 and 22).

Figure 21. Study B251 Boxplots of HbA1c change from baseline at Week 12 LOCF

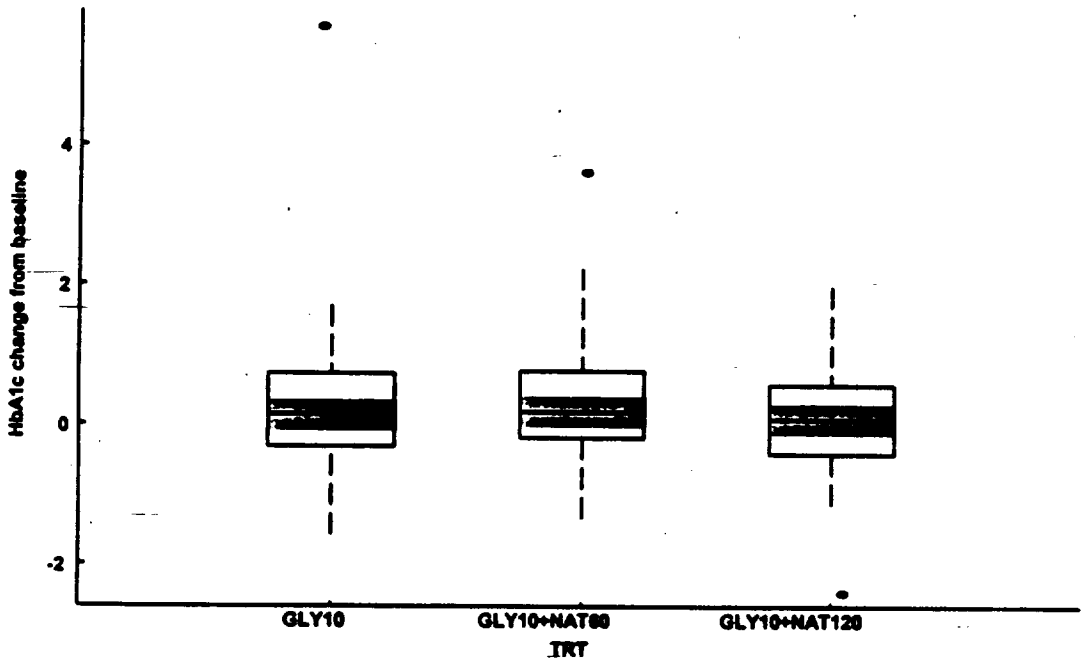
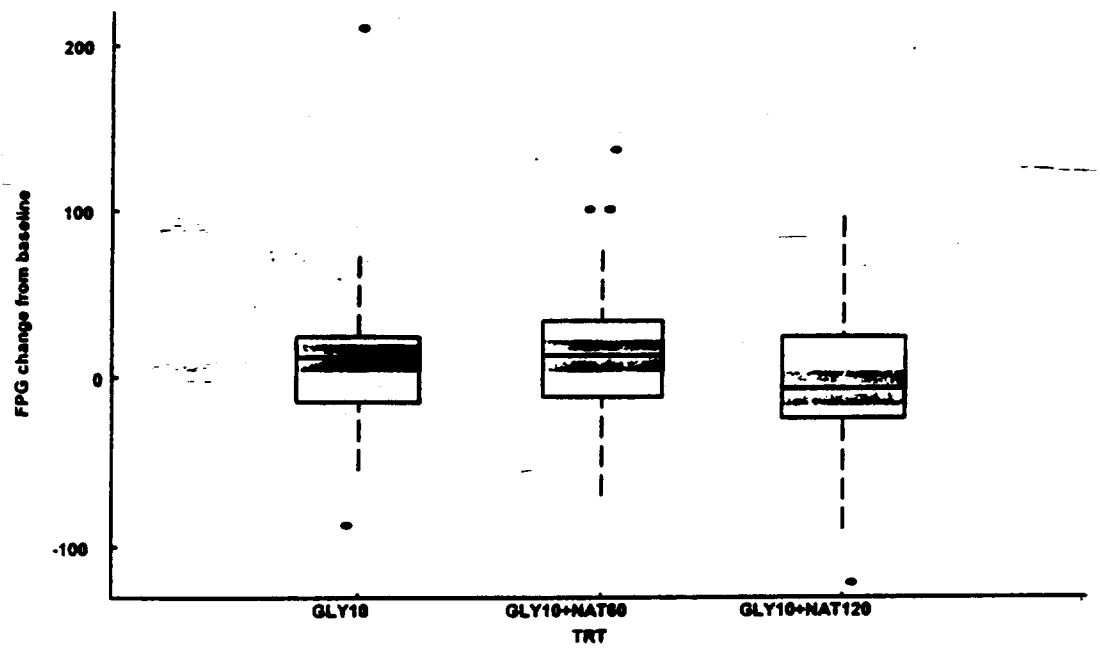


Figure 22. Study B251 Boxplots of FPG change from baseline at Week 12 LOCF



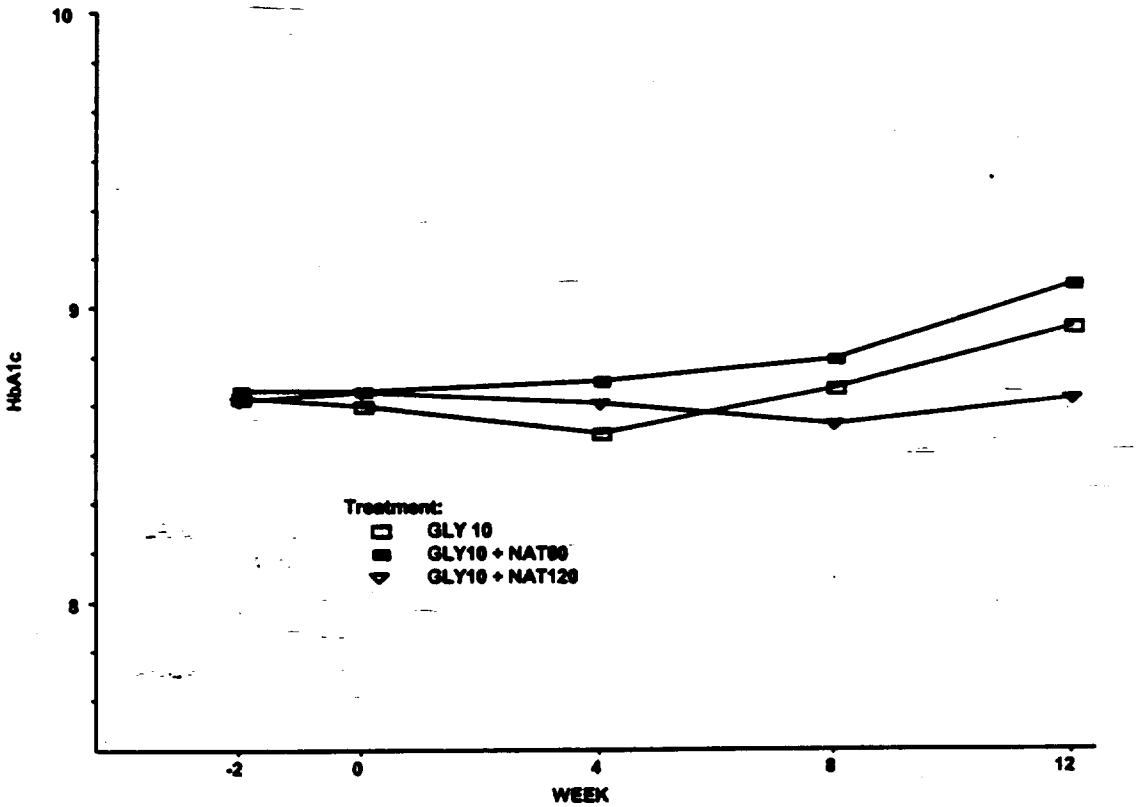
More than half the patients in each treatment group had an **increase** in HbA1c (55% in the glyburide group; 62% in the glyburide plus nateglinide 60 group and 54% in the glyburide plus nateglinide 120 group) at endpoint (Week 12 LOCF). The results for FPG were similar with percentages of 59%, 64% and 42% respectively.

Only 5 patients total were able to achieve a level of HbA1c of 6.5% (responder definition provided by the medical reviewer) and their HbA1c results follow:

	Baseline	Endpoint	Change
GLY	6.7	6.2	-0.5
GLY+NAT60	6.45	6.2	-0.25
GLY+NAT120	8.60	6.2	-2.4
GLY+NAT120	7.35	6.4	-0.95
GLY+NAT120	7.20	6.4	-.80

From Figure 23 it can be seen that a similar deterioration is seen for patients treated with glyburide alone and with glyburide plus 60 mg. Essentially no mean change is seen for the glyburide plus nateglinide 120 group. Examination of the results by various subgroups showed the same pattern; no change in the 120 group and increases in the other two groups.

Figure 23. Study B251 HbA1c at each week on study for observed cases



The results of Study B251 show that the addition of nateglinide to glyburide in patients non-respondent to glyburide treatment alone does not result in an improvement in glycemic control.

Study B252 (conducted 10/96 to 6/98)

Study B252 is a double-blind, multicenter trial designed to assess the efficacy and safety of nateglinide plus metformin compared to metformin alone. Following an open label 4-week run-in period (Weeks –4 to 0) of metformin (500 mg 3 times a day) plus sulphonylurea (pre-study dose), patients satisfying entry criteria were randomized to one of the following treatment groups:

metformin 500 mg 3X a day
nateglinide 60 mg plus metformin 500 mg
nateglinide 120 mg plus metformin 500 mg

Matching placebos were used to maintain the blind. Patients were treated for 12 weeks.

The primary efficacy endpoints in this study are change from baseline HbA1c and FPG at Week 12. HbA1c was measured at Weeks -4, 0, 4, 8, and 12. FPG was measured at Weeks -4, -2, 0, 2, 4, 8, and 12. For HbA1c, Week 0 was used as baseline while for FPG, baseline was computed as the average of Weeks -2 and 0.

The trial was powered with 170 patients in each group to find a 0.5% difference in HbA1c between metformin and each combination assuming an 18% dropout rate.

Inclusion/Exclusion Criteria

Patients could enter the 4-week metformin plus sulphonylurea run-in if they fulfilled the following criteria (this is a partial listing of all criteria):

1. Aged ≥30 years
2. Diagnosis of NIDDM
3. Metformin plus sulphonylurea therapy for at least 8 weeks prior to run-in
4. A metformin total daily dose of 1500 mg or greater for at least 4 weeks
5. FPG<11mmol/L (198 mg/dL)

Following the 4-week run-in, patients were randomized to treatment if they fulfilled the following criteria (this is a partial listing of all criteria):

1. Mean FPG≥5 mmol/l (≥90 mg/dl) at Week –4 and Week -2
2. 6%≤HbA1c≤11% at Week -4
3. 80% compliant on metformin during the run-in
4. No FPG>198 between Week –4 and Week –2 during run-in

Patient Disposition

A total of 243 patients were screened at 29 centers in the United Kingdom and 2 centers in Ireland; following the run-in treatment with metformin plus sulphonylurea, 123 patients were randomized to treatment (Table 25). There were about twice as many dropouts in the monotherapy arm than the combination arms (~30% versus 15%).

Table 25. Study B252 Patient Disposition

	Metformin 500 TID	NAT 60 + Met	NAT 120 + Met
Randomized	42 (100%)	41 (100%)	40 (100%)
Week 8	32 (76%)	35 (85%)	36 (88%)
Week 12	29 (69%)	35 (85%)	34 (85%)
ITT	42 (100%)	41 (100%)	40 (100%)

The major reason for dropout in all arms was ADE (Table 26) with most occurring during the first 8 weeks. About half the ADE's in the metformin alone group were due to hyperglycemia.

Table 26. Study B252 Reasons for discontinuation

	Metformin (n=42)	NAT 60 + Met (n=41)	NAT 120 + Met (n=40)
ADE	11 (26%)	5 (12%)	4 (10%)
Protocol violation	1 (2%)	1 (2%)	2 (5%)
Consent withdrawn	0	0	0
Death	0	0	0
Treatment Failure	0	0	0
Other	1 (2%)	0	0

Patient Demographics

Small, non-significant differences among the treatment groups were seen for race, gender and years of diabetes (Table 27). The majority of the patients were male and Caucasian. Patients ranged in age from 36 to 83 years with a mean of about 61; **nearly half the patients (46%) were 65 years or older.** All patients were previously treated with metformin and sulfonylureas as dictated by the protocol.

Table 27. Study B252 Baseline demographics

	Metformin (n=42)	NAT 60 + Met (n=41)	NAT 120 + Met (n=40)
Age (years) Mean (SD)	62 (8)	60 (10)	61 (11)
Race: Caucasian	88%	98%	95%
Gender: M/F	74%/26%	66%/34%	58%/42%
BMI Mean (SD)	28 (3)	30 (4)	28 (4)
Years of Diabetes Mean (SD)	9.2 (4)	9.1 (6)	7.6 (5)

Efficacy Results

Both HbA1c and FPG were named as primary efficacy variables in Study B252. Only the comparison of HbA1c change for metformin plus nateglinide 120 mg versus metformin alone was found to be statistically significant (sponsor's adjusted p-value of .0012).

Figures 24 and 25 illustrate that most patients exhibited an increase in HbA1c (>92%) and FPG (>82%) at Week 12 LOCF.

Figure 24. Study B252 Boxplots of HbA1c change from baseline at Week 12 LOCF

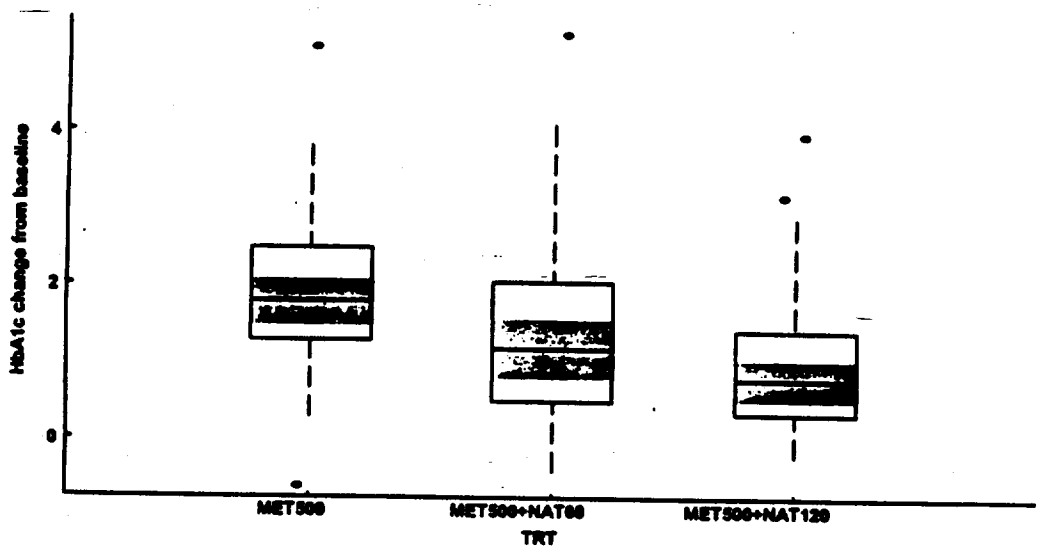
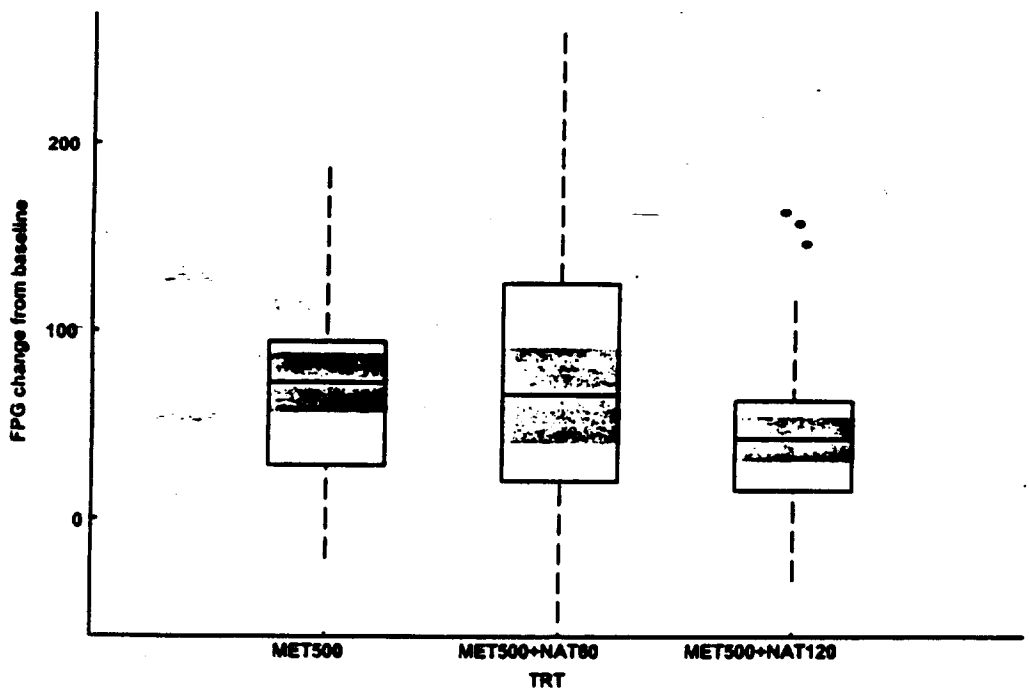
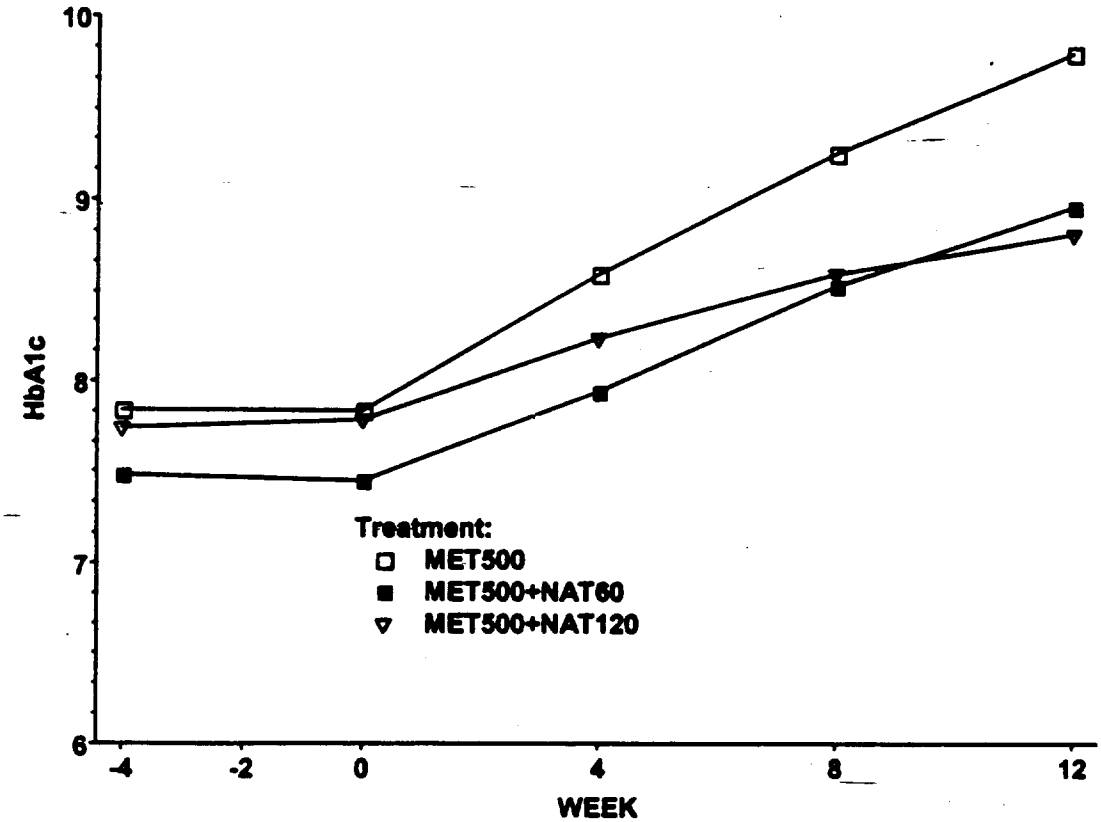


Figure 25. Study B252 Boxplots of FPG change from baseline at Week 12 LOCF



HbA1c results by week (Figure 26) show in all groups an increase as early as Week 4. At Week 12, completers show a mean increase of nearly 2% in the metformin alone group, about 1% in the metformin plus nateglinide 60 mg group and about 0.8% in the metformin plus nateglinide 120 mg group.

Figure 26. Study B252 HbA1c at each week on study for observed cases



A statistically significant treatment difference was observed between metformin plus nateglinide 120 and metformin alone. However, the results of Study B252 show no improvement in glycemic control when replacing a sulphonylurea with nateglinide in a population of patients who are poor responders to metformin plus sulfonylurea therapy. So removal of the sulfonylurea therapy and the addition of nateglinide results in deterioration of control.

Study B351 (conducted 8/97 to 4/99)

Study B351 is a double-blind, multicenter 24-week trial with four treatment arms; nateglinide monotherapy, metformin monotherapy, placebo and combination of metformin plus nateglinide. Six comparisons were considered as primary; each active treatment arm to placebo (3 comparisons), each monotherapy arm to combination (2 comparisons) and nateglinide monotherapy to metformin monotherapy. Following a single-blind 4-week diet only period (Weeks –4 to 0), patients inadequately controlled on diet alone were randomized to one of the following treatment groups:

nateglinide 120 mg three times a day (10 minutes before each meal)
metformin 500 mg 1X a day (with or after breakfast) for Week 1
500 mg 2X a day (with or after breakfast and dinner) for Week 2
500 mg 3X a day (with or after breakfast, lunch and dinner) Weeks 2-24
nateglinide 120 mg plus metformin (titrated as for monotherapy dose)
placebo

Matching placebos were used to maintain the blind. Patients were treated for 24 weeks.

The primary efficacy endpoint in this study is change from baseline HbA1c at Week 24. HbA1c was measured at Weeks -4, -2, 0, 8, 12, 16 and 24. Baseline was computed as the average of Weeks -2 and 0.

The trial was powered with 170 patients in each group to find a 0.5% difference in HbA1c between each monotherapy arm and placebo assuming a 16% dropout rate.

Inclusion/Exclusion Criteria

Patients could enter the 4-week diet only run-in if they fulfilled the following criteria (this is a partial listing of all criteria):

1. Aged ≥30 years
2. History of NIDDM for 3 months or longer
3. diet therapy for at least 4 weeks prior to run-in

Following the 4-week run-in, patients were randomized to treatment if they fulfilled the following criteria (this is a partial listing of all criteria):

1. No FPG>15 mmol/l (>270 mg/dl) between Week –4 and Week -2
2. 6.5%≤HbA1c≤11% based on mean of Week –4 and -2

Patient Disposition

A total of 1451 patients were screened at 87 US centers and 7 UK centers; 701 patients were randomized to treatment (Table 28) following the placebo run-in. About 72% of the patients completed the study; the fewest completers (61%) were in the placebo group and the most (79%) in the combination arm.

Table 28. Study B351 Patient Disposition

	Placebo	NAT 120	MET 500	NAT + MET
Randomized	172 (100%)	179 (100%)	178 (100%)	172 (100%)
Week 8	151 (88%)	167 (93%0	166 (93%)	157 (91%)
Week 12	118 (69%)	150 (84%)	146 (82%)	140 (81%)
Week 16	114 (66%)	143 (80%)	142 (80%)	138 (80%)
Week 24	105 (61%)	133 (74%)	132 (74%)	135 (79%)
ITT	167 (97%)	175 (98%)	175 (98%)	168 (98%)

The primary reasons for discontinuation (Table 29) were treatment failure and withdrawal of consent in the monotherapy arms while the primary reason in the combination arm was adverse events. Most of the withdrawals for ADE and for consent withdrawal occurred during the first 12 weeks of the study; treatment failures occurred throughout the trial.

Table 29. Study B351 Reasons for discontinuation

	Placebo (n=172)	NAT 120 (n=179)	MET 500 (n=178)	NAT + MET (n=172)
ADE	9 (5%)	4 (2%)	12 (7%)	16 (9%)
Protocol violation	4 (2%)	2 (1%)	1 (1%)	6 (4%)
Consent withdrawn	17 (10%)	18 (10%)	10 (6%)	7 (4%)
Death	0	0	1 (1%)	0
Treatment Failure	24 (14%)	10 (6%)	11 (6%)	4 (2%)
Lost-to-follow-up	7 (4%)	9 (5%)	7 (4%)	3 (2%)
Other	5 (3%)	2 (1%)	3 (2%)	1 (1%)

Patient Demographics

No significant differences regarding baseline demographics were seen (Table 30). The majority of the patients were male and Caucasian; however, unlike the other studies, 20% of the patients were of other races (12% Black). Patients ranged in age from 29 to 88 years with a mean of about 58; about 29% of the patients were 65 years or older. About 43% of the patients had been treated with anti-diabetics prior to entering this trial.

Table 30. Study B351 Baseline Demographics

	Placebo (n=172)	NAT 120 (n=179)	MET 500 (n=178)	NAT + MET (n=172)
Age (years)				
Mean (SD)	60 (11)	59 (11)	57 (11)	58 (11)
Range	30-84	31-81	29-82	32-88
Race:				
Caucasian	79%	82%	79%	83%
Black	17%	10%	10%	12%
Other	4%	8%	11%	5%
Gender: M/F	60%/40%	61%/39%	68%/32%	59%/41%
BMI				
Mean (SD)	29 (4)	30 (4)	30 (4)	30 (4)
% Previously treated with anti-diabetics	40%	42%	42%	48%
Years of Diabetes				
Mean (SD)	4.6 (5)	4.7 (5)	4.5 (5)	4.5 (5)
Range				

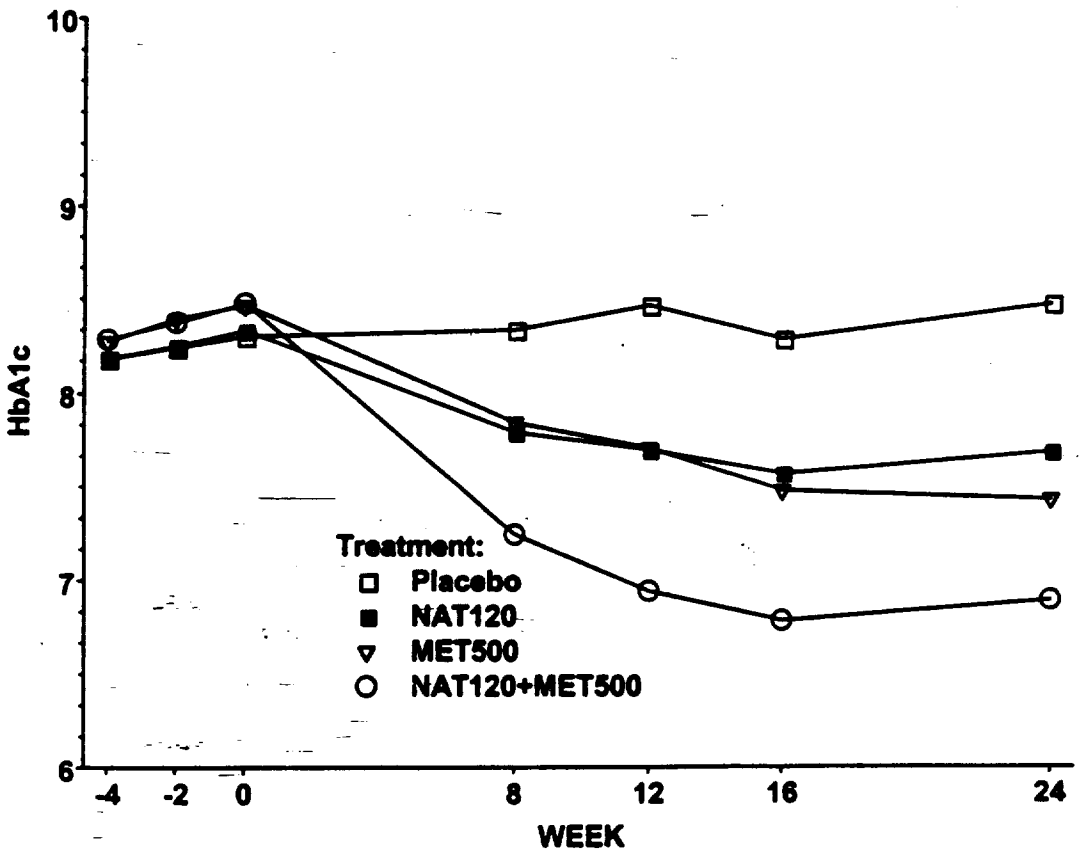
Hypertension (47%), hyperlipemia (18%), arthritis (21%), allergy (18%) and hypercholesterolmeia (17%) were the most common medical conditions.

Efficacy Results
HbA1c

The sponsor planned to test 6 null hypotheses with no adjustments to the level of significance planned. No adjustment is needed for the comparisons of each component (nateglinide alone and metformin alone) to combination therapy since both comparisons are expected to be significant. The ANCOVA model used by the sponsor included effects for treatment and center, baseline HbA1c as a covariate and the interaction terms. Small centers were pooled. This reviewer excluded non-significant interaction terms for reasons explained earlier in this review.

Figure 27 clearly illustrates that patients on combination therapy who remain on study show a benefit over placebo and over each component. The response appears to be realized by Week 16 with a small mean increase to Week 24. About 56% of the combination patients, 47% of metformin patients, 66% of nateglinide patients and 61% of the placebo patients had an increase in HbA1c between Week 16 and Week 24. The median increase, for only those patients having an increase, was 0.3% in the treatment groups and 0.4% in the placebo group.

Figure 27 Study B351 HbA1c at each week on study for observed cases



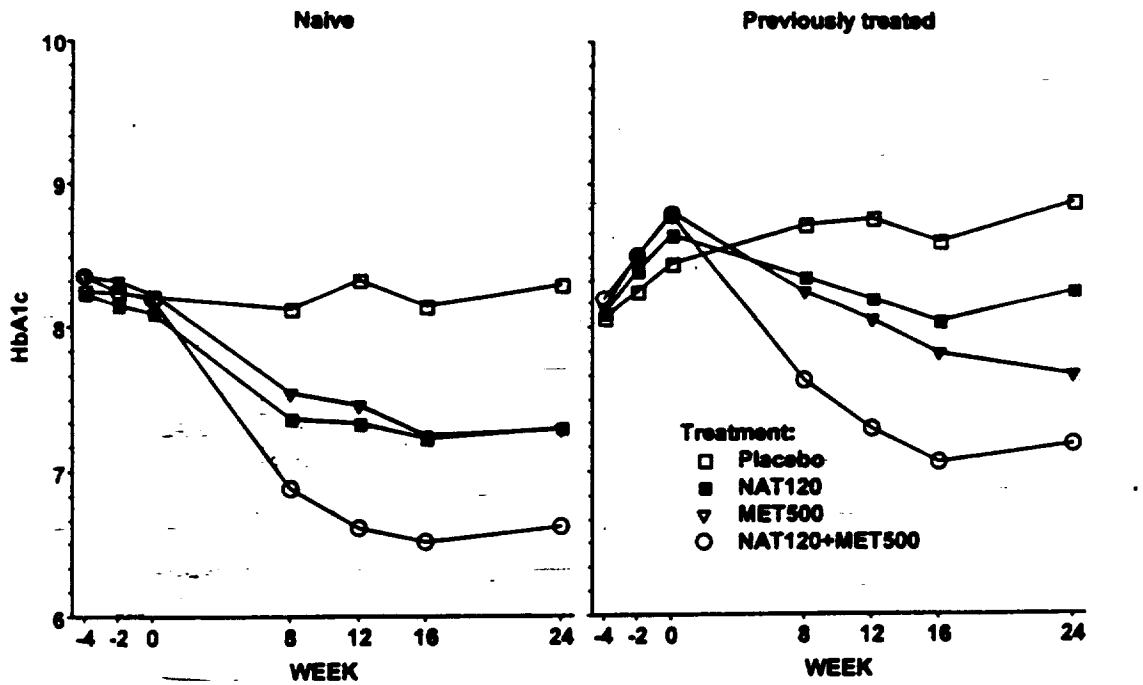
The primary endpoint was Week 24 LOCF; these results plus results for the completers at Week 24 are summarized in Table 31 below. The combination therapy arm was significantly different from each monotherapy arm for both completers and endpoint (Week 24 LOCF).

Table 31. Study B351 HbA1c Results

	Placebo Mean (SD)	NAT 120 Mean (SD)	MET 500 Mean (SD)	NAT120+MET500 Mean (SD)
Completers	(n=113)	(n=137)	(n=138)	(n=137)
Baseline	8.1 (1.0)	8.3 (1.0)	8.4 (1.2)	8.5 (1.1)
Week 24	+0.41 (1.2)	-0.57 (1.2)	-0.91 (1.0)	-1.61 (0.9)
ITT	(n=160)	(n=171)	(n=172)	(n=162)
Baseline	8.3 (1.1)	8.3 (1.0)	8.4 (1.1)	8.4 (1.1)
Week 24 LOCF	+0.42 (1.2)	-0.41 (1.2)	-0.81 (1.0)	-1.48 (1.0)
Least Squares Mean	+0.36	-0.46	-0.80	-1.47
Unadjusted p-value for comparison to combination[1]		.0001	.0001	

The combination therapy effects for naive (placebo difference of 1.9) and previously treated (placebo difference of 1.8) patients were similar (Figure 28).

Figure 28 Study B351 HbA1c at each week on study for observed cases for naive and previously treated patients

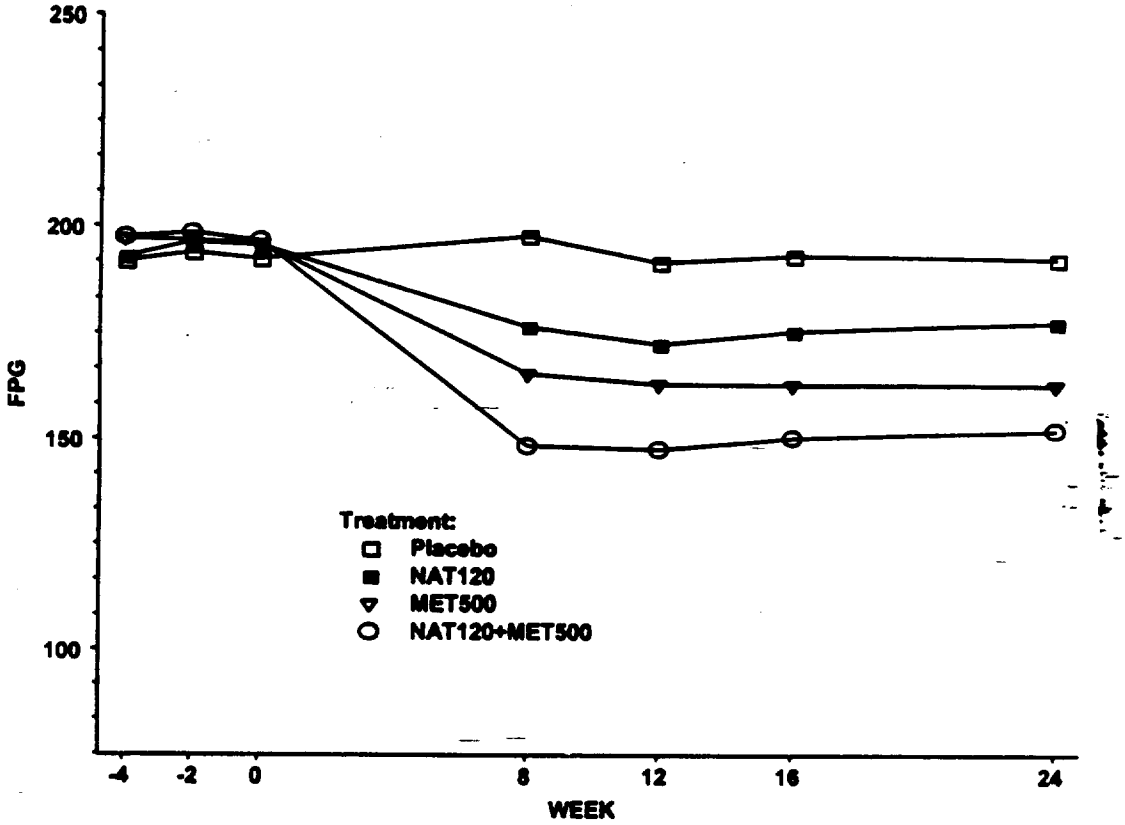


1 P-values are from pairwise comparisons from ANCOVA with treatment and center as main effects and with baseline HbA1c as covariate.

FPG

Figure 29 illustrates the fasting plasma glucose over the duration of the trial for each treatment group. The pattern of response is similar to what was seen for HbA1c.

Figure 29 Study B351 FPG at each week on study for observed cases



The combination therapy was statistically significantly different from each monotherapy arm at Week 24 (completers and ITT, Table 32). It is also worth noting that the results for metformin alone were significantly different from nateglinide alone (p<.0001).

Table 32. Study B351 FPG Results

	Placebo Mean (SD)	NAT 120 Mean (SD)	MET 500 Mean (SD)	NAT120+MET500 Mean (SD)
Completers	(n=111)	(n=139)	(n=138)	(n=135)
Baseline	186 (36)	193 (43)	194 (43)	201 (42)
Week 24	+7.8 (47)	-14.5 (44)	-30.1 (40)	-48.9 (39)
ITT	(n=166)	(n=173)	(n=174)	(n=167)
Baseline	194 (39)	196 (44)	196 (44)	198 (42)
Week 24 LOCF	+8.0 (45)	-13.2 (44)	-30.0 (41)	-44.9 (38)
Least Squares Mean	+8.5	-11.6	-28.9	-42.6
Unadjusted p-value for comparison to combination[1]		.0001	.002	

1 P-values are from pairwise comparisons from ANCOVA with treatment and center as main effects and with baseline HbA1c as covariate.

Study B354 (conducted 11/97 to 5/99)

Study B354 is a double-blind, multicenter trial designed to assess the efficacy and safety of nateglinide plus metformin compared to metformin alone. Following a single-blind 4-week period (Weeks –4 to 0) of metformin 1000 mg twice a day, patients were randomized to nateglinide 60 or 120 mg three times a day (10 minutes before each meal) plus metformin 1000 mg twice a day or placebo plus metformin 1000 mg twice a day and treated for 24 weeks. Matching placebos were used to maintain the blind.

The primary efficacy endpoint in this study is HbA1c at Week 24. HbA1c was measured at Weeks –4, -2, 0, 8, 12, 16 and 24. Baseline was computed as the average of Weeks –2 and 0.

The trial was powered with 170 patients in each group to find a 0.5% difference in HbA1c between metformin and each combination assuming an 18% dropout rate.

Inclusion/Exclusion Criteria

Patients could enter the 4-week metformin run-in if they fulfilled the following criteria (this is a partial listing of all criteria):

1. Aged ≥30 years
2. History of NIDDM for 6 months or longer
3. **Metformin therapy for at least 3 months prior to run-in**
4. A metformin total daily dose of 1500 mg or greater for at least 4 weeks

Following the 4-week metformin run-in, patients were randomized to treatment if they fulfilled the following criteria (this is a partial listing of all criteria):

1. No FPG>15 mmol/l (>270 mg/dl) between Week –4 and Week -2
2. 6.5%≤HbA1c≤11% based on mean of Week –4 and -2

Patient Disposition

A total of 680 patients were screened at 73 centers in North America (12 centers), South Africa (5 centers) and Europe (56 centers); 467 patients were randomized to treatment (Table 33) following the run-in treatment with metformin. About 90% of the patients completed the study.

Table 33. Study B354 Patient Disposition

	Metformin	NAT 60 + Met	NAT 120 + Met
Randomized	152 (100%)	155 (100%)	160 (100%)
Week 12	142 (93%)	140 (90%)	148 (93%)
Week 24	136 (90%)	137 (88%)	144 (90%)
ITT	151 (99%)	153 (99%)	159 (99%)

Given the small number of dropouts overall, it is not surprising to find no differences among the treatment groups for reasons for discontinuation (Table 34).

Table 34. Study B354 Reasons for discontinuation

	Metformin (n=152)	NAT 60 + Met (n=155)	NAT 120 + Met (n=160)
ADE	5 (3%)	7 (5%)	5 (3%)
Protocol violation	3 (2%)	2 (1%)	0
Consent withdrawn	2 (1%)	3 (2%)	4 (3%)
Death	0	1 (1%)	1 (1%)
Treatment Failure	6 (4%)	5 (3%)	3 (2%)
Other	0	0	2 (1%)

Patient Demographics

The treatment groups were comparable at baseline regarding baseline demographics (Table 35). The majority of the patients were male and Caucasian. Patients ranged in age from 30 to 84 years with a mean of about 57; about 26% of the patients were 65 years or older. According to the protocol, all patients were previously treated with metformin.

Table 35. Study B354 Baseline demographics

	Metformin (n=152)	NAT 60 + Met (n=155)	NAT 120 + Met (n=160)
Age (years) Mean (SD) Range	 56 (10) 30-82	 58 (10) 30-81	 57 (10) 31-84
Race: Caucasian	91%	90%	91%
Gender: M/F	55%/45%	61%/39%	61%/39%
BMI Mean (SD)	 30 (4)	 29 (4)	 29 (4)
Years of Diabetes Mean (SD) Range	 6.5 (6)	 7.2 (6)	 6.8 (6)

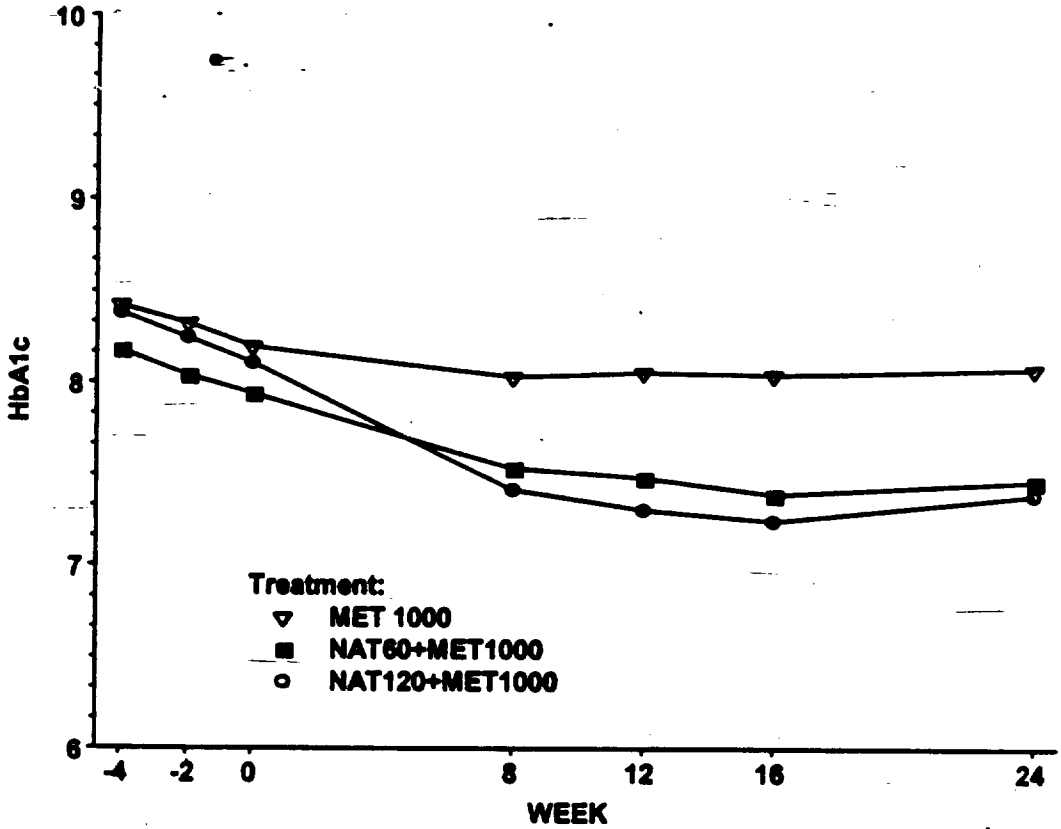
Hypertension (47%) and hyperlipemia (18%) were the most common medical conditions.

Efficacy Results

HbA1c

The HbA1c results overtime for the observed cases data illustrate a pattern comparable to the pattern seen in the other 24 week trials; a maximum effect at Week 16 followed by a small deterioration in effect by Week 24 (Figure 30 on the following page).

Figure 30 Study B354 HbA1c at each week on study for observed cases



The primary efficacy analysis is an ANCOVA of change from baseline HbA1c Week 24 LOCF. Each combination was statistically significantly different from metformin alone (Table 36). So the addition of nateglinide significantly improved glycemic control in this population of patients who were poor responders to metformin alone.

Table 36. Study B354 HbA1c Results

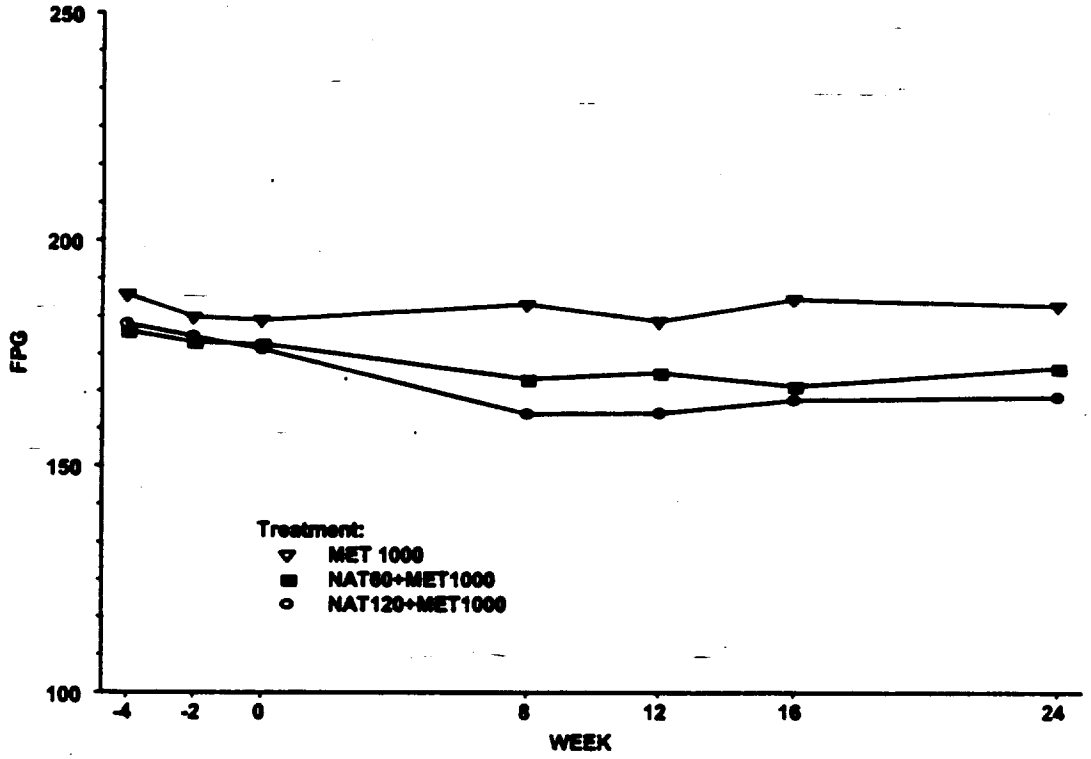
	Metformin Mean (SD)	MET + NAT 60 Mean (SD)	MET + NAT 120 Mean (SD)
Completers	(n=137)	(n=137)	(n=145)
Baseline	8.2 (1.1)	7.9 (1.0)	8.1 (1.0)
Week 24	-0.07 (0.81)	-0.41 (0.89)	-0.69 (1.0)
ITT	(n=150)	(n=152)	(n=154)
Baseline	8.2 (1.1)	8.0 (1.1)	8.2 (1.0)
Week 24 LOCF	-0.04 (0.85)	-0.38 (1.1)	-0.68 (1.0)
Least Squares Mean	+0.03	-0.34	-0.64
Unadjusted p-value for comparison to combination[1]		.001	.0001

1 P-values are from pairwise comparisons from ANCOVA with treatment and center as main effects and with baseline HbA1c as covariate.

FPG

The FPG results overtime (Figure 31) show a decrease in FPG as early as Week 8 for both combination therapies.

Figure 31 Study B354 FPG at each week on study for observed cases



The Week 24 endpoint FPG results show a statistically significant difference between metformin plus nateglinide 120mg and metformin alone; the combination of metformin plus nateglinide 60 mg is not statistically significant after adjusting for multiple comparisons. The treatment effect in the ITT population is less than what was observed in the completer population.

Table 37. Study B354 FPG Results

	Metformin Mean (SD)	MET + NAT 60 Mean (SD)	MET + NAT 120 Mean (SD)
Completers	(n=134)	(n=134)	(n=145)
Baseline	179 (38)	175 (36)	174 (33)
Week 24	+7.4 (33)	-2.5 (36)	-7.9 (32)
ITT	(n=150)	(n=152)	(n=159)
Baseline	182 (40)	177 (39)	178 (38)
Week 24 LOCF	+7.7 (33)	-0.66 (42)	-5.0 (1.0)
Least Squares Mean	+9.4	+0.50	-3.7
Unadjusted p-value for comparison to combination[1]		.04	.002

1 P-values are from pairwise comparisons from ANCOVA with treatment and center as main effects and with baseline FPG as covariate.

Reviewer's Comments on Combination Studies

1. The sponsor has conducted four clinical trials to assess the efficacy of adding nateglinide treatment to metformin treatment (B252, B351 or B354) or glyburide treatment (B251). Table 38 summarizes some design characteristics of these trials. In all 4 trials, patients only were eligible for the run-in period if they had been treated previously for at least a month with the run-in treatment. So at baseline all patients would have experienced the run-in treatment for at least 2 months. For Studies B251, B351 and B354 there is essentially no change in FPG during the run-in; in Study B252, overall mean FPG increases by about 20 mg/dL during run-in. HbA1c run-in levels are stable except for previously treated patients switched to diet in Study B351 (see Figure 28 on page 43). In all studies, after run-in, patients were randomized to treatment if they satisfied the entry criteria; FPG and HbA1c criteria are summarized in the table below.

Table 38. Design characteristics of the combination studies

Study	% Previously Treated	Run-in Treatment	Active Control	Entry FPG	Entry HbA1c	Duration of Trt.
B251	100% with glyburide	Glyburide (8 wks)	Glyburide	≥140	6.8-11	12 wks
B252	100% with MET+ Sulfonylurea	Metformin+ Sulfonylurea (4 wks)	Metformin	≥90	6.0-11	12 wks
B351	57% Naive 43% Prev. trtd. (all on diet alone for at least 4 wks prior to run-in)	Diet Only (4 wks)	Metformin	<270	6.5-11	24 wks
B354	100% with Metformin	Metformin (4 wks)	Metformin	<270	6.5-11	24 wks

2. Table 39 shows the mean change form baseline for HbA1c for the active control arms and the combination arms. Only in Study B251 was the comparison of combination therapy to active control not statistically significant. Even though the treatment difference in Study B252 is significant, the mean HbA1c levels increase for the combination arm indicating no improvement in glycemic control; the removal of the sulfonylurea clearly causes a deterioration in control in all treatment groups.

Table 39. HbA1c change from baseline, LS means (ITT/LOCF)

Study	% Previously Treated	Run-in Treatment	Active Control	Active Alone	Active + NAT 60	Active +NAT 120
B251 Week 12	100% with glyburide	Glyburide	Glyburide	+0.29	+0.22	-0.02
B252 Week 12	100% with MET+ Sulfonylurea	Metformin+ Sulfonylurea	Metformin	+1.95	+1.51	+0.98**
B351 Week 24	57% Naive 43% Prev. trtd.	Diet Only	Metformin		NA	
All				-0.80		-1.48**
Naïve				-0.91		-1.70**
Prev. trt.				-0.61		-1.17**
B354 Week 24	100% with Metformin	Metformin	Metformin	+0.03	-0.34**	-0.64**

** HbA1c change from baseline for combination therapy was statistically significantly different ($p \leq .05$) from the change from baseline for the active control monotherapy arm.

3. To further summarize the data from the combination studies, this reviewer computed the percentage of responders for combination arms and active control arms in each of the combination studies (Table 40). Responders were defined as those patients who achieved an HbA1c less than 6.5%; this definition was provided by the medical reviewer. These results further illustrate the difference in results for Studies B251 and B252 compared to Studies B351 and B354.

Table 40. Percent of patients with an HbA1c of less than 6.5% at endpoint (LOCF)

Study	% Previously Treated	Run-in Treatment	Active Control	Active Alone	Active + NAT 60	Active +NAT 120
B251 Week 12	100% with glyburide	Glyburide	Glyburide	2%	2%	5%
B252 Week 12	100% with MET+ Sulfonylurea	Metformin+ Sulfonylurea	Metformin	0%	7%	0%
B351 Week 24	57% Naive 43% Prev. trtd.	Diet Only	Metformin		NA	
All				15%		33%
Naive				18%		39%
Prev. trt.				11%		18%
B354 Week 24	100% with Metformin	Metformin	Metformin	9%	19%	16%

4. Combination Studies B251 and B252 and monotherapy Study B304 clearly demonstrate that patients previously treated inadequately with sulfonlyureas show a further loss in glycemic control when nateglinide is added to the sulfonylurea (B251) or replaces the sulfonylurea (B304 and B252).

5. The results for Studies B351 and B354 support combination metformin plus nateglinide therapy over metformin alone in patients shown to be poor responders to diet alone or metformin alone, respectively.

6. The median weight gain for combination (metformin plus nateglinide 120 mg) therapy in Studies 351 and B354 was 0.2 kg and 0.8 kg respectively. The weight gain seen in the 120 mg nateglinide group was comparable to the results seen in the fixed dose studies (compare the results below to the results in Table 20 on page 29).

Table 41. Percentage of patients with weight gain at Week 24 LOCF in Study B351

	Placebo	NAT 120
Weight Gain (kg)		
≥ 1	23%	46%
≥ 2	11%	26%
≥ 3	9%	14%

Extension Studies

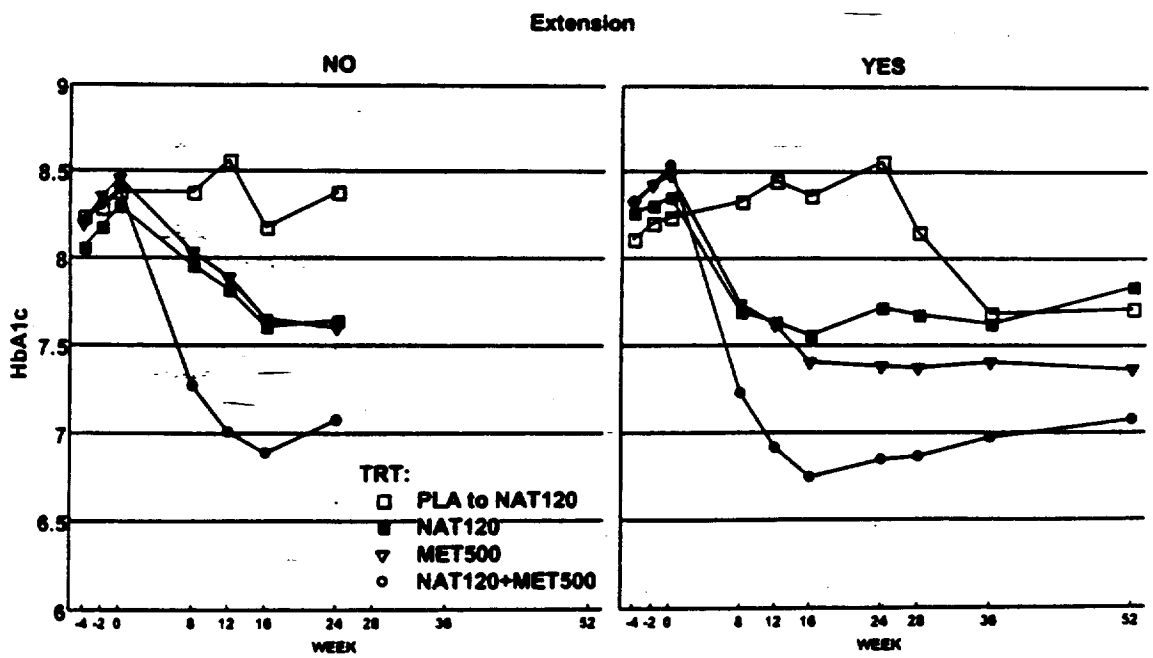
The sponsor conducted 3 long-term extension studies (Table 42) where patients could be continued on randomized therapy up to 52 weeks total. The medical reviewer in her review examined the sustainability of the nateglinide response. This reviewer was asked to add more descriptive details for the data from Study B351E-01; no statistical tests were conducted due to the large number of dropouts. The other 2 studies are inadequate for assessing long-term efficacy of nateglinide monotherapy; Study 251E is a combination study and in Study 202E, metformin was added to nateglinide 120 mg for about one-third of the patients.

Table 42. Extension Studies

	Extension Duration	% Continuing	NAT 120 Completers N (% of ext. N)	Comment
B202E-01	40 weeks	227/265 (86%)	47 (89%)	If HbA1c>8.5, added metformin
B251E-01	40 weeks	92/145 (63%)	NA (no NAT120 arm)	Elig. if HbA1c>10%
B351E-01	28 weeks	400/508 (79%)	56 (54%)	PLA switched to NAT120

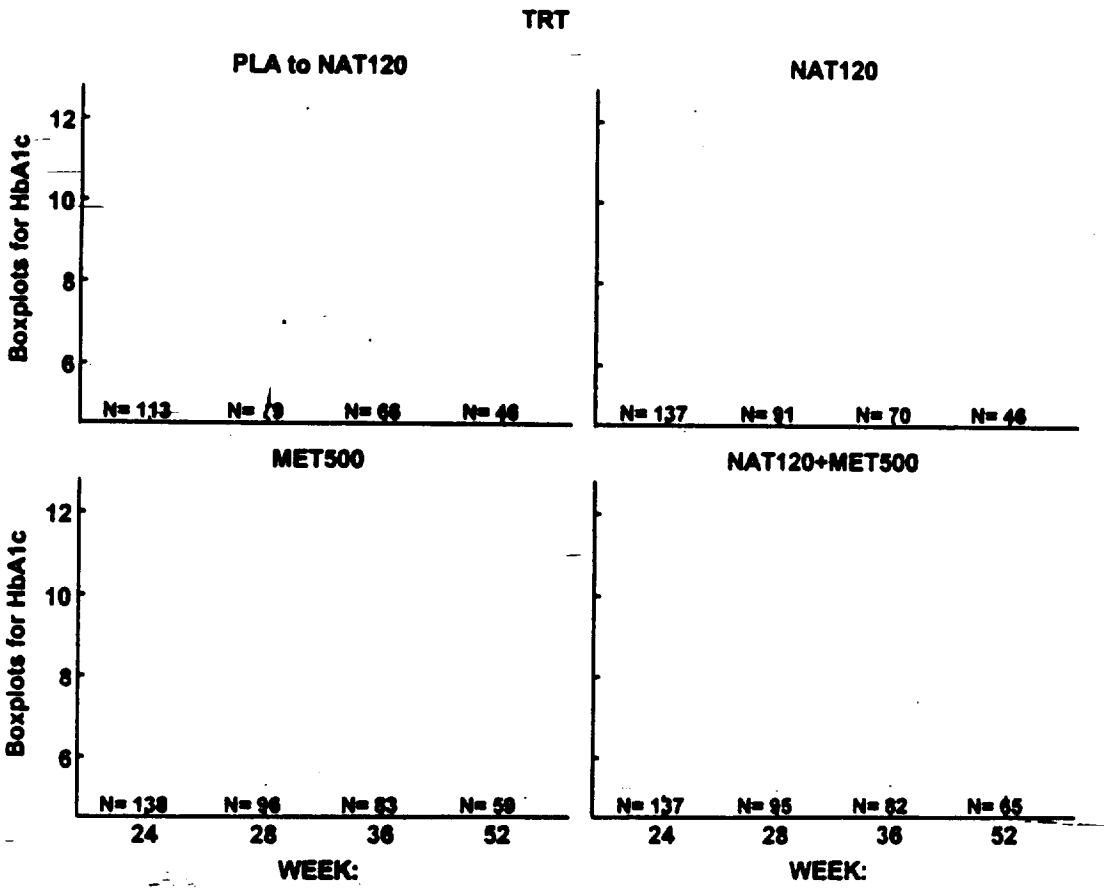
The HbA1c data for all patients in Study 351 and 351E-01 is shown in Figure 32. The graph on the left shows data for patients who completed the 24 weeks of 351 and then did not enter into the extension part of the trial; on the right, data for patients enrolled in the extension is shown. In the metformin and metformin plus nateglinide arms, patients, who continue, appear to be doing a little better at Week 24 than those that do not opt to continue. Switching from placebo to nateglinide 120 mg clearly has a dramatic effect on HbA1c (Figure 32, right side). A small increase in mean response for nateglinide 120 and nateglinide 120 plus metformin from Week 36 to Week 52 is seen without a similar increase in the metformin arm..

Figure 32. Study 351 HbA1c overtime for patients completing only the 24-week segment of the study (left figure) and for patients continuing into the extension (right figure), observed cases data.



The boxplots in Figure 33 show the distribution of the HbA1c data at each timepoint of the extension of Study 351. An examination of the sample sizes (included under each box) shows the large drop off of patients in all arms (even in the arm where patients were switched from placebo to nateglinide 120 and had a large response). The majority of patients (>75%) in all treatment arms have a Week 52 HbA1c greater than 6.5% (non-responders using the medical reviewer's definition).

Figure 33. Boxplots of HbA1c by week on Study B351E-01 and by treatment group



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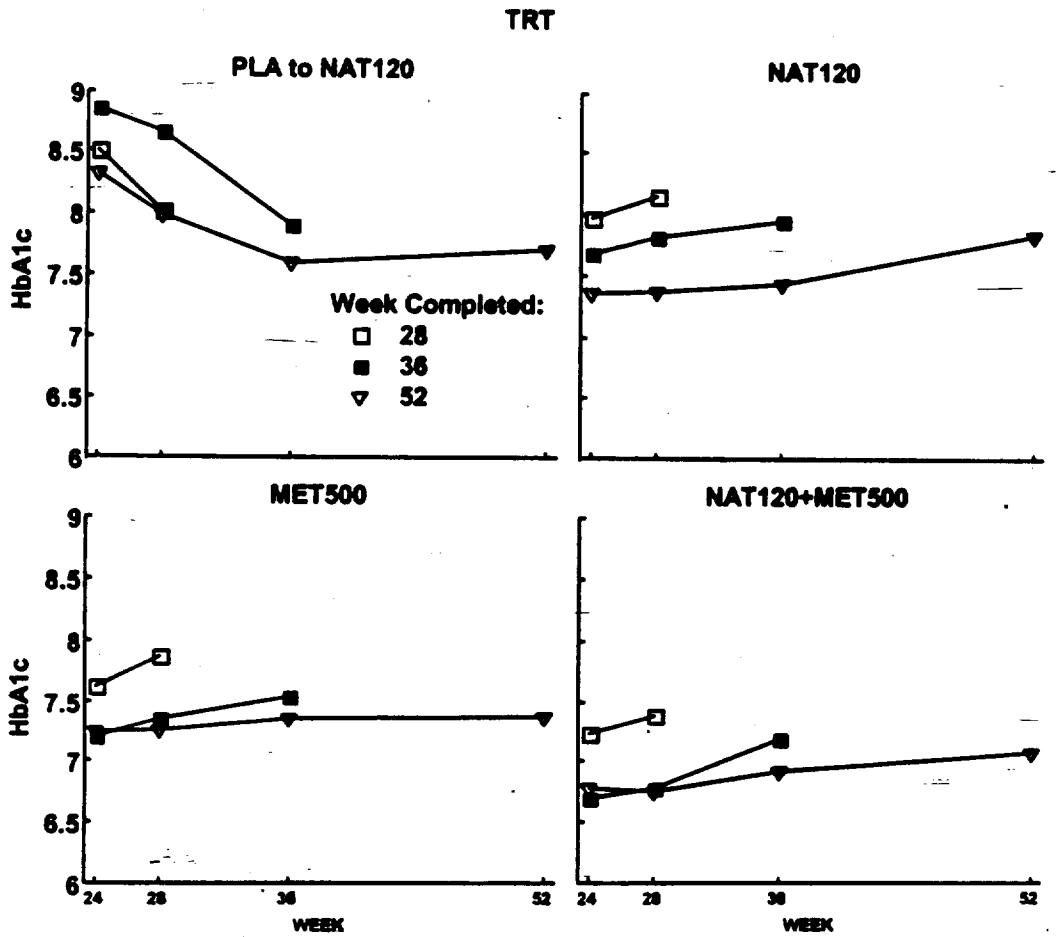
Due to the large number of dropouts, it is important to look at responses by cohorts of dropouts (the medical reviewer has created a similar depiction of the data). Figure 34 shows that patients continuing on their randomized treatment who dropout early have a higher mean at dropout than the patients completing the 52 weeks, however, their baseline means are also higher. So the lack of response during the first 24 weeks appears to suggest no further improvement with additional therapy (Week 28 dropouts).

Looking at just the Week 52 completers, an increase in the means from Week 36 to Week 52 is again evident; no such increase is seen in the metformin group.

Figure 34. Study B351E-01 HbA1c by week completed for each treatment group



The results of Study B351E-01 failed to demonstrate maintenance of glycemic control in patients treated with nateglinide 120 mg for two reasons; 1) there was a high dropout rate in all treatment arms (less than 40% of the randomized patients completed 52 weeks) and 2) the extension study design does not provide the framework for ascertaining maintenance of response[1]. This failure does not imply that patients cannot maintain control on nateglinide.

1 Maintenance of response can be studied by using an enriched design where patients are all started on nateglinide open-label and then responders are randomized to continue on nateglinide or switched to placebo or an active control for long-term treatment. Also non-responders should be defined a priori.

Reviewer's Comments on Labeling

Comments are listed below under the headings used in the sponsor's proposed labeling. Direct statements from the sponsor's proposed label (submitted 9/13/00) are shown in italics and then followed by reviewers comments. Additional suggestions are included on information that the sponsor has not included in the label that this reviewer thinks should be added. Other sections in the label were not reviewed because they contain information not reviewed by this reviewer or because the medical reviewer has recommended total deletion of the section.

Pharmacodynamics and Clinical Effects

In the 24-week, placebo-controlled, clinical trials, the mean weight gain in patients treated with Starlix was 1 kg or less.

1. Weight changes were dose-related but not correlated with improved glycemic control..
2. Approximately 15% of patients treated with nateglinide 120 mg had a weight gain of 3 kg or greater after 24 weeks of treatment; ~30% of 2 kg or greater.

Clinical Studies

All twelve studies were characterized by a lengthy washout period of prior therapy so as to adequately evaluate the treatment effect of Starlix by minimizing confounding effects of previous antidiabetic medications.

1. In studies where previously treated patients were treated (B202, B302 and B351), HbA1c and FPG continue to change during the run-in period suggesting that the washout was not complete. What is the sponsor referring to as a washout period? The length of run-in periods was generally 4 weeks.

Monotherapy

1. In this section, the sponsor presents HbA1c, FPG and incremental 2 hr PG results from Studies B302 and B351. In addition to the overall results, results for previously treated and naive patients are presented separately.
2. Only the results from Study B302 should be presented in this section since it is the sponsor's primary fixed dose study and the results are consistent with a smaller fixed dose study (B202). The inclusion of the combination study (B351) here makes the label confusing and overly cumbersome. In addition to means, a measure of variance (SD or SE) should be presented.
3. The treatment effects for naïve and previously treated patients are similar and do not warrant separate mention in the label (see page 30 and Appendices 1 and 2 of this review).
4. The modified sample sizes under Study A in the label do not match the sample sizes I obtained from the dataset I received from the sponsor.

Combination with Metformin

1. The results for Studies B351 and B354 are mentioned in this section but the results for B351 are actually shown in the previous section. The results for B351 should be moved from the Monotherapy section to this section.

The combination of the two drugs demonstrated an 84% responder rate based on a reduction of >10% from pretreatment baseline HbA_{1c}.

2. The above statement should not be included since this responder analysis was considered as only an exploratory analysis in the protocol. This definition of responder is not widely acceptable and probably has not been used in other labels for Type 2 diabetes drugs. Using a responder definition provided by the medical reviewer (HbA1c<6.5% at endpoint), the rate for the combination is 33%; much less than the 84% reported by the sponsor.

3. The revised sample sizes reported for Study B354 do not match the sample sizes that this reviewer obtained from the database. The crossed-out sample sizes are the correct numbers.

Other

In a 24-week active controlled study, patients who were stabilized on high dose sulfonylurea for at least three months and directly switched to monotherapy with Starlix 60 or 120 mg before meals experienced reduced glycemic control as evidenced by increases in FPG and HbA_{1c}.

In a 12-week study of patients inadequately controlled on glyburide 10 mg once daily, the addition of Starlix 120 mg before meals did not produce any additional benefit.

1. I recommend adding the word " [redacted] " before the word " [redacted] " in the first paragraph.

2. The language is too weak here in that patients switched from a sulfonylurea to nateglinide alone or in combination with metformin do very poorly (see results for Studies B304, B251 and B252, Figures 8, 23 and 26 and Tables 39 and 40).

Overall Conclusions

The sponsor has demonstrated with fixed dose Studies B202 and B302 that doses of 60, 120 and 180 mg significantly decrease HbA1c in naïve as well as previously treated patients compared to placebo. The highest dose of 180 mg appears to offer additional benefit to heavier patients, patients with diabetes for more than 3 years and older patients; therefore, this reviewer would recommend (assuming no safety issues) approving the 180 mg dose even though generally it appears to offer only a small benefit over the 120 mg dose.

Combination therapy of metformin plus nateglinide 120 mg significantly reduces HbA1c compared to metformin alone when patients are poor responders to metformin alone (Study B354) or diet alone (Study B351).

The extension data was inadequate to establish the maintenance of glycemic control in nateglinide-treated patients due to the large number of dropouts and to the short-comings of the extension study design.

Replacing a sulfonylurea with nateglinide (Studies B252 and B304) in patients who are poor responders to the sulfonylurea results in a significant loss in glycemic control and should not be recommended and should be warned against.

The Clinical Trials section of the labeling needs considerable revising and is grossly inadequate as submitted.

/S/

Joy D. Mele, M.S.
Mathematical Statistician

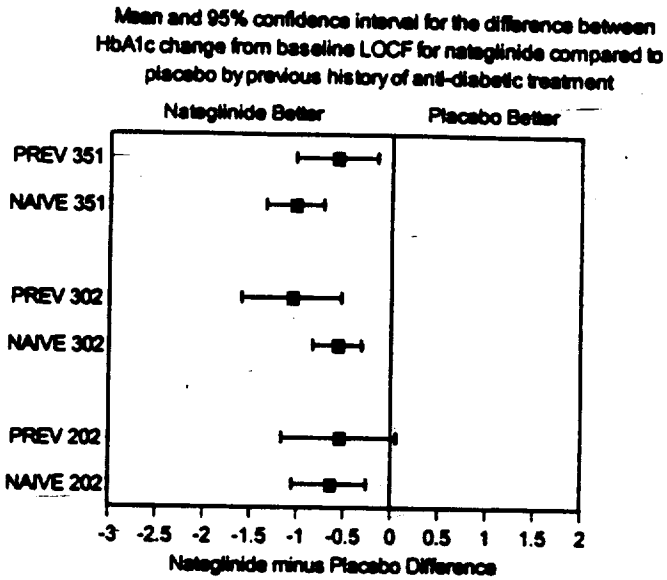
Concur:

Todd Sahlroot, Ph.D. /S/ 11/9/00
Team Leader

Ed Nevius, Ph.D. /S/ 11-8-00
Director of DOB2

cc:
Archival NDA#21-204
HFD-510
HFD-510/SMalozowski,BKoller,JWeber
HFD-715/Division 2 File, Chron, JMele, TSahlroot
Mele/x76376/DOB2/Word-starrev.doc/October 10, 2000

Appendix 1.
HbA1c change from baseline treatment differences for previously treated and naïve patients in Studies B202, 302 and 351 comparing nateglinide 120 mg to placebo



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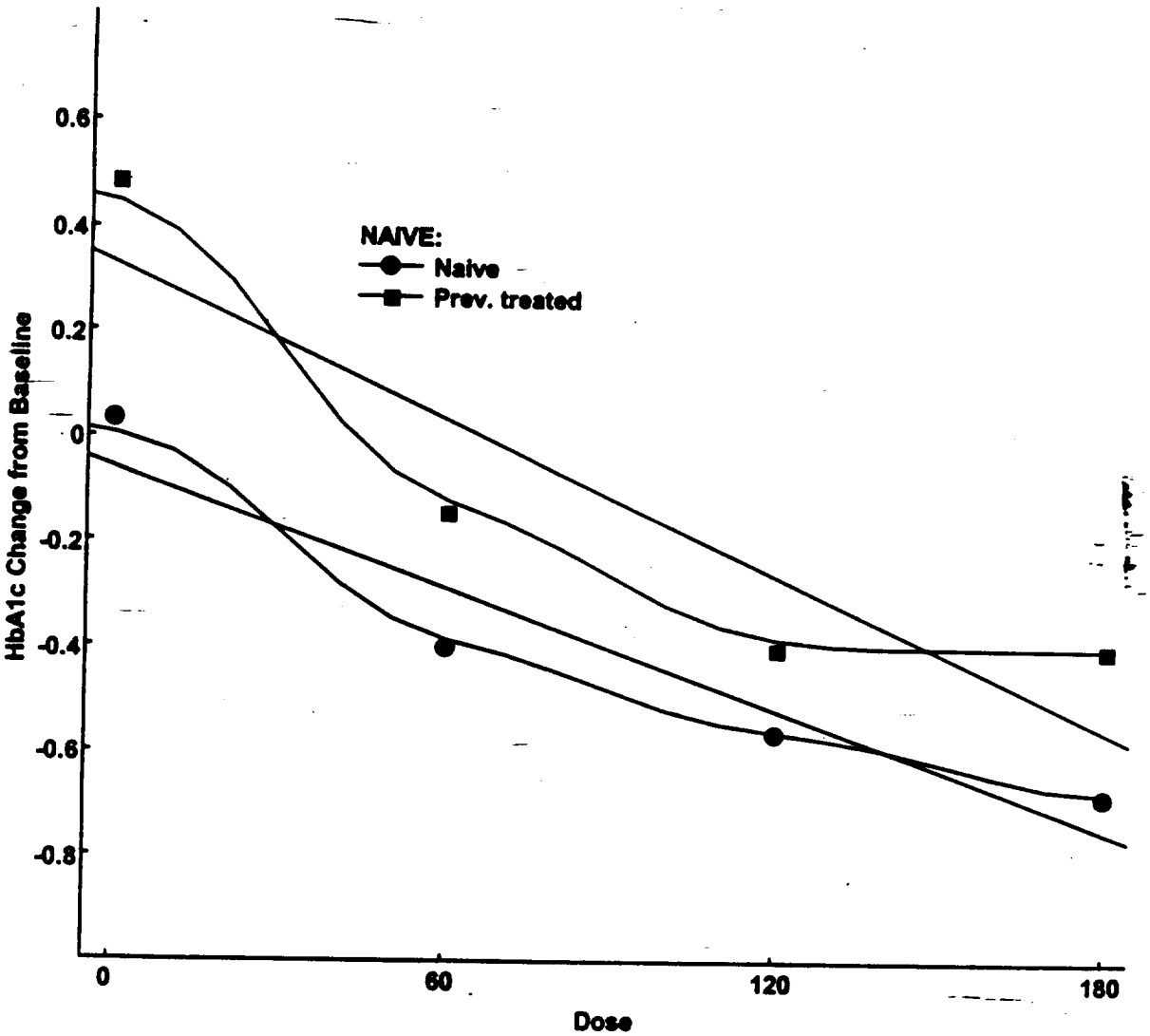
Appendix 2.

Dose Response for previously treated patients and naïve patients with fixed dos
Studies B202 and B302 combined



Appendix 3.
Relationship of weight change and HbA1c change for fixed dose Study B302