CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-357/S019

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

JUN 2 7 2000

NDA#: 20-357/SE5-019

Applicant: Bristol-Myers Squibb Company

Name of Drug: Glucophage Tablets® (metformin hydrochloride)

Indication: An adjunct to diet to improve glycemic control in patients with NIDDM[1], whose hyperglycemia cannot be satisfactorily managed by diet alone

Document Reviewed: Vols. 68.1-68.12
Submission dated February 15, 2000
Pediatric Study Reports (Pediatric Exclusivity)

Medical Reviewer: Robert Misbin, M.D. (HFD-510)

Background:

Glucophage (metformin HCl tablets) is an oral antihyperglycemic agent approved for the management of type 2 diabetes as monotherapy and concomitant use with a sulfonylurea or insulin for adults. For pediatric diabetes, insulin is the current standard of care. This submission provides for a new indication of metformin in the pediatric population.

Controlled Clinical Studies:

Study CV138-039 was a multicenter, randomized, double-blind, placebo controlled study of the efficacy and safety of metformin hydrochloride for the treatment of pediatric subjects with type 2 diabetes mellitus for 16 weeks. The primary endpoint was change from baseline in fasting plasma glucose (FPG) at 16 weeks of double-blind treatment. The study was conducted in 56 sites in the U.S., Russia, Ukraine, Belorussia and Poland from September 30, 1998 to November 24, 1999. The 16-week double-blind treatment period was followed by a 48-week open-label period.

In the sample size determination, a total of 72 subjects (36 subjects per treatment group) were to provide 80% power to detect a 40 mg/dl difference in mean change from baseline in FPG between the metformin and placebo groups at a 2-sided 0.05 significance level assuming a standard deviation of 60 mg/dl. 72 pediatric subjects (8-16 years of age) had confirmed newly diagnosed or previously diagnosed Type 2 diabetes mellitus, a FPG≥126 mg/dL and ≤240 mg/dL, and HbA_{1c} ≥7.0% at screening.

Protocol amendment #1 revised the upper limit of FPG for entry into the study from 180 mg/dL to 240 mg/dL to improve the chance of detecting a difference between the metformin and the placebo treatments. The

[1] NIDDM: non-insulin-dependent diabetes mellitus

required days off oral therapy prior to study entry was revised from 14 days to 28 days.

In Amendment #2 (March 23, 1999), the minimum age for inclusion was reduced from 10 years of age to 8 years of age. In addition, an interim analysis was instituted at the end of the week 8 double-blind period in 36 subjects. The purpose of the interim analysis was to minimize exposure of pediatric subjects with type 2 diabetes to placebo treatment. The one interim analysis was planned after 36 randomized subjects (½ of sample size) completed the last double-blind visit at or prior to Week 8 (½ of week 16). A Group Sequential Test (Fleming, Harrington, and O'Brien, CCT, 1984) with the 2 p-values of 0.025 for the interim analysis and 0.03355 for the final analysis preserved an overall 2-sided significance level of 0.05. The Data Safety Monitor Board (DSMB) was to make the overall recommendation after considering all available data.

In the double-blind treatment phase, the weekly titration of dose started with 2 tablets daily to a maximum of 4 tablets daily with back-titration if a subject was intolerant.

Subjects were rescued according to the capillary glucose threshold of ≥ 230 mg/dl at Week 2, ≥180 mg/dl at Week 4, and ≥140 mg/dl at Weeks 6-16.

Interim Analysis

The interim cohort included subjects who had completed or had potentially completed the Week-8 visit by the cutoff date of September 20, 1999 and had a baseline and at least one post-baseline efficacy measurement. Based on the interim analysis, the double-blind period was terminated early by the sponsor at the recommendation of the DSMB and agreement by FDA. All remaining subjects were switched to open-label metformin by November 25, 1999. Table 1 displays the disposition of subjects at interim analysis.

Table 1 Disposition of subjects at interim

	J	K
Randomized	28	32
No potential Week 8 data	6	9
No Follow-up	2	4
Interim Cohort	**20**	**19**
Rescue	14 (70%)	3 (16%)
Prematurely discontinued	1 (5%)	1 (5%)
Completed Week 8	4 (20%)	16 (84%)

The analysis of covariance result is displayed in Table 2.

Table 2 Interim analysis of FPG (mg/dl)

	J	K	Difference
Baseline Mean (SD)	206.6 (54.6)	169.0 (49.3)	
Last Double-Blind Visit	214.2 (76.2)	128.9 (35.1)	
Adjusted Mean Change (SE)	17.4 (12.8)	-50.4 (13.2)	67.8 (18.4) p=0.001

Final Analysis

Disposition of Subjects

A total of 481 subjects were screened, of which 82 subjects (62 in the U.S. & 20 in Europe) were randomized and received treatment, 42 in the metformin group and 40 in the placebo group. Table 3 displays subject disposition.

Table 3 Disposition of Subjects

Patient Status	Metformin	Placebo	
Screened			481
Randomized	42	40	
Discontinued	6 (14.3%)	4 (10.0%)	
Required Rescue	4 (9.5%)	26 (65.0%)	
Unblinded following interim	13 (31.0%)	7 (17.5%)	
Completed 16-Week	19 (45.2%)	3 (7.5%)	

Approximately 70% (57) of the 82 randomized subjects were females and 30% were males. The mean age was 13.8 years (range 10, 17) and 60% (49/82) were 14 years or older. The race was 37% White, 29% Black, 22% Hispanic/Latino, 5% Asian/Pacific Islander, and 7% Other. The mean body mass index was 34.1 kg/m^2 (range 18.1, 82.2). The median weight was 88.8 kg (range 32, 196.4). The mean baseline FPG was greater in the placebo groups (198.5 mg/dl) than the metformin group (166.6 mg/dl), and so was the baseline mean HbA_{1c} (9.0% placebo and 8.3% metformin). Fifty percent (20/40) of subjects in the placebo group and 21% (9/42) of metformin subjects had baseline FPG ≥ 200 mg/dl.

Eighty-three percent of the metformin-treated subjects and 77.5% of the placebo-treated subjects received 200 mg/day as a final dose during double-blind therapy.

Efficacy Analysis

Primary Efficacy Variable - FPG (mg/dl)

The analysis of covariance was performed on change in FPG from baseline at Week 16 or last double-blind visit (Table 4). At baseline the mean FPG in the placebo group was higher than the mean FPG in the metformin group. The endpoint analysis showed that metformin was statistically significantly better than the placebo in mean change from baseline FPG. The adjusted mean FPG changes from baseline were -42.9 mg/dl and 21.4 mg/dl for the metformin and placebo treated subjects, respectively.

Table 4 ANCOVA analysis of FPG (mg/dl) at Week 16 or last double-blind visit

	Metformin N=37		Placebo N=36		Difference (metformin-placebo)	
Baseline Mean FPG (SD)	162.43	(48.72)	192.33	(49.09)		
Endpoint Mean FPG (SD)	125.86	(39.39)	207.25	(81.65)		
LSM FPG Change from Baseline (SE)	-42.88	(9.72)	21.40	(9.86)	-64.28	(14.16)
95% CI					(-92.52	-36.04)
p-value						<0.001

The change from baseline to Week 16 FPG by baseline FPG is displayed in Figure 1 and the box plot of the change from baseline FPG is displayed in Figure 2.

Figure 1 Change from baseline to Week 16 FPG (mg/dl) by baseline FPG

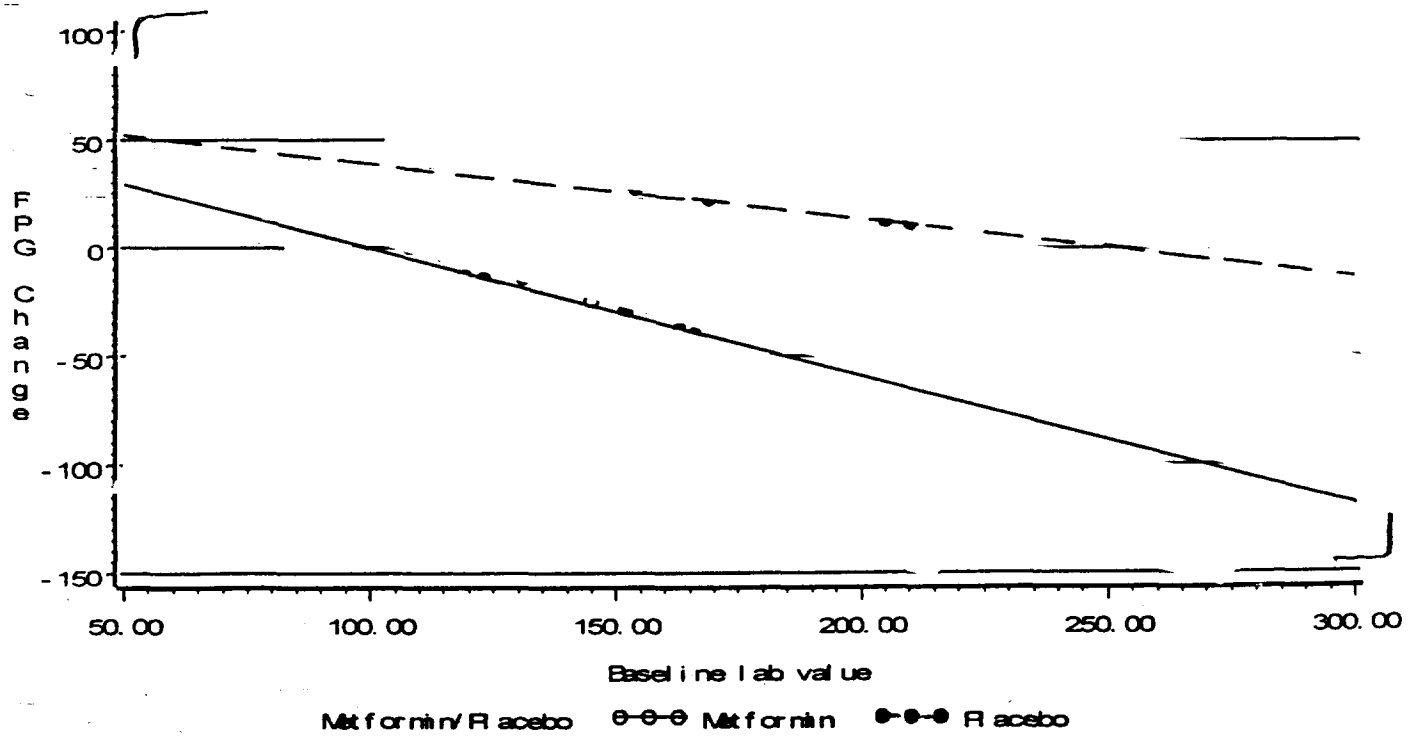
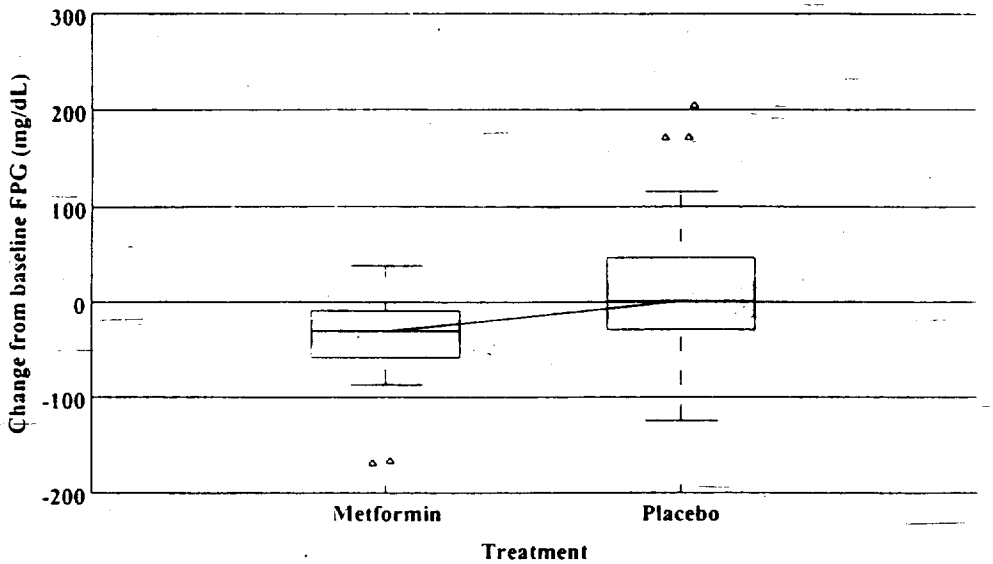


Figure 2 Box plot of median FPG change from baseline to week 16 - ITT



Change from baseline FPG (mg/dl) to Week 16 or prior	Metformin n=37	Placebo n=36
25th pct	-58	-29
Median	-30	2
75th pct	-8	47

Subgroup Analysis

The change from baseline FPG was analyzed for subgroups of gender and race. The results are displayed in Table 5. The sponsor applied analysis of covariance (baseline as covariate) to the subgroups separately. This reviewer used all randomized subjects in the analysis of covariance (baseline and subgroup as covariates).

Table 5 Summary of subgroup analysis

Subgroup		Metformin			Placebo	
	n	Adjusted Mean	(S.E.)	n	Adjusted Mean	(S.E.)
Gender						
Male	11	-40.52	17.79	10	28.54	18.60
Female	26	-43.84	11.65	26	18.63	11.70
Race						
White	15	-33.49	15.08	13	28.18	16.34
Black	10	-51.19	18.65	10	12.06	18.68
Hispanic/Latino	7	-55.79	22.43	9	3.87	19.51
Other	5	-39.37	26.42	4	65.97	29.36

Conclusion:

The study showed metformin was superior to placebo in reduction in FPG in pediatric subjects (10 to 16 years of age). The metformin-treated subjects had a mean reduction of 43 mg/dl of FPG from baseline (162 mg/dl) to Week 16 or endpoint (126 mg/dl) while the placebo-treated subjects had a mean increase of 21 mg/dl from baseline (192 mg/dl) to Week 16 or endpoint (207 mg/dl).

/S/

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Concur: Dr. Sahlroot /S/ 6/19/00

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cc: Archival NDA 20-357
HFD-510/RMisbin, JWeber
HFD-715/Division file, TSahlroot, LPian
Chron.