CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-866

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-866
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Indication(s):	Treatment of Type 2 Diabetes Mellitus
Applicant:	VeroScience, LLC
Date(s):	April 13, 2008
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1. EXECUTIVE SUMMARY

VeroScience submitted a complete response (CR) to the New Drug Application (NDA) 20-866 approvable letter dated October 15, 1999 . The CR consisted of 3 submissions. The Cycloset Safety Trial (165-AD-04-03-US-1) study report was submitted on December 12, 2007 as amendment # 27. Electronic datasets were submitted on March 07, 2008 as amendment #28. The CR to FDA approvable letter of Cycloset for type 2 diabetes (Amendment #29) was filed on April 13, 2008 to address all other issues listed in the approvable letter.

The original NDA was filed on August 18, 1997 by Ergo Research Corp. A not approvable letter citing deficiencies of efficacy and safety was issued on November 20, 1998. The company provided a complete response on April 15, 1999. An approvable letter was issued on October 15, 1999. The original submission included four multicenter, double-blind, placebo-controlled, 24-week studies in patients with type 2 diabetics to compare the glycemic control of up to 4.8 mg/day of bromocriptine to placebo in a monotherapy study and in 2 sulfonylurea add-on studies. The 4th study in obese type 2 diabetes taking doses up to 3.2 mg/day was a supportive study. The primary efficacy variable, HbA1c change from baseline, was consistently statistically significant between bromocriptine-treated patients and placebo-treated patients. The estimates for treatment difference in mean HbA1c change from baseline were -0.4%, -0.5%, and -0.6% from a mean baseline of 9.3% for the monotherapy and the two sulfonylurea add-on studies, respectively. The estimate was -0.4% in the obese diabetics study. The most frequent AE (adverse event) was nausea (27% vs. 5%). For cardiovascular safety, the rate of myocardial infarction (MI) was 1.9 per 100 patient-year exposure for bromocriptine (3 cases/334) and 0.6 per 100 patient-year exposure (1 case/329) for placebo. Due to safety concerns, the Agency issued an approvable letter on October 15, 1999 requesting the sponsor to conduct a safety study of bromocriptine in patients with type 2 diabetes. The primary safety endpoint of the safety study was the rate of all-cause SAEs (Serious Adverse Events) using person-year as the primary measure of exposure to study treatment. The non-inferiority of bromocriptine to placebo in hazard ratio was assessed using a margin of 1.5. The secondary endpoints were: (1) the rate of serious cardiovascular adverse events (i.e. revascularization, myocardial infarction, inpatients hospitalization for heart failure or angina, and stroke) and (2) the rate of each of these specific SAEs.

Subsequent to the original submission, the ownership of the NDA was transferred and the manufacturer changed for the study drug (Table 1). VeroScience completed the safety study 165-AD-04-03-US-1 in January of 2007 and unblinded the dataset on May 25 of 2007.

Table 1 NDA timeline

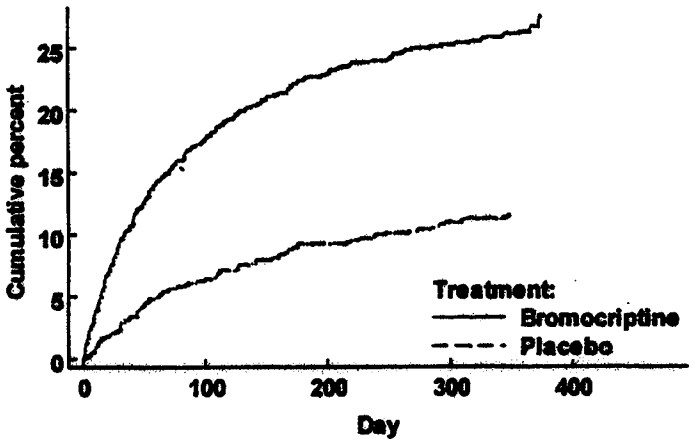
	Date	Sponsor	Manufacturer
Filing	8/18/97	ErgoScience	Geneva (Broomfield, CO)
Approvable	10/15/99		
NDA Transfer	11/03	PLIVA	PLIVA (Zagreb, Croatia)
Safety trial initiation	7/04		
IND, NDA	5/06	VeroScience(Tiverton,	Patheon (Cincinnati, OH) to-be-

	Date	Sponsor	Manufacturer
Transfer		RI)	marketed upon NDA approval
Safety trial completion	1/07		

A bioequivalence study, BON-P6-262 was conducted to bridge the Patheon-manufactured and PLIVA-manufactured tablets. However, product manufactured by Geneva for the original NDA was no longer available; therefore, FDA agreed to a clinical efficacy bridge between an efficacy subset of the safety study (165-AD-04-03-US-1) and efficacy data from the Phase 3 studies in the original NDA.

Study 165-AD-04-03-US-1 was a one year safety study of a diverse type 2 diabetic patient population. Patients were randomized to bromocriptine or placebo in a ratio of 2:1. Of the 3070 ITT patients, 42% (1283) discontinued; 47% (961/2054) of bromocriptine patients discontinued and 32% (322/1016) of placebo patients discontinued ($p<0.01$). Half of the bromocriptine discontinuations were due to adverse events (24%) compared to 1/3 of the placebo discontinuations. The HR [95% CI] was 2.6 [2.1, 3.2]. Figure 1 displays the cumulative percent of AE discontinuations by days on treatment.

Figure 1 Cumulative percent of patients with AE discontinuation



Primary and secondary variables:

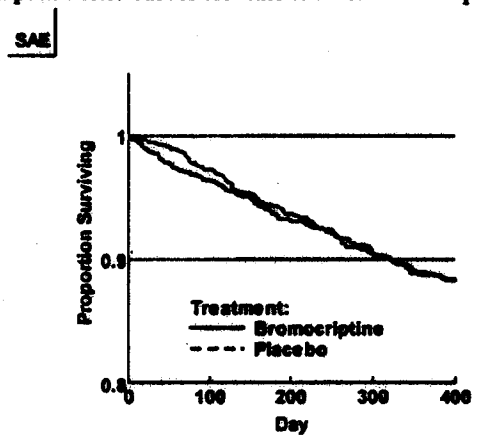
Table 2 displays the analysis results of time to 1st SAE for the primary (all cause serious) and the secondary (composite CV serious) safety variables.

Primary variable – time to 1st SAE

A total of 285 patients had at least one SAE: one before treatment, 274 during treatment and 10 after treatment. The primary objective was to demonstrate non-inferiority of bromocriptine to placebo on the hazard ratio (HR) for SAEs. The prespecified non-inferiority margin was HR=1.5.

Treatment groups were compared on time to first SAE using the logrank test. The hazard ratios (one-sided 96% CI) were 1.02 (0.79, 1.33) for the intent-to-treat (ITT) population and 1.10 (0.84, 1.50) for the PP (per protocol) population. The percentages of SAE were 8.6% (176/2054) in the bromocriptine group and 9.7% (98/1016) in the placebo group. Figure 2 displays the Kaplan-Meier curves for all-cause SAEs.

Figure 2 Kaplan-Meier curves for time to 1st SAE – ITT population



Secondary variables – Composite and individual components of cardiovascular SAEs

The secondary variables included a composite CV SAE and its components; MI, stroke, inpatient hospitalization for angina, inpatient hospitalization for heart failure and coronary revascularization surgery. The HRs (bromocriptine/placebo) for time to 1st CV SAEs were all less than 1 from a Cox proportional hazards analysis (Table 2).

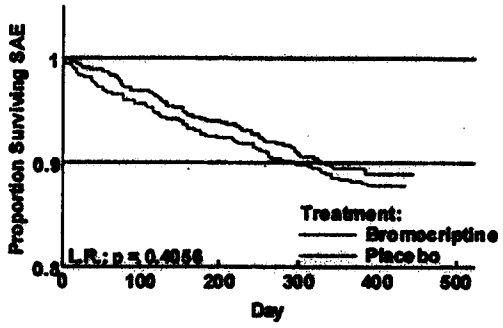
Table 2 Time to 1st SAE analysis for primary and secondary safety variables

	Bromocriptine		Placebo		HR	1-sided CI	
	#	%	#	%		lower	upper
Primary variable						96% CI	
all-cause serious AE	176	(8.57)	98	(9.65)	1.02	[0.82,	1.27]
Secondary variable						97.5% CI	
serious composite cardiovascular AE	31	(1.51)	30	(2.95)	0.58	[0.35,	0.96]
Components of secondary endpoint							
myocardial infarction	6	(0.29)	8	(0.79)	0.44	[0.15,	1.26]
stroke	4	(0.19)	6	(0.59)	0.37	[0.10,	1.32]
inpatient hospitalization for angina	9	(0.44)	9	(0.89)	0.55	[0.22,	1.38]
inpatient hospitalization for heart failure	7	(0.34)	5	(0.49)	0.81	[0.26,	2.57]
revascularization surgery	9	(0.44)	6	(0.59)	0.85	[0.30,	2.40]
revascularization surgery as SAE outcome	9	(0.44)	10	(0.98)	0.51	[0.21,	1.24]

Figure 3 displays time to 1st SAE analysis in the per protocol population. The event rates are 139/1153 (12.1%) in the bromocriptine group and 78/717 (11.8%) in the placebo group. The HR [95% CI] was 1.1 [0.9, 1.5].

Figure 3 Kaplan-Meier curves for time to 1st SAE – PP population

EPP
Y



1.1 Conclusions and Recommendations

Cycloset was non-inferior to placebo on the primary safety endpoint, time to first all-cause SAE, with a HR of 1.02 and a one-sided 96% upper confidence limit of 1.27 which was within the 1.5 non-inferiority margin. The incidence rates for SAEs were 9.6% for placebo and 8.6% for cycloset. For the secondary safety endpoint, composite cardiovascular SAEs, the HR was 0.58 and the upper confidence limit was 0.96 for the 97.5% CI. The incidence rates were 3.0% for placebo and 1.5% for Cycloset. The individual components of the composite CV endpoint were consistent with the composite CV endpoint (HR<1). The HRs for the 3 components MI, stroke and inpatient hospitalization for angina, were 0.44, 0.37 and 0.55, respectively. The upper confidence limits for the 97.5% CI were all within the 1.5 non-inferiority margin (1.26, 1.32, and 1.38, respectively). The HRs for inpatient hospitalization for heart failure and coronary revascularization surgery were 0.81 and 0.85, respectively, with upper 97.5% confidence limits of 2.57 and 2.40, respectively.

The dropout rates were high in this one-year safety study, 47% (961/2054) in the cycloset group and 31% (322/1028) in the placebo group. The primary reason for dropouts was AE; 24% (498/2054) in the cycloset group and 10% (107/1028) in the placebo group. This differential high dropout rate complicates the process of estimating without bias the true hazard ratio. Therefore, the claim in the label that '[redacted] is unwarranted. b(4)

With respect to efficacy subsets for the purpose of bridging the current trial product to the early phase 3 trials, bromocriptine was superior to placebo in HbA1c change from baseline to week 24. For the 24-week completers, the least squared mean differences [95% CI] between

bromocriptine group and placebo group were -0.59% [-0.8, -0.37] for all patients with a screening HbA1c ≥7.5% and -0.68 [-0.98, -0.39] for the metformin/sulfonylurea subset (Table 19). The mean differences were -0.43% [-0.62, -0.24] for the bridging subset and -0.43 [-0.69, -0.17] using the last-observation-carried-forward data (Table 27).

1.2 Brief Overview of Clinical Studies

In this complete response to the approval letter to NDA, a large simple cycloset safety study was conducted. The proposed indication is treatment of type 2 Diabetes Mellitus. The study was a randomized, doubled-blind, placebo-controlled trial for 12 months in 74 centers across the U.S which included 17 centers from the U. S. Veteran Affairs Healthcare System. The study was to assess safety and tolerability during treatment of type 2 diabetes comparing usual diabetes therapy (UDT) plus Cycloset or UDT plus placebo. A total of 3095 patients were randomized in a 2 to 1 ratio; 2067 to the cycloset group and 1028 to the placebo group. The primary variable was time to first all-cause SAE and the secondary variables were a composite CV SAE and its components which were MI, stroke, inpatient hospitalization for angina, inpatient hospitalization for heart failure and coronary revascularization surgery. The non-inferiority margin for the hazard ratio (cycloset/placebo) was 1.5.

1.3 Statistical Issues and Findings

In the study, there were discrepancies between the protocol and the statistical analysis plan (SAP) in the definition of the primary endpoint and the procedure for interim analysis. The protocol defined the rate of all-cause SAEs as 'the total number of all-cause SAEs while on study treatment or within 30 days of last study treatment dose, divided by the total number of person-years of exposure to study treatment.' (p.101, Section 16.1.1 Appendix). The primary endpoint defined in the SAP was 'the time from first treatment dose to first SAE for each patient while exposed to study treatment....' (p. 199, Section 16.1.9). In meeting minutes dated February 13, 2007, the FDA response to sponsor question 1 requesting FDA review and concurrence of the SAP were 'As requested in the meeting minutes on April 6, 2000, near complete follow-up will be critical with ascertainment of vital and critical status, including myocardial infarction (MI), stroke and death. The submission should include documentation of all events including events following a time-to-event endpoint and events occurring following discontinuation of study drug'. Furthermore, 'Analyses of primary and secondary endpoints are time to event analyses of the hazard ratio between cycloset and placebo. As a sensitivity analysis, incidence rates should be compared between cycloset and placebo using risk ratios.'

One interim analysis and a futility analysis were scheduled at the same time for the primary safety endpoint, all-cause SAEs, when the last patient completed 6 months of study treatment. The objective was to determine whether the hypothesis of non-inferiority of UDT plus Cycloset as compared to UDT plus placebo has been demonstrated. The non-inferiority margin was defined as hazard ratio of 1.5.

In the protocol, Pocock's alpha spending function was proposed to preserve the overall type 1 error rate. The assumption was that 80% of the total person-years exposure to study drug would have been observed at the interim look. The 2-sided Type 1 error rates at the interim and final

analyses were determined to be 0.086 and 0.014, respectively. The 2-sided confidence intervals were 91.4% and 98.5%, respectively.

In the SAP, the Lan-Demets alpha spending function for allocating alpha to O'Brien-Fleming boundaries was used with the overall 1-sided significance level of 5% (0.1, 2-sided, this significance level was agreed to by the Agency). A 1-sided alpha value of 0.04068 (0.081, 2-sided) was used at the interim analysis and 0.03938 (0.079, 2-sided) at the time of the final analysis. The corresponding 2-sided confidence intervals for the rate ratio were 91.9% for the interim and 92.1% for the final analysis. At the final analysis, the 98.5% confidence interval of Pockock is wider than and therefore, more likely to exceed the 1.5 non-inferiority margin than the 92.1% confidence interval of O'Brien-Fleming.

The sponsor conducted a Cox proportional hazard analysis of time to first SAE as the primary analysis and Poisson regression of total events over person years of exposure as an exploratory analysis (Table 3).

The HRs from the Cox regression and the Poisson regression were consistent.

Table 3 Sponsor's analyses on time to 1st SAE and Poisson SAE event rate analysis

	Cycloset	Placebo	Hazard Ratio (1-sided, upper 96% CL)
n	2054	1016	
# patient with ≥1 SAE	176	98	
Incidence rate (%)	**8.6%**	**9.6%**	**1.02 (-, 1.27)-Cox regression**
# total SAE	241	128	
Adjusted Person-Years	1538.2	883.4	
Event Rate/100 Person-Years	**15.67**	**14.49**	**1.08 (-, 1.38)-Poisson regression**

2. INTRODUCTION

2.1 Overview

Bromocriptine mesylate, an ergot derivative, is a dopamine receptor D_2 agonist that enhances dopamine release. The proposed indications are: a) monotherapy or b) adjunctive therapy to oral hypoglycemic agents or insulin for glycemic control in patients with type 2 diabetes. NDA 20-866 was filed on August 18, 1997. An approvable letter was issued by the Agency on October 19, 1999 requiring a large safety trial for approval. In May 2006, the sponsor submitted a Statistical Analysis Plan for this safety study to evaluate efficacy of the new manufactured medication in 4 prespecified subgroup populations within the overall trial design (Table 4).

The purpose of these efficacy analyses was to establish similarity of the efficacy of the newly manufactured product used in the safety study to the efficacy of the drug product shown to be effective in the original NDA program.

Table 4 Phase 3 studies and one pilot add-on to insulin study

Study	Adjunct therapy	

Study	Adjunct therapy	
M	monotherapy	24-week
K	sulfonylurea	24-week
L	sulfonylurea	24-week
Safety Trial subsets	1. any or two OHAs 2. sulfonylurea with or without another OHA 3. metformin with or without another OHA 4. metformin and sulfonylurea	24-week
1-97-2.1	insulin	12-week

2.2 Data Sources

The electronic datasets for the safety study are located at the following links:

\\FDSWA150\NONECTD\N20866\N_000\2008-03-07

\\FDSWA150\NONECTD\N20866\N_000\2008-06-25

The following link is for the electronic dataset of the insulin sensitivity study #1-96-2.2:

\\Fdswa150\nonectd\N20866\N_000\2008-09-24

3. STATISTICAL EVALUATION

3.1 Evaluation of Safety

The sponsor submitted 2 'final' versions of the protocol, dated June 16, 2004 and April 26, 2005. A Statistical Analysis Plan (SAP) was last updated on January 4 2007. In this review the SAP analysis plan supersedes the analysis in the protocols.

Study Design and Endpoints

The study was a randomized, doubled-blind, placebo-controlled trial for 12 months to assess safety and tolerability during treatment of type 2 diabetes comparing usual diabetes therapy (UDT) plus Cycloset or UDT plus placebo. The study was conducted the U.S.

Prior to randomization, a screening evaluation (week -2) was to confirm that the patient had an HbA1c <10% within 3 months of the Screening visit, and a 2-week baseline lead-in period in which the dosage of patient's screening therapy may be adjusted and to apply the package insert recommendations and warnings as part of usual care (e.g. liver function tests for patients on thiazolidinediones).

Following a 2-week lead-in period, up to 3300 patients were to be randomized in a 2:1 ratio (2200 to Cycloset and 1100 to placebo) in anticipation of 2000 bromocriptine patients and 1000 placebo patients completing the study at week 52 of which the first 6 weeks was a dose titration period. The enrollment was planned in 50-100 US clinical centers including 19 centers from the Veteran Affairs Healthcare System. All patients continued with diet and exercise therapy.

The UDT regimen consisted of either diet, oral hypoglycemic agents (no more than 2), or insulin (with no more than 1 oral hypoglycemic agent). A patient's usual care diabetes regimen or dose of medications could change during the course of the trial based on the quarterly HbA1c tests that followed the ADA guidelines (January, 2005). However, patients could not take more than 2 diabetes medications during study. An oral agent could be added for patients on diet, one non-study oral agent, or insulin monotherapy. If patients were on two non-study oral agents, insulin could be substituted for one of the oral agents. The dose of insulin could be increased at any time.

The main inclusion criteria were 30-80 years of age with HbA1c<10% for ≥ 12 weeks prior to screening and Body Mass Index (BMI)<43 kg/m^2. Patients were either on diet, less than 2 oral hypoglycemic agents (OHA) or insulin (with or without one OHA) for 4 weeks prior to randomization.

Dosing:

Dosing administration was in accordance with the effective dosages administered during the pivotal Phase 3 clinical trials. During the weekly dose titration period for 6 weeks, the initial daily dose of 1 tablet (0.8 mg Cycloset or placebo) was increased by 1 tablet per week up to the target dosage level of 6 tablets per day at Week 6. Patients remained on the highest dose level tolerated. The minimum tolerated dose was 1.6 mg (2 tablets). Patients who were unable to tolerate 2 tablets of study drug per day were returned to the previous lower dosage level for one more week and rechallenged. If unable to tolerate 2 tablets by the end of the 3rd week, patients were withdrawn from the study and replaced. Doses were administered immediately with the morning meal at approximately the same time each day.

Clinical visits were at Screening (Week -1), randomization (Week 0), and follow up weeks 3, 6, 12, 24, 36 and 52.

Safety variables:

The primary variable was the rate of all-cause serious adverse events. The secondary variables included the rate of disease-specific serious cardiovascular adverse events (myocardial infarction, stroke, inpatient hospitalization for heart failure or angina, and revascularization) as well as the corresponding individual variable rates.

Other variables:

Other measurements included HbA1c, fasting plasma glucose and lipids, weight and waist circumference, blood pressure, and patient tolerability during 12 months of therapy.

Statistical analysis:

In the protocol, the primary variable was the rate of all-cause SAEs and for each treatment group it was defined as the total number of all-cause SAEs while on study treatment or within 30 days of last study treatment dose, divided by the total number of person-years of exposure to study treatment. However, in the meeting dated February 13, 2007, it was agreed that 'Analyses of primary and secondary variables are time to event analyses of the hazard ratio between cycloset and placebo. As a sensitivity analysis, incidence rates should be compared between cycloset and placebo using risk ratios.'

In the statistical analysis plan (SAP), the primary variable was the time from 1st treatment dose to 1st SAE for each patient while exposed to study treatment. The treatment exposure period was the interval between the date of 1st treatment dose to within 30 days after the end of the last course of treatment or to the date of last contact whichever is earlier. The primary analysis was to test the hypothesis that the hazard ratio (HR) of all-cause SAEs for UDT plus Cycloset is not greater than that for UDT plus placebo by more than a non-inferiority margin of 1.5.

The HR and one-sided 96.1% confidence interval (adjusted for one interim analysis) was obtained from the Cox regression model with treatment and center effects (74 centers). The treatment-by-time interaction was tested to check the proportional hazards assumption. In order to have adequate sample sizes to test the treatment-by-center effect, centers were pooled into 4 center clusters by two regions (Atlantic and Pacific) and two types of hospitals (VA and Non-VA).

Additionally, the overall rate of all cause SAE based on Poisson regression was performed to account for multiple events per person.

Also, since many AEs were recorded, further analyses were performed to assess differences between treatment groups with respect to non-serious AEs, withdrawals due to an AE, and SAEs as categorized by system organ classification.

Interim Analysis & Futility Analysis

The study had one interim analysis for the primary safety variable of all-cause SAEs when the last patient completed 6 months of study treatment. The purpose of the interim analysis was to test the hypothesis of non-inferiority of bromocriptine compared to placebo.

A planned interim analysis was conducted when the last patient completed 6 months of study treatment (July 6, 2006). Using the Lan-DeMets' alpha spending function for O'Brien-Fleming boundaries (Lan & DeMets, 1983) and an overall one-sided significance level of 5%, gave alpha levels of 0.04068 at the interim analysis and 0.03938 at the final analysis. Wald-type confidence intervals were used for the natural logarithm of the ratio of the all-cause SAE rates.

The one-sided significance level of approximately 0.04 at both the interim analysis and the final analysis was because the information fraction, 0.917 at interim was very close to 1 (see formula 1.1). The information is the number of patients with SAEs observed (265) over the total expected number of patients with SAEs. The calculation is as follows. The SAE rate was 0.1167 at the interim analysis, and the 691 patients who had not completed or had withdrawn from the study contributed 546.6 person-years up to July 6. To calculate the total expected number of patients with SAEs, the 691 patients were assumed to complete a full year plus 30 days which provides 691+691*30/365.25=747.76 person-years. There would be at most 747.76-546.6=201.16 person years remaining in the study, so the expected additional SAEs were 0.1167x201.16=23.5 (24). The information fraction is then 265/(265+24)=0.917. The O'Brien-Flemming's boundaries used the following alpha at the interim analysis.

(1.1)

$$\alpha_{interim} = 2 - 2\Phi(z_{\alpha/2}/\sqrt{0.917}) = 0.04068$$

A futility analysis using a stochastic curtailment procedure was conducted at the time of the interim analysis to calculate the conditional power of achieving non-inferiority at the end of the study given that the null hypothesis is not rejected at the time of the interim analysis. The purpose of the futility analysis was to stop early by accepting the null hypothesis that H_0: $\lambda_c/\lambda_p \geq 1.5$ if the conditional power of rejecting the null hypothesis at the final analysis is less than 20%.

The expected numbers of additional all-cause SAEs were determined from observed hazard rates at the interim analysis and the projected person years for the two treatment groups.

Sample size determination:

The sample size was based on the placebo SAE rate (per 100 patient-year) from the results of 3 previous Cycloset clinical trials (0.066), as well as 2 large studies, the United Kingdom Prospective Diabetes Study (UKPDS) (0.042) and the Antihypertensive and lipid-lowering treatment to Prevent Heart Attack Trial (ALLHAT-LLT) study (0.053). Under the assumption that patients in the current protocol had greater risk than historic data, it appeared that an 80/1000 person-year estimate was reasonable for SAE.

At a 2-sided alpha level of 0.1 and a power of 0.9 and the non-inferiority margin of 1.5, the total number of all-cause SAEs needed was 235 and the required total sample size was 2991 using a log rank test or a Poisson process. Adjusting for 10% withdrawal rate, a total of 3300 patients was planned in order to ensure 2,000 Cycloset patients and 1,000 placebo patients completing the study.

For CV SAEs, the power was 0.6 assuming a rate of 3.43% or 103 to 113 CV SAEs for a sample size of 3000 to 3300.

Data Safety Monitoring Committee (DSMC)

The responsibilities of the DSMC were to monitor the SAEs, review the interim analysis and futility analysis and to provide recommendations regarding study continuance.

Patient Disposition, Demographic and Baseline Characteristics

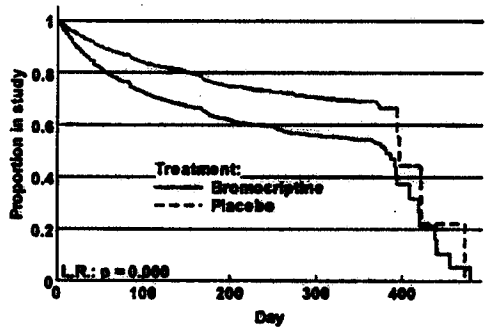
A total of 4074 patients were screened for the trial. Of these, 979 (24%) were screen failures and 3095 were randomized, 2067 to the bromocriptine group and 1028 to the placebo group in a 2:1 ratio. Twenty-five of the 3095 randomized patients were immediately dropouts and 3070 patients received at least one dose of study drug and were included in the intent-to-treat population (ITT) (Table 5).

Table 5 Patient Disposition

	Bromocriptine		Placebo		Total	
	n	%	n	%	n	%
					4074	(100%)
Screen failure					979	(24%)
Randomized	2067	(100%)	1028	(100%)	3095	(100%)
Immediate dropout	13	(0.6%)	12	(1.2%)		25 (0.8%)
ITT	2054	(99.4%)	1016	(98.8%)		3070 (99.2)
Completed	1093	(52.9%)	694	(67.5%)	1787	(43.9%)
Discontinued	961	(46.5%)	322	(31.3%)	1283	(41.4%)
Reason for discontinuation						
Death	5	(0.2%)	2	(0.2%)	7	(0.2%)
Adverse event	498	(24.1%)	107	(10.4%)	605	(14.9%)
Withdrawal of consent	187	(9.0%)	72	(7.0%)	259	(6.4%)
Other: lost to follow-up	120	(5.8%)	56	(5.4%)	176	(4.3%)
Other	77	(3.7%)	40	(3.9%)	117	(2.9%)
Protocol deviation	33	(1.6%)	27	(2.6%)	60	(1.5%)
Investigator's decision	21	(1.0%)	13	(1.3%)	34	(0.8%)
Sponsor decision	17	(0.8%)	3	(0.3%)	20	(0.5%)
Not reported*	3	(0.1%)	2	(0.2%)	5	(0.2%)

Figure 4 displays Kaplan-Meier curves for the time to discontinuation, where completers are treated as censored observations. The hazard ratio for bromocriptine to placebo for discontinuation was 1.7 (1.5, 1.9) ($p<0.01$).

Figure 4 Kaplan-Meier curves for time to drop out



The 5 'Not reported' patients were all at investigator Jambur Chandrashekar, M.D. Site # 120. Table 6 displays the disposition of patients at Site #120 which showed only one placebo patient completed the study.

Table 6 Patient Disposition – Site #120

	Bromocriptine		Placebo		Total	
	#	%	#	%	#	%
Screened					19	
Randomized	10	(100%)	5	(100%)	15	(100%)
ITT	10	(100%	5	(100%)	15	(100%)
Completed	0	(0%)	1	(20%)	1	(7%)
Adverse event	3	(30%)	0	(0%)	3	(20%)
Withdrawal of consent	1	(10%)	0	(0%)	1	(7%)
Other: lost to follow-up	3	(30%)	2	(40%)	5	(33%)
Not reported	3	(3%)	2	(40%)	5	(33%)

Table 7 displays AE withdrawals by visit week. Table 8 shows the number of deaths by visit week. Most AE withdrawals occurred at Week 52, followed by Week 12 for both treatment groups.

Table 7 Number (%) of patient discontinuation by week

	AE		Other reasons	
	Bromocriptine n=2054	Plb n=1016	Bromocriptine n=2054	Plb n=1016
	1 (0%)	1 (0.1%)	15 (0.7%)	3 (0.3%)
Week 1	28 (1.4%)	2 (0.2%)	8 (0.4%)	6 (0.6%)
Week 2	28 (1.4%)	4 (0.4%)	11 (0.5%)	10 (1%)
Week 3	50 (2.4%)	8 (0.8%)	18 (0.9%)	8 (0.8%)
Week 4	21 (1%)	5 (0.5%)	13 (0.6%)	6 (0.6%)
Week 5	17 (0.8%)	4 (0.4%)	8 (0.4%)	4 (0.4%)
Week 6	73 (3.6%)	14 (1.4%)	45 (2.2%)	15 (1.5%)
Week 12	82 (4%)	19 (1.9%)	85 (4.1%)	41 (4%)
Week 24	66 (3.2%)	13 (1.3%)	91 (4.4%)	43 (4.2%)
Week 36	29 (1.4%)	11 (1.1%)	89 (4.3%)	40 (3.9%)
Week 52	103 (5%)	26 (2.6%)	72 (3.5%)	35 (3.4%)

Table 8 Number (%) of deaths by week

Death	Bromocriptine n=2056	Placebo n=1016
Week 12	1	0
Week 24	2	1
Week 36	1	0
Week 52	1	1

Demographics & baseline characteristics:

Table 9 displays demographics and baseline characteristics. Percentages for males and females were 57% and 43%, respectively. The percentages for race were 68% Caucasians, 17% Blacks and 13% Hispanics. The mean age of patients was 60 years. 33% of patients were ≥65 years of age. The mean BMI was 32.4 kg/m^2 and the mean weight 207 lbs.

Table 9 Demographics and baseline characteristics (ITT population)

		Bromocriptine	Placebo	Total
Gender	F	913 (44.4%)	418 (41.1%)	1331 (43.4%)
	M	1141 (55.6%)	598 (58.9%)	1739 (56.6%)
Race	Asian	22 (1.1%)	10 (1%)	32 (1%)
	Black	348 (16.9%)	168 (16.5%)	516 (16.8%)
	Caucasian	1381 (67.2%)	698 (68.7%)	2079 (67.7%)
	Hispanic	277 (13.5%)	131 (12.9%)	408 (13.3%)
	Other	26 (1.3%)	9 (0.9%)	35 (1.1%)
AGE	n	2054	1016	3070
	mean (SD)	59.5 (10.2)	60.2 (10)	59.7 (10.1)
	median [min,	60 [27, 80]	60 [29, 80]	60 [27, 80]
Age group	< 35	23 (1.1%)	8 (0.8%)	31 (1%)
	35 to 49	325 (15.8%)	143 (14.1%)	468 (15.2%)
	50 to 64	1041 (50.7%)	517 (50.9%)	1558 (50.7%)
	65 to 79	651 (31.7%)	344 (33.9%)	995 (32.4%)
	>= 80	14 (0.7%)	4 (0.4%)	18 (0.6%)
BMI	n	2052	1015	3067
	mean (SD)	32.4 (5.1)	32.3 (5.1)	32.4 (5.1)
	median [min,	32.2 [13.7, 49]	32 [19.4, 42.9]	32.1 [13.7,
Waist Circumference (inches)	n	2027	1000	3027
	mean (SD)	41.8 (5.1)	42 (5.5)	41.9 (5.2)
	median [min,	42 [26, 59]	42 [26, 82]	42 [26, 82]
Fasting Plasma Glucose (mg/dl)	n	2046	1012	3058
	mean (SD)	142.1 (40.8)	141.3 (41.2)	141.8 (40.9)

		Bromocriptine	Placebo	Total
	median [min,	134 [46, 358]	133 [49, 340]	134 [46, 358]
HbA1c	n	2049	1015	3064
	mean (SD)	7 (1)	7 (1.1)	7 (1.1)
	median [min,	6.8 [3.8, 11]	6.8 [4.8, 11]	6.8 [3.8, 11]
LDL	n	1963	975	2938
	mean (SD)	98.4 (33.4)	97.1 (30.4)	97.9 (32.4)
	median [min,	94 [17, 364]	93 [20, 228]	94 [17, 364]
Duration of diabetes diagnosis	n	2053	1014	3067
	mean	7.9 (7.4)	8.0 (7.4)	7.9 (7.4)
	median [min,	5.6 [0.1, 55.3]	5.8 [0.3, 46.8]	5.7 [0.1,
(%)	< 6 months	22 (1.1%)	17 (1.7%)	39 (1.3%)
	6 months to <1	144 (7%)	79 (7.8%)	223 (7.3%)
	1 to <5 years	759 (37%)	334 (32.9%)	1093 (35.6%)
	5 to <10 years	553 (26.9%)	292 (28.7%)	845 (27.5%)
	10 to <20 years	416 (20.3%)	205 (20.2%)	621 (20.2%)
	>= 20	159 (7.7%)	87 (8.6%)	246 (8%)
	Not Reported	1 (0%)	2 (0.2%)	3 (0.1%)
Total cholesterol	n	2052	1015	3067
	mean (SD)	179.3 (43.3)	176.9 (39.3)	178.5 (42)
	median [min,	173 [80, 643]	171 [83, 393]	172 [80, 643]
Diastolic BP (mm Hg)	n	2042	1013	3055
	mean (SD)	75.7 (8.9)	76.2 (9.2)	75.8 (9.0)
	median [min,	76 [43, 110]	77 [45, 104]	76 [43, 110]
HDL	n	2052	1015	3067
	mean (SD)	46.2 (11.8)	46.1 (12.1)	46.2 (11.9)
	median [min,	45 [12, 112]	44 [16, 121]	44 [12, 121]
Pulse	n	2053	1015	3068
	mean (SD)	70.8 (10.5)	70.5 (10.3)	70.7 (10.4)
	median [min,	70 [41, 147]	70 [40, 117]	70 [40, 147]
Systolic BP (mm Hg)	n	2042	1013	3055
	mean (SD)	128 (14)	129 (13.6)	128.3 (13.9)
	median [min,	128 [85, 190]	129 [92, 180]	128 [85, 190]
Triglycerides	n	2052	1015	3067
	mean (SD)	181 (144.7)	174.8 (121.6)	179 (137.5)
	median [min,	150 [33, 2951]	147 [33, 1699]	149 [33,
Weight	n	2054	1016	3070

		Bromocriptine	Placebo	Total
	mean (SD)	207 (38.2)	207.3 (40.5)	207.1 (39)
	median [min,	205 [85, 327]	204 [102.4,	205 [85,

Table 10 displays number and percent of patients with CV related history at baseline. The percentages of stroke and revascularization surgery were significant higher in placebo than bromocriptine.

Table 10 Number (%) of patients with CV related history at baseline

	Bromocriptine n=2054	Placebo n=1016	Total n=3070	RR [95% CI] Placebo/ Bromocriptine	p
MI	186 (9.1%)	106 (10.4%)	292 (9.5%)	1.2 [0.9, 1.4]	0.22
Angina Pectoris	214 (10.4%)	101 (9.9%)	315 (10.3%)	0.95 [0.8, 1.2]	0.68
Stroke	86 (4.2%)	63 (6.2%)	149 (4.9%)	1.5 [1.1, 2.0]	0.01
Revascular Surgery	204 (9.9%)	128 (12.6%)	332 (10.8%)	1.3 [1.0, 1.5]	0.03
Hypertension	1548 (75.4%)	767 (75.5%)	2315 (75.4%)	1.0 [0.96, 1.0]	0.94
Hypercholesterolemia	1575 (76.7%)	767 (75.5%)	2342 (76.3%)	0.98 [0.9, 1.0]	0.47
Hypertriglyceridemia	853 (41.5%)	422 (41.5%)	1275 (41.5%)	1.0 [0.9, 1.1]	0.99
Other	634 (30.9%)	342 (33.7%)	976 (31.8%)	1.1 [0.98, 1.2]	0.12

Therapeutic Regimen at Screening:

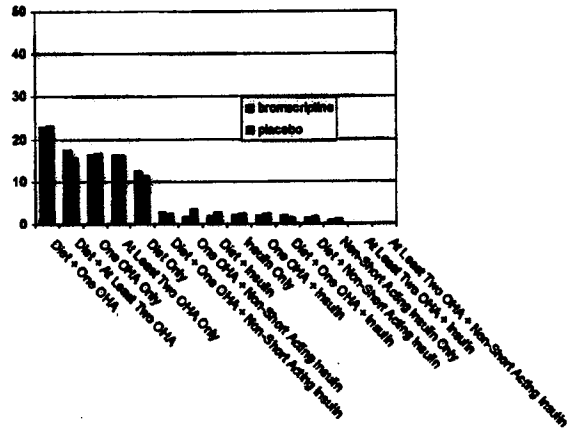
Table 11 and Figure 5 display the number and percent of patients by therapeutic regimen at screening.

Table 11 Number (%) of patients by therapeutic regimen at screening

Therapeutic Regimen at Screening	Bromocriptine		Placebo	
	n	%	n	%
Diet + One OHA	469	(22.8)	234	(23.0)
Diet + At Least Two OHA	358	(17.4)	158	(15.6)
One OHA Only	337	(16.4)	169	(16.6)
At Least Two OHA Only	328	(16.0)	165	(16.2)
Diet Only	257	(12.5)	114	(11.2)
Diet + One OHA + Non-Short Acting Insulin	54	(2.6)	24	(2.4)
One OHA + Non-Short Acting Insulin	35	(1.7)	35	(3.4)
Diet + Insulin	42	(2.0)	26	(2.6)
Insulin Only	43	(2.1)	24	(2.4)

Therapeutic Regimen at Screening	Bromocriptine		Placebo	
One OHA + Insulin	42	(2.0)	23	(2.3)
Diet + One OHA + Insulin	38	(1.9)	14	(1.4)
Diet + Non-Short Acting Insulin	29	(1.4)	16	(1.6)
Non-Short Acting Insulin Only	19	(0.9)	12	(1.2)
At Least Two OHA + Insulin	1	(0.0)	1	(0.1)
At Least Two OHA + Non-Short Acting Insulin	1	(0.0)	1	(0.1)

Figure 5 Percent of patients on screening therapeutic regimen

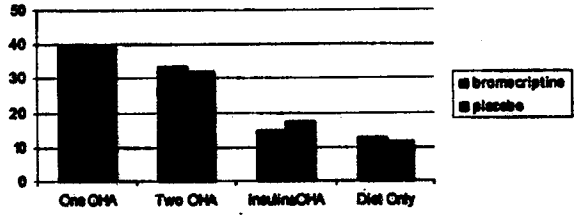


For purposes of subgroup analysis, regimens were grouped into 4 categories: one OHA, at least two OHA, any insulin use and diet only (Table 12 and Fig. 6).

Table 12 Screening therapy subgroup

Screening therapy	Bromocriptine		Placebo	
	n	%	n	%
One OHA	806	(39.3)	403	(39.7)
at least 2 OHA	686	(33.4)	323	(31.8)
Insulin±OHA	304	(14.8)	176	(17.3)
Diet only	257	(12.5)	114	(11.2)

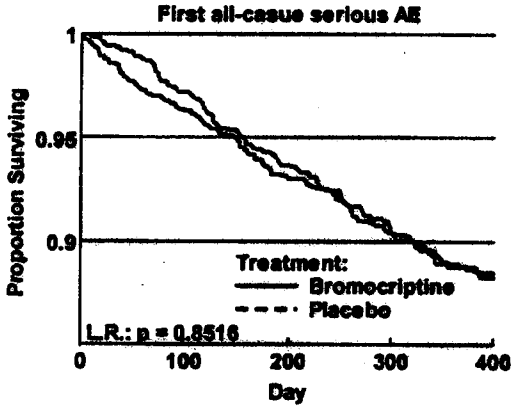
Figure 6 Percent of patients on screening therapeutic regimen

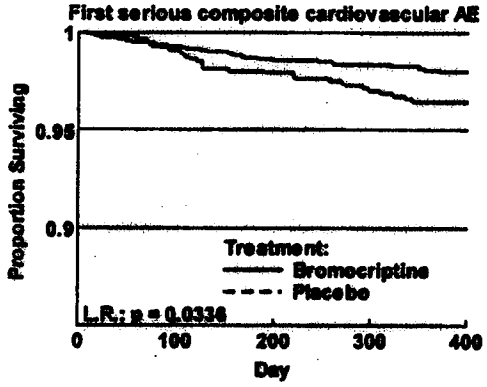


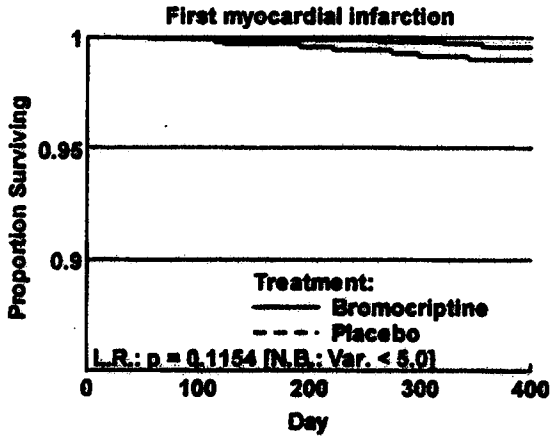
Primary (all cause) and secondary (CV) SAEs:

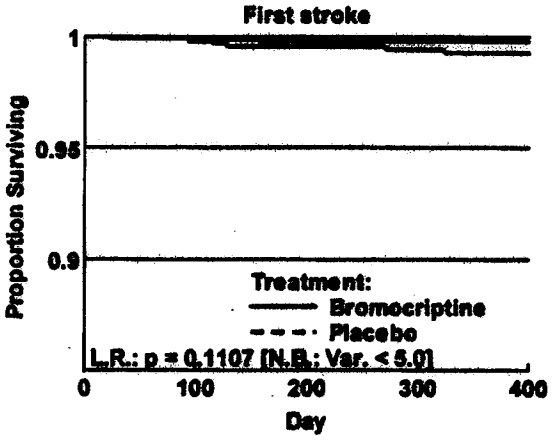
Figure 7 displays Kaplan-Meier curves for the time to 1st primary and secondary SAEs.

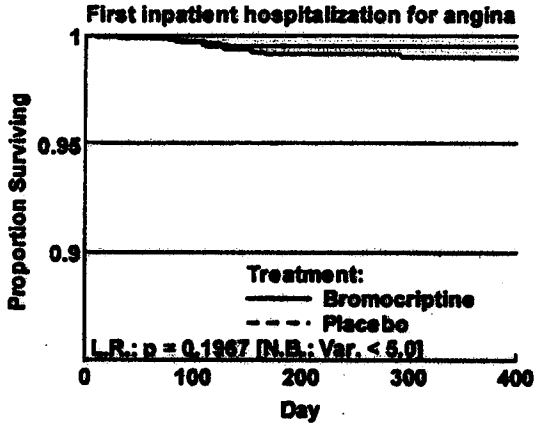
Figure 7 Kaplan-Meier curves for time to 1st SAE and composite CV SAE and components

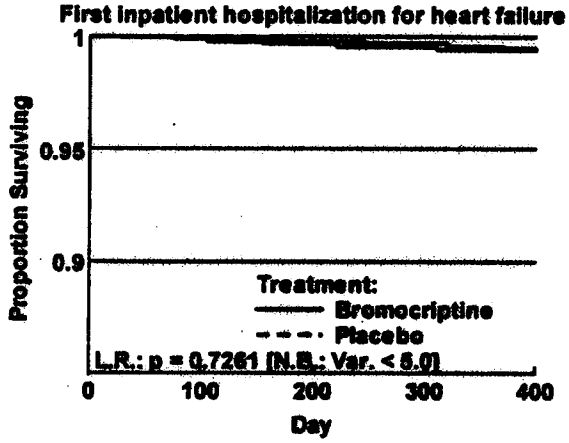


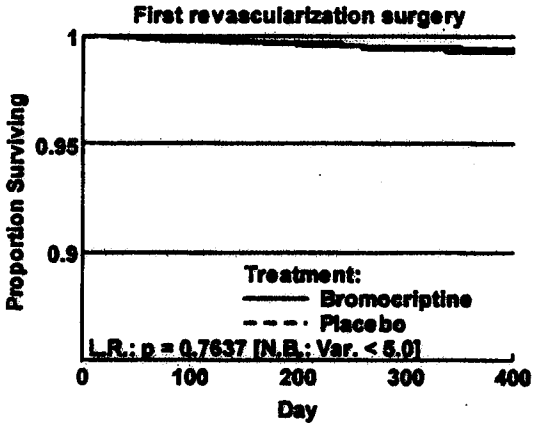



First myocardial infarction
Proportion Surviving
1
0.95
0.9
Treatment:
Bromocriptine
Placebo
L.R.: p = 0.1154 [N.B.: Var. < 5.0]
0
100
200
300
400
Day


First stroke
Proportion Surviving
1
0.95
0.9
Treatment:
Bromocriptine
Placebo
L.R.: p = 0.1107 [N.B.: Var. < 5.0]
0
100
200
300
400
Day


First inpatient hospitalization for angina
1
0.95
0.9
Proportion Surviving
Treatment:
Bromocriptine
Placebo
L.R.: p = 0.1967 [N.B.: Var. < 5.0]
0
100
200
300
400
Day


First inpatient hospitalization for heart failure
1
0.95
0.9
Proportion Surviving
Treatment:
Bromocriptine
Placebo
L.R.: p = 0.7261 [N.B.: Var. < 5.0]
0
100
200
300
400
Day



The number of SAEs before the first dose, during (before 30 days of last dose), and after 30 days following last dose of treatment were 1, 369 and 17, respectively in the ITT population.

Of the 17 SAEs occurring 30 or more days after the last dose of treatment, 12 patients (14 events) were in the bromocriptine group and 3 patients (3 events) were in the placebo group. 7 of the bromocriptine patients and 1 placebo patients discontinued their treatment early. The incidence rates were 0.3% (3/1016) for placebo and 0.58% (12/2054) for bromocriptine. Figure 8 displays the SAE start days and the preferred term of the17 cases by treatment group. The 1.04 HR with 96% CI [0.81, 1.34] for time to first SAE included the 'after treatment' events (Fig. 9).

Figure 8 After treatment SAE by event day

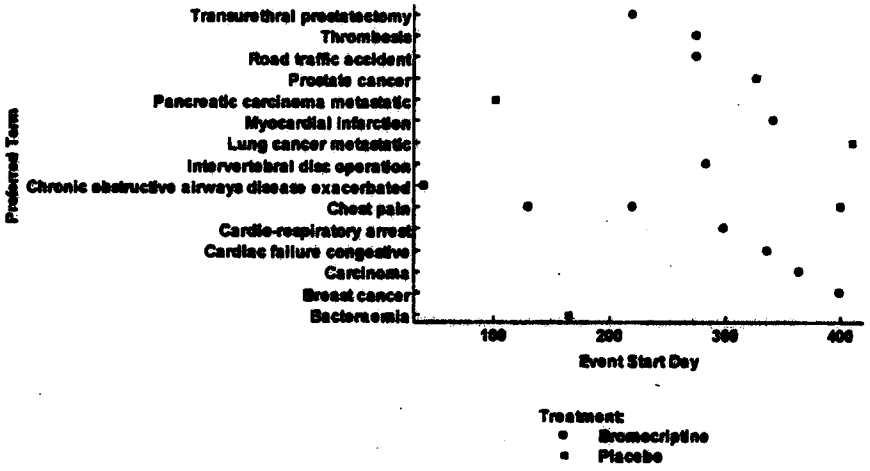


Figure 9 Kaplan-Meier curve of 1st SAE during and after treatment

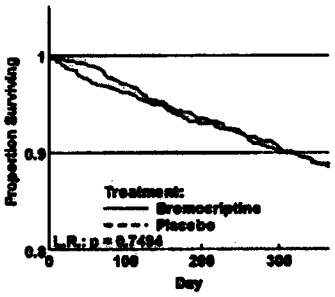


Figure 10 displays Kaplan-Meier curves for time to 1st SAE by screening diabetic therapy. The HR estimates were numerically greater for the diet only population for the primary and secondary composite variable (Table 13). Figure 11 displays the HR [CI] by screening regimen on a log scale.

Table 13 HR [CI]*by screening regimen

Screening Regimen	Diet only	Insulin	One OHA	Two OHA
n Cycloset/n Placebo	257/114	304/176	806/403	686/323
1st SAE:	2.0 [0.7, 5.4]	0.9 [0.6, 1.5]	1.1 [0.8, 1.8]	1.0 [0.6, 1.5]
1st Composite cardiovascular SAE	1.1 [0.1, 12.2]	0.7 [0.2, 2.0]	0.4 [0.2, 1.1]	0.7 [0.3, 1.5]

* 95% Wald confidence limit

Figure 10 Kaplan-Meier curve of 1st SAE by screening regimen

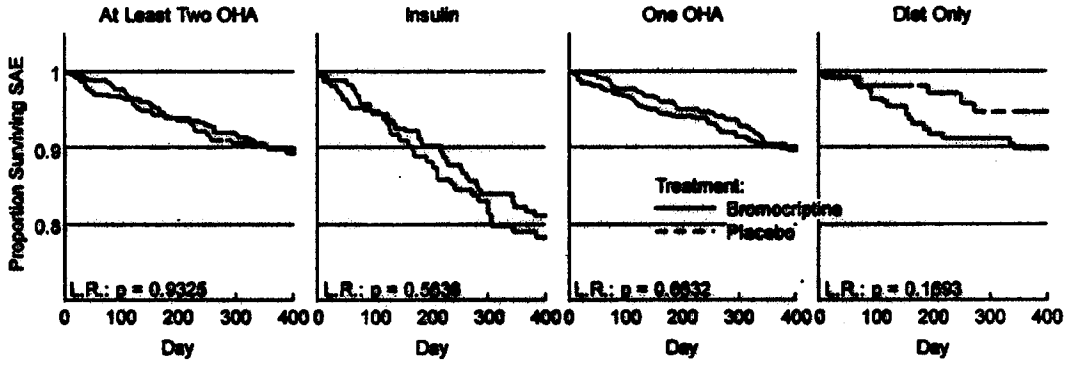
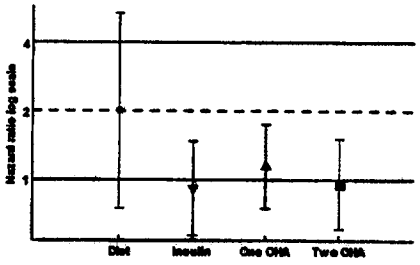


Figure 11 HR [95% CI] of 1st SAE by screening regimen of OHA



Efficacy analysis:

The purpose of the efficacy analysis in the safety study was to bridge efficacy between the no longer available bromocriptine formulation manufactured by Geneva in the original NDA and the to be marketed bromocriptine manufactured by Pliva.

The efficacy analyses were confined to ITT patients not adequate controlled at baseline (HbA1c $\geq$ 7.5% at screening) with one or two oral treatments (no insulin). A total of 559 patients were in the bridging subset of which 421 (75%) patients completed 24 weeks.

Table 14 displays the 4 disjoint groups of patients in the bridging subset by metformin use and sulfonylurea use. Approximately 47% patients were on both metformin and sulfonylurea, 10% were on neither metformin nor sulfonylurea, and 22% patients were on metformin but not sulfonylurea and 22% vise versa.

The sponsor's efficacy subgroups were analyzed by background comedication groups which were not disjoint but consisted of overlapping patient groups: metformin +/- another oral hypoglycemic agents (OHA) (ITTM, n=282), sulfonylurea +/- another OHA (ITTS, n=282), metformin plus sulfonylurea (ITTE, n=192).

Table 14 Number (%) of patients in the bridging subset by metformin or sulfonylurea use – Week 24 completers

ITTM	ITTS		
Frequency Percent	No sulfonylurea	Yes sulfonylurea	Total
No metformin	40	90	130
	10%	22%	32%
Yes metformin	90	192	282
	22%	47%	68%
Total	130	282	412
	32%	68%	100%

24-week completers:

The descriptive statistics were presented for the bridging analysis set (screening HbA1c ≥7.5%) and subsets of the bridging analysis set (Table 15). Table 16 displays the analysis of covariance (covariate=baseline HbA1c) results. Note that the subsets overlap; that is, each pair of subsets share some of the same patients. Therefore, some of the consistency of results between subgroups may be due to the correlation induced by sharing some of the same data.

Table 15 Descriptive statistics for analysis sets

Bridging Study Analysis Set

Treatment	n	HbA1c	Mean	SD	Median	Minimum	Maximum
Bromocriptine	261	Baseline	8.29	0.70	8.10		
		Endpoint	7.76	1.17	7.50		
		Change	-0.53	1.01	-0.60		
Placebo	151	Baseline	8.36	0.76	8.20		
		Endpoint	8.41	1.31	8.20		
		Change	0.04	1.21	0.00		

b(4)

Metformin+sulfonylurea Analysis Set

Treatment	n	HbA1c	Mean	SD	Median	Minimum	Maximum
Bromocriptine	121	Baseline	8.33	0.72	8.10		
		Endpoint	7.66	1.14	7.50		
		Change	-0.67	0.93	-0.70		
Placebo	71	Baseline	8.29	0.76	8.10		
		Endpoint	8.30	1.27	8.10		
		Change	0.02	1.10	0.00		

b(4)

Metformin Study Analysis Set

Treatment	n	HbA1c	Mean	SD	Median	Minimum	Maximum
Bromocriptine	181	Baseline	8.28	0.71	8.00		
		Endpoint	7.68	1.13	7.40		
		Change	-0.60	0.93	-0.60		
Placebo	101	Baseline	8.31	0.78	8.10		
		Endpoint	8.41	1.37	8.10		
		Change	0.09	1.15	0.00		

b(4)

Sulfonylurea Study Analysis Set

Treatment	n	HbA1c	Mean	SD	Median	Minimum	Maximum
Bromocriptine	176	Baseline	8.31	0.70	8.10		
		Endpoint	7.75	1.18	7.60		
		Change	-0.56	1.04	-0.60		
Placebo	106	Baseline	8.33	0.74	8.10		
		Endpoint	8.35	1.22	8.20		
		Change	0.02	1.13	0.00		

b(4)

Table 16 ANCOVA results for efficacy analysis sets

Analysis set	Bromocriptine LSM	Placebo LSM	LSM Difference	SE	95% CI Lower	
Bridging Study (HbA1c ≥7.5 at screening)	-0.53	0.06	-0.59	0.11	-0.80	-0.37
metformin/sulfonylurea	-0.67	0.01	-0.68	0.15	-0.98	-0.39

Analysis set	Bromocriptine LSM	Placebo LSM	LSM Difference	SE	95% CI Lower	
Metformin Study Analysis Set	-0.60	0.09	-0.69	0.13	-0.94	-0.44
Sulfonylurea Study Analysis Set	-0.56	0.03	-0.58	0.13	-0.84	-0.32

Analyses of efficacy subsets (ITT, LOCF):

Table 17 displays the analysis using the LOCF data.

Table 17 ANCOVA results for efficacy subsets in HbA1c change from baseline to Week 24, LOCF

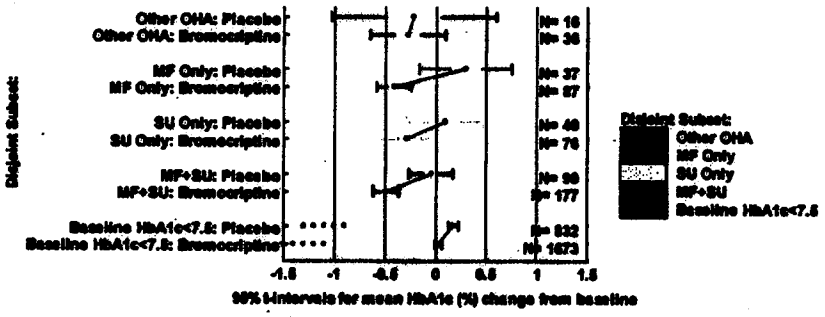
Efficacy Subset	n	Bromocriptine LSM (SE)	n	Placebo LSM (SE)	Bromocriptine-Placebo LSM difference (95% CI)	p
bridging (any oral agent)	376	-0.37 (0.07)	183	0.06 (0.09)	-0.43 [-0.62, -0.24]	<0.01
metformin	264	-0.46 (0.08)	127	0.03 (0.10)	-0.48 [-0.70, -0.26]	<0.01
sulfonylurea	253	-0.45 (0.08)	130	-0.05 (0.11)	-0.41 [-0.63, -0.18]	<0.01
Metformin/sulfonylurea	177	-0.52 (0.09)	90	-0.08 (0.12)	-0.43 [-0.69, -0.17]	<0.01

Disjoint subsets of the bridging study:

This reviewer conducted analyses of disjoint subsets in order to remove the correlation induced by the previous analyses. Overall results here were consistent with the previous results.

Patients with baseline HbA1c≥7.5% were included in the bridging subset (n=559). Of the 559 patients 267 (48%) were on both metformin and sulfonylurea, 52 (9%) were on neither metformin nor sulfonylurea, 124 (22%) were on metformin but not sulfonylurea and 116 (21%) were on sulfonylurea but not metformin. The number in the metformin subset was 391 (70%) (267+124) and in the sulfonylurea subset was 383 (69%) (267+116). Figure 12 displays the 95% t-intervals for mean HbA1c change from baseline to Week 24 in 5 disjoint subsets by treatment groups: the subsets with screening HbA1c ≥7.5% were metformin+sulfonylurea, metformin only, sulfonylurea only, and OHA other than metformin or sulfonylurea. The last subset included patients whose screening HbA1c was less than 7.5%.

Figure 12 95% t-intervals for mean HbA1c change from baseline to Week 24 – ITT population



Efficacy at Week 24 – all patients:

Table 18 displays descriptive statistics for HbA1c change from baseline to Week 24 (LOCF) in the ITT population. The completers population was similar to the ITT population in HbA1c mean change from baseline (Tables 19). Figure 13 displays the cumulative distribution of HbA1c change from baseline to week 24 for the ITT population. The overall effect size was small due to the inclusion of patients with baseline HbA1c < 7.5%.

Table 18 Descriptive statistics for HbA1c change from baseline to Week 24 – ITT, LOCF

HbA1c	Bromocriptine n=2049	Placebo n=1015	
Baseline Mean (SD)	6.99 (1.05)	7.01 (1.10)	b(4)
[Min, Max]			
Baseline Median	6.80	6.80	
Change Mean (SD)	-0.06 (0.78)	0.15 (0.84)	
[Min, Max]			b(4)
Change Median	0.00	0.10	

Table 19 Descriptive statistics HbA1c change from baseline to Week 24 – Completers

HbA1c	Bromocriptine n=1440	Placebo n=814
Baseline Mean (SD)	6.96 (1.03)	7.00 (1.08)
Change Mean (SD)	-0.07 (0.86)	0.18 (0.88)
Change Median	-0.10	0.10

Figure 13 Cumulative distribution of HbA1c change from baseline to Week 24 ITT, LOCF

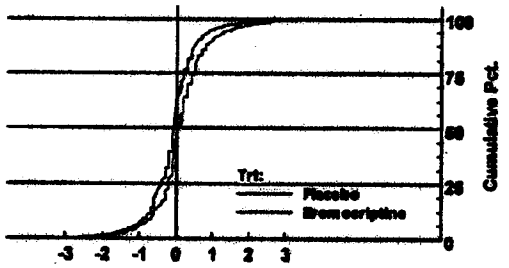


Table 26 displays descriptive statistics for HbA1c at weeks 12, 24, 36 and 52 in the completers population.

Table 20 Descriptive statistics for HbA1c – All Completers

			Bromocriptine					Placebo			
Week	n	HbA1c	Mean	SD	Min	Max	n	Mean	SD	Min	Max
12	1198	Baseline	6.93	1.02			727	6.99	1.07		
		Change	-0.23	0.68				0.03	0.68		
24	1196	Baseline	6.94	1.02			720	6.99	1.08		
		Change	-0.10	0.82				0.16	0.86		
36	1192	Baseline	6.93	1.02			724	6.99	1.07		
		Change	-0.03	0.85				0.15	0.95		
52	1212	Baseline	6.94	1.02			730	6.99	1.07		
		Change	0.10	0.93				0.24	0.95		

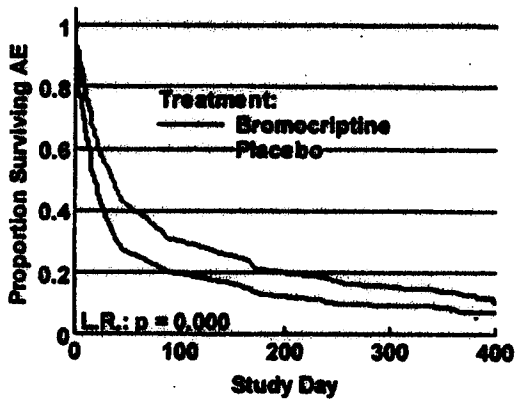
b(4)

Evaluation of Safety

Time to 1st AE event:

The percentages of patients with at least 1 AE during treatment phase were 89% (1832/2050) for bromocriptine and 83% (840/1015) for placebo. Log rank test for time to 1st AE was statistically significant (p<0.01). The HR [95% CI] of bromocriptine to placebo was 1.4 [1.3, 1.5]. Figure 14 displays Kaplan-Meier curves for time to 1st AE. The treatment-by-quarterly time period interaction effect was statistically significant (P=0.1) indicating a violation of the assumption of proportional hazards required for the logrank test. The HR was 1.3 at the first 3 months compared to 1.0, 1.1 and 1.0 during the remaining time period. The early increase in the HR was the result of the earlier increase of AEs in the bromocriptine group compared to the placebo group. However, the sponsor stated that 'The proportional hazard assumption was not rejected by the test of treatment by time interaction (P=0.1416).'

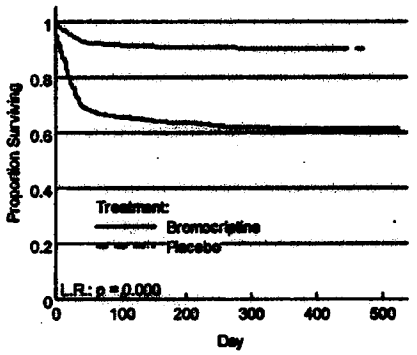
Figure 14 Kaplan-Meier curve of time to 1st AE - ITT



AE: Nausea

The most frequent AE was nausea (32% vs. 8%) during treatment for the ITT population. The percentage for patients with at least 1 episode of nausea was 32% for bromocriptine and 8% for placebo. The mean starting days for bromocriptine and placebo were 34 days and 43 days, respectively. The mean duration for nausea was 31 days for bromocriptine and 24 for placebo. Figure 15 displays the Kaplan-Meier curve for time to first nausea episode. The first most frequent AE was nausea with 15.4% in the bromocriptine group and 3.9% in the placebo group. The hazard ratio and 95% confidence interval were 5 [4, 6].

Figure 15 Kaplan-Meier curves for time to first nausea



Vital Signs:

No significant changes in weight, BMI and waist circumference were observed for both groups. The mean systolic blood pressure was 130 mm Hg at baseline with -2.5 and -1.0 LSM changes from baseline for bromocriptine (n=2056) and placebo (n=1022), respectively. The -1.6 mm Hg [-2.6, -0.5] LSM difference [95% CI] was significant ($p<0.01$). The LSM changes for diastolic BP was -1.8 for bromocriptine (n=2055) and -0.9 (n=1022) for placebo. The -0.9 mm Hg [-1.5, -0.3] LSM difference was significant ($p<0.01$).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Gender:

For both the primary and secondary variables, the percentages of patients with at least 1 SAE were greater in males than females: 10% vs. 7% for SAE and 2.9% vs. 0.8% for CV SAE. Tables 21 and 22 display the percentages of patients with at least 1 SAE and HRs of time to 1st SAE, respectively, by gender. The HR of bromocriptine to placebo was homogeneous between genders ($p=0.5$). Figure 16 displays the HR (95% CI) for each variable by gender. The HR is not estimated if there were no events in one or both of the treatment groups.

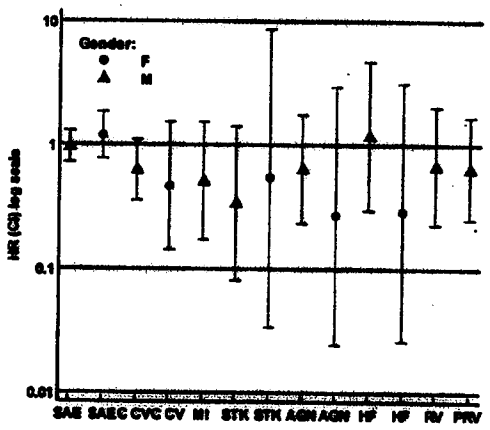
Table 21 Percentage of patient with at lease 1 SAE - primary and secondary variables by gender

	Female n=1331		Male n=1739	
	Bromocriptine n=913	Placebo n=418	Bromocriptine n=1141	Placebo n=598
First all-cause serious AE	64 (7%)	30 (7.2%)	112 (9.8%)	68 (11.4%)
First serious composite cardiovascular AE	5 (0.5%)	6 (1.4%)	26 (2.3%)	24 (4%)
Component of composite CV SAE				
First myocardial infarction	0 (0%)	1 (0.2%)	6 (0.5%)	7 (1.2%)
First stroke	1 (0.1%)	1 (0.2%)	3 (0.3%)	5 (0.8%)
First inpatient hospitalization for angina	1 (0.1%)	2 (0.5%)	8 (0.7%)	7 (1.2%)
First inpatient hospitalization for heart failure	1 (0.1%)	2 (0.5%)	6 (0.5%)	3 (0.5%)
First revascularization surgery	2 (0.2%)	0 (0%)	7 (0.6%)	6 (1%)
First revascularization surgery as SAE outcome	0 (0%)	2 (0.5%)	9 (0.8%)	8 (1.3%)

Table 22 HR (95% CI) of time to 1st SAE for primary and secondary variables by gender

	Male n=1739 (1141:598)			Female n=1331 (913:418)		
	HR	Lower	Upper	HR	Lower	Upper
First all-cause serious AE	1.0	(0.7)	(1.3)	1.2	(0.8)	(1.8)
First serious composite cardiovascular AE	0.6	(0.4)	(1.1)	0.5	(0.1)	(1.5)
Individual component of serious composite CV						
First myocardial infarction	0.5	(0.2)	(1.5)	-		
First stroke	0.3	(0.1)	(1.4)	0.5	(0.0,	8.7)
First inpatient hospitalization for angina	0.6	(0.2)	(1.8)	0.3	(0.0,	2.9)
First inpatient hospitalization for heart failure	1.2	(0.3)	(4.7)	0.3	(0.0,	3.1)
First revascularization surgery	0.7	(0.2)	(2.0)	-		
First revascularization surgery as SAE outcome	0.6	(0.2)	(1.7)	-		

Figure 16 HR (95% CI) for the primary and secondary variables by gender



Race:

The numbers of Caucasian, Black, Hispanic, Asian and 'Other' patients were 2079 (68%), 516 (17%), 408 (13%), 32 (1%) and 35 (1%), respectively. For Asians, the 2 patients/22 (9%) SAEs were both in the bromocriptine group. For 'Other', 2/26 (8%) of the 3 SAEs were in the bromocriptine group and 1/9 (11%) was in the placebo group (HR=0.7 [0.1, 7.7]). Table 23 displays the percentages and Table 24 the HR (95% CI) of the primary and secondary variables by the 3 major races. Figure 25 displays the HR with the 95% CI by race. The HR was homogeneous among races.

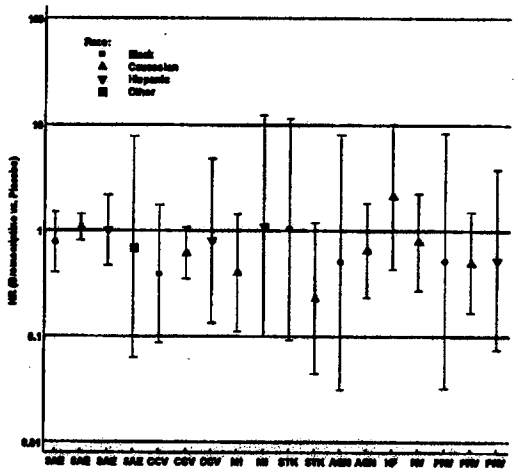
Table 23 Percentage of patient with at least 1 SAE for primary and secondary variables by race

	Caucasian n=2079		Black n=516		Hispanic n=408	
	bro n=1381	plb n=698	bro n=348	plb n=168	bro n=277	plb n=131
all-cause serious AE	131 (9.5%)	72 (10.3%)	22 (6.3%)	15 (8.9%)	19 (6.9%)	10 (7.6%)
composite cardiovascular AE	25 (1.8%)	24 (3.4%)	3 (0.9%)	4 (2.4%)	3 (1.1%)	2 (1.5%)
Individual component of CCV						
myocardial infarction	4 (0.3%)	6 (0.9%)	0 (0%)	1 (0.6%)	2 (0.7%)	1 (0.8%)
stroke	2 (0.1%)	5 (0.7%)	2 (0.6%)	1 (0.6%)	0 (0%)	0 (0%)
inpatient hospitalization for angina	8 (0.6%)	7 (1%)	1 (0.3%)	1 (0.6%)	0 (0%)	1 (0.8%)
inpatient hospitalization for HF	7 (0.5%)	2 (0.3%)	0 (0%)	3 (1.8%)	0 (0%)	0 (0%)
revascular surgery	8 (0.6%)	6 (0.9%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
revascular surgery as SAE outcome	6 (0.4%)	7 (1%)	1 (0.3%)	1 (0.6%)	2 (0.7%)	2 (1.5%)

Table 24 HR (95% CI) of time to 1st SAE for primary and secondary variables by race

	Caucasian n=2079 (1381:698)			Black n=516(348:168)			Hispanic n=408(277:131)		
	HR	low	up	HR	low	up	HR	low	up
First all-cause serious AE	1.1	(0.8	1.4]	0.8	(0.4	1.5]	1.0	(0.5	2.2]
First serious composite cardiovascular AE	0.6	(0.3	1.1]	0.4	(0.1	1.7]	0.8	(0.1	4.8]
Individual component of serious composite CV									
First myocardial infarction	0.4	(0.1	1.4]				1.1	(0.1	12.2]
First stroke	0.2	(0.0	1.2]	1.0	(0.1	11.3]			
First inpatient hospitalization for angina	0.7	(0.2	1.8]	0.5	(0.0	8.0]			
First inpatient hospitalization for heart failure	2.1	(0.4	10.2]						
First revascularization surgery	0.8	(0.3	2.3]	-			0.5	(0.1	3.8]
First revascularization surgery as SAE outcome	0.5	(0.2	1.5]	0.5	(0.0	8.3]			

Figure 17 HR (95% CI) of time to 1st SAE for the primary and secondary variables by race



VA vs. non-VA sites

Table 25 displays percentage of patients with at least 1 SAE for the primary and secondary variables by site (VA vs. non-VA) and Table 26 the results of Cox regression. The HR was homogenous between VA and non-VA subgroups for SAE and CV SAE. The HR for MI was 1.6 at VA sites compared to 0.26 at non-VA sites (Fig. 18). The p-value for the treatment-by-VA group interaction was 0.17.

Table 25 Percentage of patient with at least 1 SAE for primary and secondary variables by race

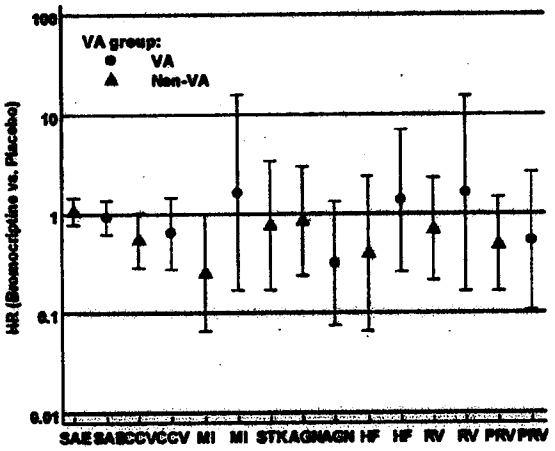
	Non-VA n=2227		VA n=843	
	bromocriptine n=1491	placebo n=736	bromocriptine n=563	placebo n=280
First all-cause serious AE	110 (7.4%)	60 (8.2%)	66 (11.7%)	38 (13.6%)
First serious composite cardiovascular AE	19 (1.3%)	20 (2.7%)	12 (2.1%)	10 (3.6%)
First myocardial infarction	3 (0.2%)	7 (1%)	3 (0.5%)	1 (0.4%)
First stroke	4 (0.3%)	3 (0.4%)	0 (0%)	3 (1.1%)
First inpatient hospitalization for angina	6 (0.4%)	4 (0.5%)	3 (0.5%)	5 (1.8%)
First inpatient hospitalization for HF	2 (0.1%)	3 (0.4%)	5 (0.9%)	2 (0.7%)
First revascularization surgery	6 (0.4%)	5 (0.7%)	3 (0.5%)	1 (0.4%)
First revascularization surgery as SAE outcome	6 (0.4%)	7 (1%)	3 (0.5%)	3 (1.1%)

Table 26 HR (95% CI) for primary (SAE) and secondary variables by Veteran hospital use

	Non-VA n=2227 (1491:736)			VA n=843 (563:280)		
	HR	95% CI		HR	95% CI	
First all-cause serious AE	1.1	(0.8,	1.5)	0.9	(0.6,	1.4)
First serious composite cardiovascular AE	0.5	(0.3,	1.0)	0.6	(0.3,	1.5)
Component of composite CV SAE						
First myocardial infarction	0.3	(0.1,	1.0)	1.6	(0.2,	15.7)
First stroke	0.8	(0.2,	3.4)	-		

	Non-VA n=2227 (1491:736)			VA n=843 (563:280)		
	HR	95% CI		HR	95% CI	
First inpatient hospitalization for angina	0.8	(0.2,	3.0)	0.3	(0.1,	1.3)
First inpatient hospitalization for heart failure	0.4	(0.1,	2.4)	1.4	(0.3,	7.0)
First revascularization surgery	0.7	(0.2,	2.3)	1.6	(0.2,	15.5)
First revascularization surgery as SAE outcome	0.5	(0.2,	1.5)	0.5	(0.1,	2.7)

Figure 18 HR (95% CI) of time to 1st SAE for the primary (SAE) and secondary variables by VA group status



Region – Atlantic or Pacific

Table 27 displays the frequency and percent of patients by region. Table 28 displays the HR by region and figure 19 displays HR and the 95% CI by region on a logarithmic scale. The HR was homogenous between regions. But the p-value for treatment-by-region interaction for HR was significant (p=0.1) for 1st inpatient hospitalization for angina,

Table 27 Percentage of event in primary and secondary variables by subgroup

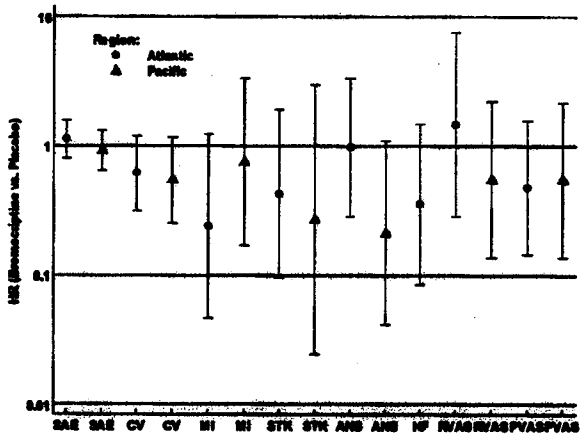
	Atlantic n=1750		Pacific n=1320	
	Bromocriptine n=1168	Placebo n=582	Bromocriptine n=886	Placebo n=434
First all-cause serious AE	96 (8.2%)	50 (8.6%)	80 (9%)	48 (11.1%)
First serious composite cardiovascular AE	18 (1.5%)	17 (2.9%)	13 (1.5%)	13 (3%)
Component of composite CV SAE				
First myocardial infarction	2 (0.2%)	5 (0.9%)	4 (0.5%)	3 (0.7%)
First stroke	3 (0.3%)	4 (0.7%)	1 (0.1%)	2 (0.5%)
First inpatient hospitalization for angina	7 (0.6%)	4 (0.7%)	2 (0.2%)	5 (1.2%)
First inpatient hospitalization for heart failure	3 (0.3%)	5 (0.9%)	4 (0.5%)	0 (0%)
First revascularization surgery	5 (0.4%)	2 (0.3%)	4 (0.5%)	4 (0.9%)

	Atlantic n=1750		Pacific n=1320	
	Bromocriptine n=1168	Placebo n=582	Bromocriptine n=886	Placebo n=434
First revascularization surgery as SAE outcome	5 (0.4%)	6 (1%)	4 (0.5%)	4 (0.9%)

Table 28 HR (95% CI) for primary (SAE) and secondary endpoints by region

	Atlantic			Pacific		
	HR	95% CI		HR	95% CI	
First all-cause serious AE	1.1	[0.8	1.6]	0.9	[0.6	1.3]
First serious composite cardiovascular AE	0.6	[0.3	1.2]	0.5	[0.3	1.2]
Component of composite CV SAE						
First myocardial infarction	0.2	[0.0	1.2]	0.8	[0.2	3.4]
First stroke	0.4	[0.1	1.9]	0.3	[0.0	3.0]
First inpatient hospitalization for angina	1.0	[0.3	3.4]	0.2	[0.0	1.1]
First inpatient hospitalization for heart failure	0.4	[0.1	1.5]			
First revascularization surgery	1.5	[0.3	7.5]	0.5	[0.1	2.2]
First revascularization surgery as SAE outcome	0.5	[0.1	1.6]	0.5	[0.1	2.2]

Figure 19 Log HR (95% CI) for the primary (SAE) and secondary variables by geographical region



Age group - <65 and ≥65 years

The number of patients were 2057 and 1013, respectively, for the <65 year and ≥65 year age groups. Tables 29 and 30 display the percentages of patients with at least 1 SAE and HR (95% CI) of time to 1st SAE, respectively and Figure 20 the HR of time to first SAE of the primary and secondary variables for bromocriptine vs. placebo for the two age groups. The HR was homogeneous between age groups.

Table 29 Percentage of event in primary and secondary variables by subgroup

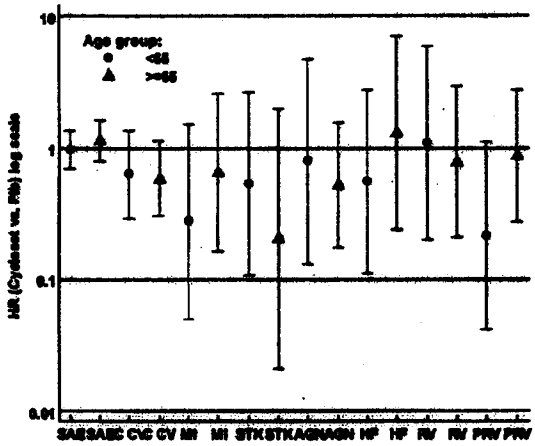
	<65 years n=2057	≥65 years n=1013

	bromocriptine n=1389	placebo n=668	bromocriptine n=1013	placebo n=348
First all-cause serious AE	95 (6.8%)	53 (7.9%)	81 (12.2%)	45 (12.9%)
First serious composite cardiovascular AE	14 (1%)	12 (1.8%)	17 (2.6%)	18 (5.2%)
First myocardial infarction	2 (0.1%)	4 (0.6%)	4 (0.6%)	4 (1.1%)
First stroke	3 (0.2%)	3 (0.4%)	1 (0.2%)	3 (0.9%)
First inpatient hospitalization for angina	3 (0.2%)	2 (0.3%)	6 (0.9%)	7 (2%)
First inpatient hospitalization for HF	3 (0.2%)	3 (0.4%)	4 (0.6%)	2 (0.6%)
First revascularization surgery	4 (0.3%)	2 (0.3%)	5 (0.8%)	4 (1.1%)
First revascularization surgery as SAE outcome	2 (0.1%)	5 (0.7%)	7 (1.1%)	5 (1.4%)

Table 30 Time to first event HR of bromocriptine vs. placebo by age groups

	<65 years n=2057(1389:668)			≥65 years n=1013(665:348)		
	HR	Lower	Upper	HR	Lower	Upper
All-cause SAE	1.0	(0.7,	1.4)	1.1	(0.8,	1.6)
Composite CV	0.6	(0.3,	1.4)	0.6	(0.3,	1.1)
Individual Component of CV						
MI	0.3	(0.1,	1.5)	0.6	(0.2,	2.6)
Stroke	0.5	(0.1,	2.6)	0.2	(0.0,	2.0)
Inpatient hospitalization for angina	0.8	(0.1,	4.7)	0.5	(0.2,	1.5)
Inpatient hospitalization for heart failure	0.6	(0.1,	2.7)	1.3	(0.2,	7.1)
Revascularization surgery	1.1	(0.2,	5.9)	0.8	(0.2,	2.9)
Coronary revascularization surgery:						
Revascularization surgery as SAE outcome	0.2	(0.0,	1.1)	0.9	(0.3,	2.7)

Figure 20 HR (95% CI) for the primary (SAE) and secondary variables by age group



6. Appendix

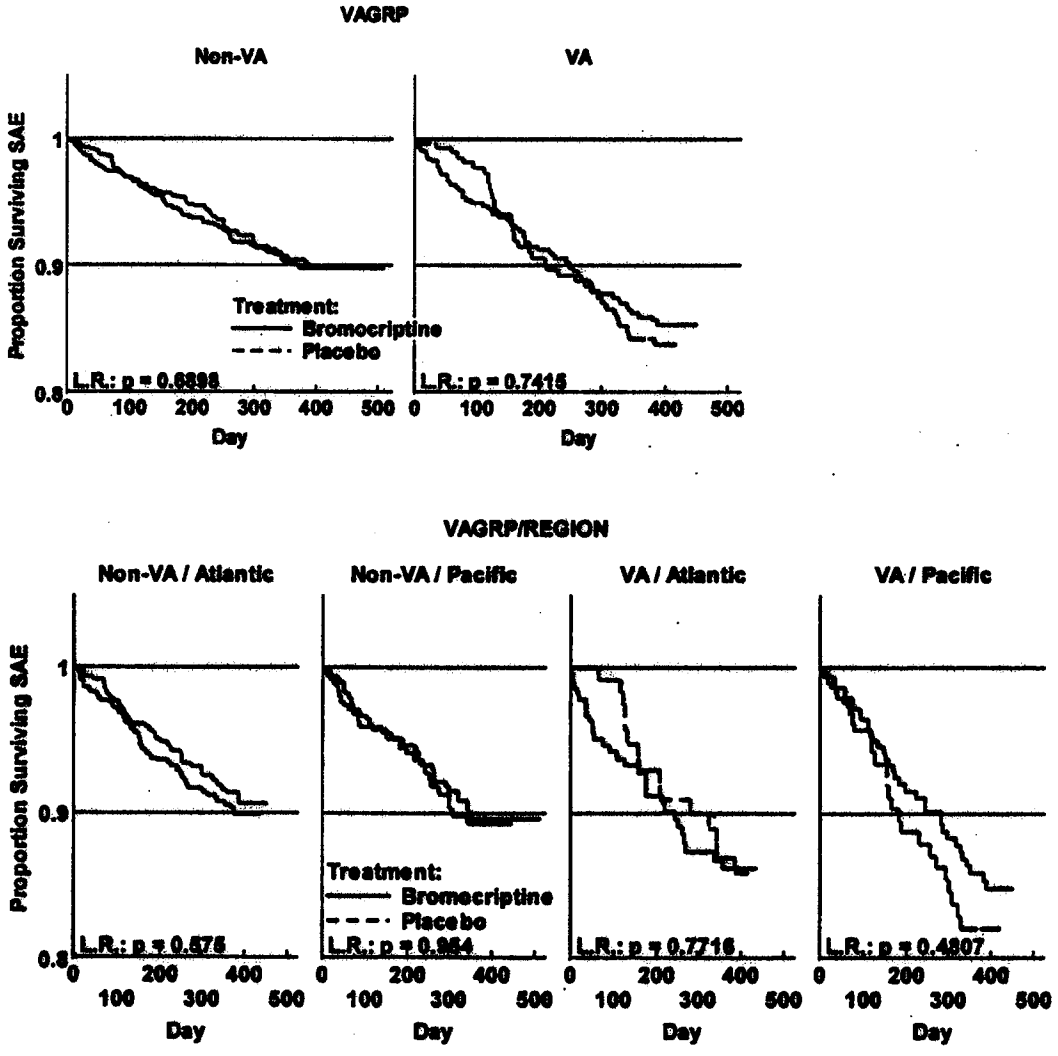
Table 31 displays the frequency and percent of patient's 1st AE during treatment by System Organ Class ordered by total frequency.

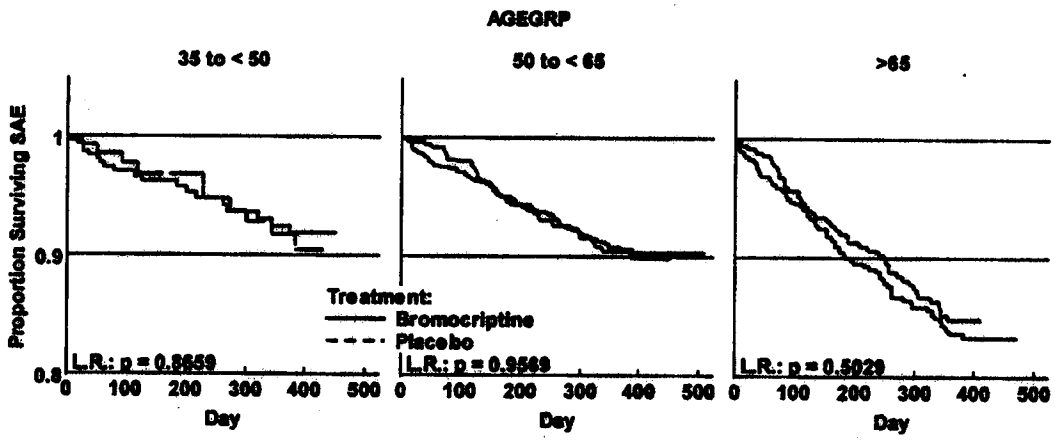
Table 31 Number and % of patient 1st AE by System Organ Class

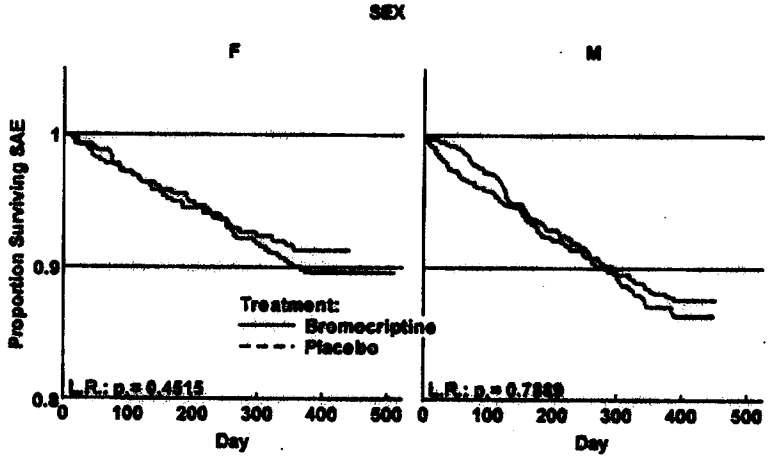
AE Body System Organ Class	Bromocriptine n=2067	Placebo n=1038	Total n=3095
Gastrointestinal disorders	594	181	775
	28.74	17.61	
Nervous system disorders	309	110	419
	14.95	10.70	
Infections and infestations	201	143	344
	9.72	13.91	
General disorders and administration site conditions	182	59	241
	8.81	5.74	
Musculoskeletal and connective tissue disorders	81	74	155
	3.92	7.20	
Respiratory, thoracic and mediastinal disorders	62	50	112
	3.00	4.86	
Endocrine disorders	64	36	100
	3.10	3.50	
Investigations	40	29	69
	1.94	2.82	
Skin and subcutaneous tissue disorders	40	25	65
	1.94	2.43	
Injury, poisoning and procedural complications	40	24	64
	1.94	2.33	
Psychiatric disorders	28	21	49
	1.35	2.04	
Metabolism and nutrition disorders	33	13	46
	1.60	1.26	
Eye disorders	30	15	45
	1.45	1.46	
Cardiac disorders	30	13	43
	1.45	1.26	
Vascular disorders	25	13	38
	1.21	1.26	
Reproductive system and breast disorders	20	9	29
	0.97	0.88	
Renal and urinary disorders	17	6	23
	0.82	0.58	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13	4	17
	0.63	0.39	
Blood and lymphatic system disorders	7	3	10
	0.34	0.29	
Immune system disorders	5	4	9
	0.24	0.39	
Surgical and medical procedures	5	3	8
	0.24	0.29	
Ear and labyrinth disorders	2	4	6
	0.10	0.39	

AE Body System Organ Class	Bromocriptine n=2067	Placebo n=1038	Total n=3095
Hepatobiliary disorders	2	1	3
	0.10	0.10	
Congenital, familial and genetic disorders	1	0	1
	0.05	0.00	
Pregnancy, puerperium and perinatal conditions	1	0	1
	0.05	0.00	
No AE	235	188	423
	11.37	18.29	

Figure 21 Kaplan-Meier curve for subgroups




AGEGRP
35 to < 50
50 to < 65
>65
Proportion Surviving SAE
1
0.9
0.8
Treatment:
Bromocriptine
Placebo
L.R.: p = 0.8659
L.R.: p = 0.9569
L.R.: p = 0.5029
0
100
200
300
400
500
Day


SEX
F
M
Proportion Surviving SAE
1
0.9
0.8
Treatment:
Bromocriptine
Placebo
L.R.: p = 0.4515
L.R.: p = 0.7869
0
100
200
300
400
500
Day

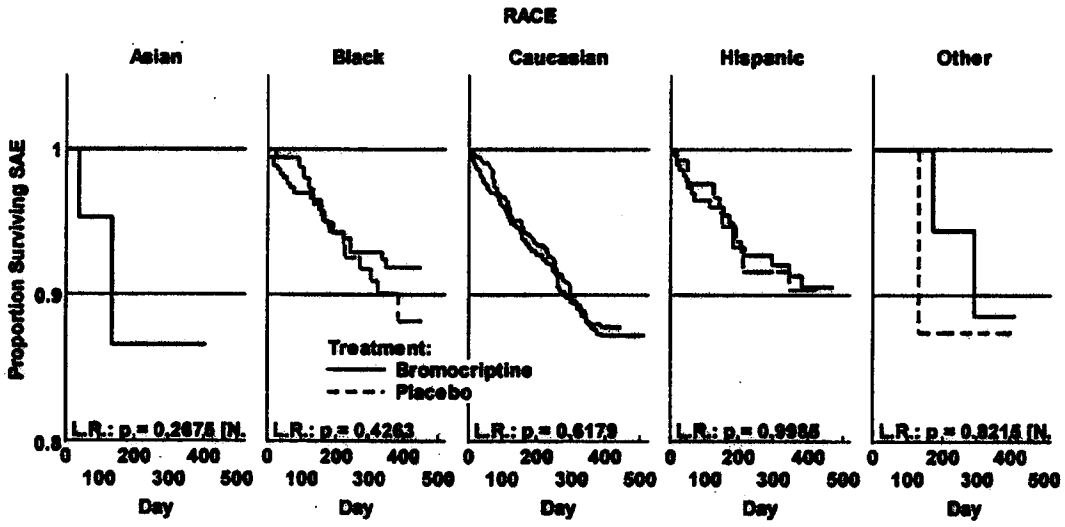


Table 32 Descriptive statistics of HbA1c at Week 24 by TZD use as concomitant medication for patients with baseline HbA1c ≥ 7.5% - ITT, LOCF

TZD Use

Description of Planned Arm	N Obs	Variable	Mean	Std Dev	Median	Minimum	Maximum
Bromocriptine	41	BASELINE	8.22	0.66	8.00		
		ENDPOINT	7.95	1.23	7.70		
		CHANGE	-0.26	1.18	-0.30		
Placebo	30	BASELINE	8.23	0.64	8.15		
		ENDPOINT	8.29	1.24	8.25		
		CHANGE	0.06	1.30	0.00		

b(4)

No TZD Use

Description of Planned Arm	N Obs	Variable	Mean	Std Dev	Median	Minimum	Maximum
Bromocriptine	536	BASELINE	8.35	0.73	8.10		
		ENDPOINT	8.04	1.23	7.85		
		CHANGE	-0.31	1.03	-0.30		
Placebo	257	BASELINE	8.46	0.80	8.20		
		ENDPOINT	8.43	1.24	8.20		
		CHANGE	-0.03	1.13	0.00		

b(4)

HbA1c change from baseline at Week 24 by therapeutic regimen at screening:

Table 33 displays the descriptive statistics for 4 categories of therapeutic regimen at screening for baseline HbA1c ≥ 7.5% patients at Week 24. The 4 categories were one OHA, at least two OHA, any insulin use and diet only.

Table 33 Descriptive statistics of HbA1c by screening therapeutic regimen for baseline HbA1c ≥ 7.5%

Diet only

Description of Planned Arm	N Obs	Variable	Mean	Std Dev	Median	Minimum	Maximum
Bromocriptine	37	BASELINE	8.26	0.81	8.00		
		Endpoint	8.17	1.43	7.80		
		CHANGE	-0.09	1.38	0.00		
Placebo	13	BASELINE	8.34	0.97	8.00		
		Endpoint	8.08	1.73	7.50		
		CHANGE	-0.25	2.07	-0.10		

b(4)

Insulin

Description of Planned Arm	N Obs	Variable	Mean	Std Dev	Median	Minimum	Maximum
Bromocriptine	166	BASELINE	8.48	0.74	8.30		
		Endpoint	8.35	1.34	8.20		
		CHANGE	-0.13	1.16	-0.10		
Placebo	91	BASELINE	8.60	0.76	8.50		
		Endpoint	8.51	1.10	8.30		
		CHANGE	-0.09	0.85	-0.10		

b(4)

One OHA

Description of Planned Arm	N Obs	Variable	Mean	Std Dev	Median	Minimum	Maximum
Bromocriptine	142	BASELINE	8.32	0.73	8.00		
		Endpoint	8.01	1.19	7.75		
		CHANGE	-0.31	0.94	-0.30		
Placebo	64	BASELINE	8.37	0.78	8.15		
		Endpoint	8.45	1.39	8.05		
		CHANGE	0.07	1.32	-0.10		

b(4)

Two OHA

Description of Planned Arm	N Obs	Variable	Mean	Std Dev	Median	Minimum	Maximum
Bromocriptine	232	BASELINE	8.27	0.68	8.10		
		Endpoint	7.81	1.09	7.70		
		CHANGE	-0.46	0.92	-0.40		
Placebo	119	BASELINE	8.37	0.77	8.20		
		Endpoint	8.36	1.21	8.20		
		CHANGE	-0.00	1.11	0.00		

b(4)

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Lee-Ping Pian
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Todd Sahlroot
11/18/2008 03:13:33 PM
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Statistical Review and Evaluation

APR 19 1998

NDA#: 20-866/Class 3S

Applicant: Ergo Research Corporation

Name of Drug: Ergoset® (bromocriptine mesylate)

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

Document Reviewed: Vols. 1.1, 1,2, 1.78-1.114
Submission dated August 22, 1997

Medical Reviewer: John Gueriguian M.D.

Background:

Bromocriptine mesylate, an ergot derivative, is a dopamine receptor D_2 agonist that enhances the release of dopamine. The mechanism of bromocriptine in treating NIDDM is its effect on central neuroendocrine activity. Ergoset is a low-dose (up to 4.8 mg/day), fast-release oral agent.

Controlled Clinical Studies:

In the four multicenter, double-blind, placebo-controlled studies (Studies K, L, M, and G) known as "TRIAD" (timed, regulated intervention in adult diabetes), bromocriptine was used as monotherapy (Study M) or as adjunct to sulfonylureas (SOHAs) (Studies K & L) in improving glycemic control in obese type II diabetic patients. Patients in the four studies started at a dose of 0.8 mg/day (1 tablet) Ergoset or placebo with a weekly increase of 1 tablet to 4.8 mg (6 tablets) for Studies K, L, and M and 3.2 mg/day (4 tablets) for Study G. Study G, which included patients on diet and/or SOHAs, was a supportive study. All studies were conducted over 26 weeks with a 2-week run-in period and a 24-week treatment period. The timing of study drug administration was 8:00 AM (±30 mins). Patients with normal diurnal prolactin profiles at baseline were excluded. The dates for starting, stopping of the trial and the final protocol were as follows:

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

Study	Protocol	Start	Stop
K	April 25, 1995	January 3, 1995	March 29, 1996
L	April 26, 1995	January 17, 1995	April 23, 1996
M 1-94-3.3.04 (v. 13)	July 25, 1996	January 16, 1995	October 19, 1996
1-94-3.3.04-A* (v. 13)	September 28, 1995		

* Seattle center data were pooled with protocol 1-94-3.3.04

Study Objectives

Protocols K and L

Studies K and L were conducted during the same period of time under similar protocols. The primary objective was to demonstrate a clinically significant difference, which was defined as a reduction of 1.0% or greater, in the level of glycated hemoglobin A_{1c} in obese-NIDDM type II diabetics maintained on oral hypoglycemic agents and an ADA weight-maintaining diet. Secondary objectives were to determine the impact of bromocriptine on elevated levels of diurnal glucose, diurnal insulin, body fat, serum lipids, and blood pressure. The entry criteria were patients 30 to 72 years of age with a minimum body mass index (BMI) of 26 kg/m^2 for men, and 28 kg/m^2 for women, and a maximum of 40 kg/m^2 for men and women. For glycated hemoglobin A_{1c}, it was greater than or equal to 7.8% and less than or equal to 12.5%.

Protocol M

The aim of this study is to establish the safety and efficacy of orally administered bromocriptine as a first-line monotherapy in reducing hyperglycemia in obese-NIDDM type II diabetics ($7.5\% \leq A_{1c} \leq 11.0\%$) maintained on diet therapy alone. The primary objective is to demonstrate a clinically significant difference, which is defined as a reduction of 1.0% or greater, in the level of glycated hemoglobin A_{1c} in subjects treated with bromocriptine plus an ADA weight-maintaining diet when compared to a placebo control group on an ADA weight-maintaining diet.

Efficacy Variables

The primary efficacy variable was glycated hemoglobin A_{1c}. The treatment group was compared with respect to the change from baseline (Week 0) to the final visit.

In the protocol of Study M, but not in K and L, it was stated that 'In an attempt to identify those subjects most likely to benefit from continued treatment, an additional secondary analysis will be performed. All subjects treated with study drug who exhibit a decrease from baseline in hemoglobin A_{1c} of at least 0.3% by Week 8 of the study will be classified as "Responders". All "Responders" in the active drug treated group will be compared with the remaining active drug treated subjects. Comparisons will be based upon change from baseline in hemoglobin A_{1c} to final visit.'

Study Conduct for K & L

The following is a summary of study procedure from pre-screen (Week -2) visit to completion of dosing adjustment.

Week -2 A check of blood in the fasted state (hematology, biochemistry, glycated hemoglobin A_{1c}, insulin, lipid profile, and thyroid hormone assays) and urine chemistries as well as HbA_{1c} level were conducted. A complete physical examination and medical history inquiry might also be conducted at this time. All patients received a nutritional evaluation.

Week -1 The first diurnal hormone blood chemistries were obtained, and those patients with normal prolactin* profiles were excluded from the study.

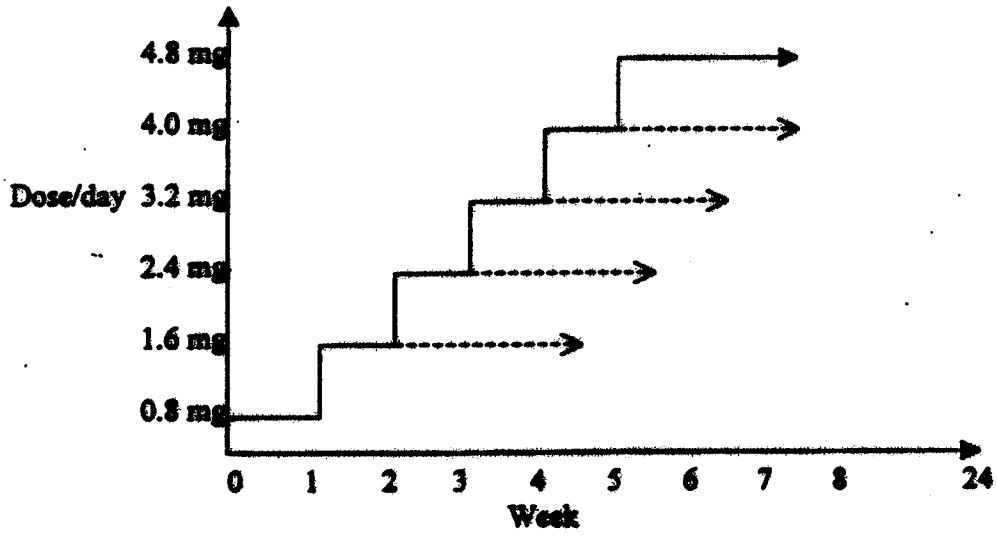
Week 0 Patients were randomized and placed on an ADA weight-maintaining diet, which were monitored throughout the study. The dosing of the study drug was 1 tablet of bromocriptine (0.8mg) or 1 placebo table daily for one week.

Week 1-6 If no intolerance was experienced during the first week, patients then received a daily dose of 2 tablets of the study drug (1.6 mg bromocriptine, or 2 placebo tablets) for the next

* A normal diurnal prolactin profile was characterized as having prolactin levels at 7:00 am, 8:00 am, 9:00 am, 5:00 pm, 6:00 pm and 7:00 pm that were all less than or equal to 5.5 ng/ml for males or 7.0 ng/ml for females.

week. Patients were dropped from the study and replaced if he or she could not able to tolerate the 2 tablets per day dose.

The daily dosage of study drug was increased by 1 tablet per week, up to a target dosage level of 6 tablets/day at Week 6 as the following graph shows. If patient was unable to tolerate the next higher dosage level of study drug, patient returned to the previous lower dosage level for one more week. At that time the next higher dosage level was re-administered. If the subject was still unable to tolerate the higher dosage level, the dosage level should be returned to the next lower dosage level and maintained at that level for the duration of the study.



Concomitant Medications

In studies K and L, patients were treated with an oral hypoglycemic agent with the exception of biguanides, such as Metformin. The dose had to be stable for at least 60 days prior to the first screening visit. During the study, patients remained on the same oral hypoglycemic agent (OHA) and the dosage level of the OHA at the time of the patient entry was not adjusted.

Efficacy Analysis Population

Both an intent-to-treat analysis and evaluable patient analysis were performed for the primary efficacy variable. The evaluable patients

were those who were compliant with respect to diet and dosage of study medication. With respect to diet, patients were considered compliant if they were within their average target daily caloric consumption ±25% over the 24-week clinical trial period. With respect to compliant to study medication, patients were considered compliant if they consumed 80% of their dosage of study drug within ±30 minutes of their assigned administration time during each four-week period.

Efficacy Analysis in the Study Report

A. The primary efficacy variable was HbA_{1c}. Treatment groups were compared with respect to the change from baseline (Week 0) to Week 24 and the change from baseline (Week 0) to endpoint. The endpoint analysis employed a last-observation-carried-forward (LOCF) approach. Only patients with at least one postbaseline visit were included in the endpoint analysis. Only patients with Week-24 data were included in the Week-24 analysis.

In addition, the treatment groups were compared for the following patient populations for the primary efficacy variable:

1. Weight-maintained - defined as all patients who completed the study whose final weight differed less than 2% from baseline.

2. Evaluable - defined as all patients who completed the study who were compliant with respect to both diet and study medication.

3. Hyperinsulinemic - defined as all patients who had a baseline fasting insulin value of greater than 15 micro U/ml and a baseline postprandial (average of six postmeal time points) insulin level of greater than 60 micro U/ml.

B. Secondary variables were diurnal glucose, diurnal insulin, diurnal triglycerides, diurnal free-fatty acids, fasting total cholesterol, fasting HDL, fasting LDL, systolic blood pressure, diastolic blood pressure, and body density.

The diurnal variables were analyzed as follows:

1. Fasting - the first premeal time point
2. Postprandial - the average of the six postmeal time points
3. Postbreakfast - the average of the two postbreakfast time points

4. Postlunch - the average of the two postlunch time points
5. Postdinner - the average of the two postdinner time points

C. Predictive "Responder" Analysis

An additional set of analysis was performed on patients who met the criteria for predictive "responders" in that they achieved at least a 0.3% decrease in HbA_{1c} at Week 8 and completed 24 weeks of treatment.

Analyses included all primary and secondary efficacy variables for the predictive responders. With the exception of HbA_{1c}, the predictive responders were compared with all placebo patients completing the study. For HbA_{1c}, an additional analysis comparing predictive responders with bromocriptine nonresponders was also performed.

For the primary efficacy variable, the predictive responder analysis was conducted for all patient populations described above (section A.) Analyses were based on change from baseline to Week 24 only.

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Study K

Patient Disposition

A total of 247 patients were randomized at eight centers, 123 to the bromocriptine group and 124 to the placebo group. One patient enrolled at two centers as No. 1312007 (bromocriptine) and No. 1312271 (placebo) was excluded from randomization. Three Ergoset patients and one placeb patient had no post-baseline data were excluded from the intent-to-trea population. Efficacy evaluable population further excluded patients with inclusion criteria violations (4 each group).

Ninety-three patients (76.2%) in the bromocriptine group and 106 (86.2% in the placebo group completed the study. Reasons of premature withdra from the study are displayed in Table 1.

Table 1 Disposition of Patients – Study K

Patient Status	Ergoset	Placebo	Total
Randomized	123	124	247
Intent to Treat	119	122	241
Efficacy Evaluable	115	118	233
Completed	93 (76%)	106 (86%)	199 (81%)
Withdrawn	29 (24%)	17 (14%)	46 (19%)
Protocol violation	4	1	5
Adverse events	14 (11%)	3 (2.4%)	17
Request to withdraw	5	8	13
Noncompliance	6	4	10
Other	-	1	1

For protocol violations, 8 patients (4 in each treatment group) did not meet inclusion/exclusion criteria. All 8 patients were included in the intent-to-treat analysis. For the 5 protocol violations that led to premature withdrawal from the study, two Ergoset patients and one placebo patient started Metformin at various times during the study; on Ergoset patient had a high creatinine and another Ergoset patient started Lopressor.

For withdrawal due to adverse events, 6 of the 14 Ergoset patients cite nausea as one of the reasons for discontinuation. Dizziness, fatigue, and myocardial infarctions were each reported as a cause by two patient for discontinuation (8). Two of the 3 placebo patients having

hyperglycemia and another placebo patient having a mild cerebrovascular accident withdrew from the study.

Number of patients by center is displayed in Table 2.

Table 2 Number of Patients by Center – Study K

Study Center	Ergoset	Placebo	Total
San Antonio, TX	24	25	49
Chicago, IL	20	21	41
Waltham, MA	16	16	32
Winston-Salem, NC	16	16	32
Brimingham, MI	20	20	40
Dallas, TX	8	9	17
Springfield, MA	9	8	17
Hartford, CT	9	8	17
Total	122	123	245

Demographic and Baseline Characteristics

The demographic and baseline characteristics are displayed in Table 3 for the intent-to-treat population.

Table 3 Demographic & Baseline Characteristics – Study K

	Ergoset (n=122)	Placebo (n=123), (n=120)*
Age (years)		
Mean (SD)	54.5 (9.0)	54.3 (9.1)
Range, Min - Max	31.0 - 72.0	33.0 - 73.0
Race		
White	96 (79%)	97 (79%)
Black	11 (9%)	7 (6%)
Hispanic	14 (12%)	18 (15%)
Asian	1 (0.8%)	0
Other	0	1 (0.8%)
Sex		
Male	88 (72%)	96 (78%)
Female	34 (28%)	27 (22%)
Body Mass Index (kg/m^2)*		
Mean (SD)	32.4 (3.5)	32.6 (3.8)
Range	25.0 - 40.3	25.4 - 39.7
Weight (lbs)*		
Mean (SD)	210.9 (31.9)	214.0 (32.1)
Range	145.0 - 311.0	136.0 - 300.0

	Ergoset (n=122)	Placebo (n=123), (n=120)*
Hemoglobin A_{1c}		
Mean (SD)	9.3 (1.3)	9.4 (1.2)
Range	7.2 – 12.5	6.8 – 12.4
Prolactin		
Mean (SD)	9.5 (4.6)	9.5 (6.0)
Range	3.2 – 26.9	1.8 – 43.2

Study L

Patient Disposition

A total of 541 patients were screened at 10 centers. Of the total 249 randomized patients, 122 were in the Ergoset group and 127 were in the placebo group. Three Ergoset patients and one placebo patient who had no post baseline visit were excluded from the ITT population. One Ergoset patient with unstable SOHA over the past 60 days was also excluded from the ITT population. Furthermore, 9 Ergoset patients and placebo patient were excluded from the efficacy evaluable patients for inclusion criteria violation. A total of 199 (80%) patients completed the study of which 90 (74%) were in the Ergoset group and 109 (86%) wer in the placebo group. The percentage of withdrawals is statistically significantly greater in the Ergoset group than in the placebo group (p=0.026). Table 4 displays the patient disposition.

Table 4 Disposition of Patients – Study L

Patient Status	Ergoset	Placebo	Total
Randomized	122	127	249
Intent-to-treat	118	126	244
Efficacy evaluable	109	125	234
Completed	90 (74%)	109 (86%)	199 (80%)
Withdrawn	32 (26%)	18 (14%)	50 (20%)
Protocol violation	6	2	8
Adverse events	17 (14%)	4 (3%)	21
Laboratory abnormality	1	0	1
Request to withdraw	4	6	10
Noncompliance	4	4	8
Did not meet selection criteria	0	1	1
Primary care request	0	1	1

Ten patients from the Ergoset group and one patient from the placebo group had inclusion/exclusion-related violations which did not lead to

premature withdrawal from the study. For the 8 protocol violations (6 Ergoset & 2 placebo) that led to premature withdrawal from the study, 4 (3 Ergoset, 1 Placebo) started Metformin therapy during the study. Two Ergoset patients had high TSH levels and one patient had a normal prolactin profile on Day 3. One patient in the placebo group used a sympathomimetic agent prior to the first screening visit.

Seventeen patients (14%) in the Ergoset group and four (3%) in the placebo group were discontinued from the study because of adverse events. In the Ergoset group, nausea was one of the causes for treatment discontinuation in five patients and dizziness/lightheadedness in six.

Number of patients by center is displayed in Table 5.

Table 5 Number of Patients by Study Center – Study L

Study Center	Ergoset	Placebo	Total
San Antonio, TX	16	17	33
Renton, WA	14	13	27
Richmond, VA	21	20	41
Irvine, CA	6	6	12
New Britain, CT	10	10	20
Orlando, FL	3	4	7
Albuquerque, NM	17	18	35
Cleveland, OH	10	12	22
Indianapolis, IN	5	6	11
San Diego, CA	20	21	41
Total	122	127	249

Demographic and Baseline Characteristics

The demographic and baseline characteristics are displayed in Table 6 for the intent-to-treat population.

Table 6 Demographic & Baseline Characteristics – Study L

Patient Status	Ergoset (n=122)	Placebo (n=127)
Age (years)		
Mean (SD)	55.8 (9.1)	55.5 (8.7)
Range, Min - Max	30 - 70	38 - 71
Race		
White	82 (67%)	91 (72%)

Patient Status	Ergoset (n=122)	Placebo (n=127)
Black	10 (8%)	5 (4%)
Hispanic	22 (18%)	25 (20%)
Asian	3 (3%)	1 (1%)
Other	5 (4%)	5 (4%)
Sex		
Male	86 (71%)	88 (69%)
Female	36 (30%)	39 (31%)
Body Mass Index (kg/m^2)		
Mean (SD)	31.7 (3.9)	31.8 (3.7)
Range	25.9 - 40.7	26.1 – 40.4
Weight (lbs)		
Mean (SD)	203.7 (31.8)	204.5 (32.0)
Range	142 - 295	139 - 294
Hemoglobin A_{1c}		
Mean (SD)	9.3 (1.2)	9.4 (1.1)
Range	7.2 – 12.1	7.3 – 12.9
Prolactin		
Mean (SD)	9.2 (3.6)	9.6 (5.6)
Range	2.4 – 27	2.1 - 48

Study M

Patient Disposition

A total of 514 patients were screened in 13 centers. The Seattle center (Protocol 1-94-3.3.04-A, dated 9/28/95) was pooled with this study (Protocol 1-94-3.3.04, dated 7/25/96). The New York center enrolled no patients. A total of 159 patients were randomized, 80 to the Ergoset and 79 to the placebo group at 12 centers. Three Ergoset patients and two placebo patients with no post baseline data were excluded from the ITT population. Six Ergoset and 5 placebo patients were excluded from efficacy evaluable population for entry criteria violation. Table 7 displays the patient disposition.

Table 7 Disposition of Patients – Study M

Patient Status	Ergoset	Placebo	Total
Randomized	80	79	159
Intent-to-treat	77	77	154
Efficacy Evaluable	71	72	143

Patient Status	Ergoset	Placebo	Total
Completed	60 (75%)	62 (78%)	122 (77%)
Withdrawn	20 (25%)	17 (22%)	37 (23%)
Protocol violation	5	3	8
Adverse events	10 (13%)	4 (5%)	14
Laboratory abnormality	0	1	1
Request to withdraw	0	5	5
Noncompliance	4	4	8
Primary care request	1	0	1

Ten patients in the Ergoset treatment group and four in the placebo treatment group discontinued because of adverse events. In the Ergoset group, three patients each discontinued for reasons of hyperglycemia and rhinitis and one for sinusitis. One patient in Ergoset withdrew because of nausea, one because of nausea, dyspepsia, and rhinitis, one because of hepatitis, and one because of hypertension. One each of the placebo patients withdrew because of melanoma skin, hyperglycemia, vasodilation, and angina pectoris. For protocol violations that led to premature withdrawal from the study, six patients (3 each group) took SOHAs starting at various times during the study. One Ergoset patient had a HbA_{1c} less than 7.5% at Week -2, and another Ergoset patient had a high TSH value at Week -2. Table 8 displays patient number by center.

Table 8 Number of Patients by Study Center – Study M

Study Center	Ergoset	Placebo	Total
San Antonio, TX	22	24	46
San Diego, CA	7	6	13
Chicago, IL	14	15	29
Dallas, TX	2	1	3
Orlando, FL	1	1	2
Waltham, MA	3	3	6
New Britain, CT	6	6	12
Seattle, WA	8	6	5
New Orleans, LA	2	3	5
Birmingham, MI	6	6	12
Winston-Salem, NC	7	6	13
Richmond, VA	2	2	4
New York, NY	0	0	0
Total	80	79	159

The center enrollment was from 0, 2, 3,.. to 46 patients. Two of the larger centers, San Antonio and Chicago, enrolled almost half (47%) of the total patients.

Baseline demographics is displayed in Table 9.

Table 9 Demographic & Baseline Characteristics – Study M

Patient Status	Ergoset (n=80)	Placebo (n=79)
Age (years)		
Mean (SD)	54.9 (9.4)	53.8 (9.2)
Range, Min - Max	32 - 72	36 - 69
Race		
White	58 (73%)	64 (81%)
Black	8 (10%)	3 (4%)
Hispanic	12 (15%)	10 (13%)
Asian	1 (1%)	2 (3%)
Other	1 (1%)	0
Sex		
Male	57 (71%)	63 (80%)
Female	23 (29%)	16 (20%)
Body Mass Index (kg/m^2)		
Mean (SD)	31.3 (3.5)	32.0 (3.6)
Range	25.9 - 39.2	26.1 – 39.8
Weight (lbs)		
Mean (SD)	205.6 (32.5)	212.3 (28.6)
Range	150 - 294	143 - 284
Hemoglobin A_{1c}		
Mean (SD)	9.0 (1.1)	8.8 (1.0)
Range	6.8 – 11.3	6.7 – 11.2
Prolactin (7:00 am)		
Mean (SD)	10.0 (9.5)	9.7 (4.0)
Range	2.1 – 83.6	4.0 – 22.7

Concomitant Medication

Glyburide was the most common SOHA in both treatment groups and was used by almost equal proportions of bromocriptine (72%) and placebo patients (69%).

Study Medication Dosages

The distribution of patients according to the final dosage of study medication is in the following tables for studies K, L, and M. The corresponding graph is displayed in Fig 1.

Table 10 Number (%) of Patients by Final Daily Dosage – Study K

Treatment	Final Dose – No. of Tablets (mg)							
	1(0.8mg)	2(1.6mg)	3(2.4mg)	4(3.2mg)	5(4.0mg)	6(4.8mg)	unknown	Total
Ergoset	4 (3.3%)	7 (5.7%)	4 (3.3%)	8 (6.6%)	7 (5.7%)	91 (74.6%)	1 (0.8%)	122
Placebo	3 (2.4%)	5 (3.9%)	3 (2.4%)	4 (3.2%)	3 (2.4%)	109 (85.8%)	0 (0%)	127

Table 11 Number (%) of Patients by Final Daily Dosage – Study L

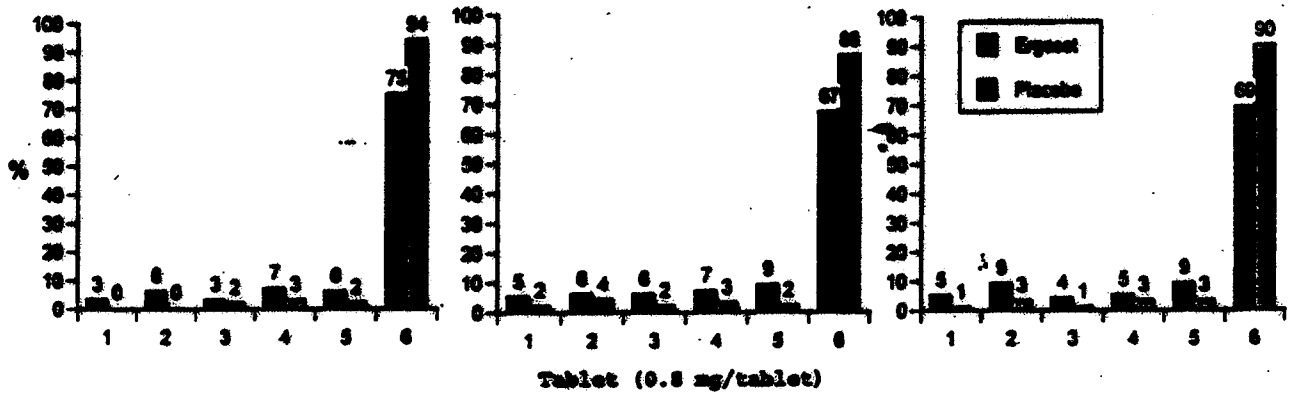
Treatment	Final Dose - No. of Tablets (mg)						
	1(0.8mg)	2(1.6mg)	3(2.4mg)	4(3.2mg)	5(4.0mg)	6(4.8mg)	Total
Ergoset	6 (4.9%)	7 (5.7%)	7 (5.7%)	8 (6.6%)	11 (9.0%)	82 (67.2%)	122*
Placebo	3 (2.4%)	5 (3.9%)	3 (2.4%)	4 (3.2%)	3 (2.4%)	109 (85.8%)	127

*One patient had a final dose of 8 tablets (6.4 mg)/day

Table 12 Number (%) of Patients by Final Daily Dosage – Study M

Treatment	Final Dose - No. of Tablets (mg)						
	1(0.8mg)	2(1.6mg)	3(2.4mg)	4(3.2mg)	5(4.0mg)	6(4.8mg)	Total
Ergoset	4 (5.0%)	7 (8.8%)	3 (3.8%)	4 (5.0%)	7 (8.8%)	55 (68.8%)	80
Placebo	1 (1.3%)	2 (2.5%)	1 (1.3%)	2 (2.5%)	2 (2.5%)	71 (89.9%)	79

Fig. 1: Distribution of Patients by Final Dose - Studies K, L, & M



Primary Efficacy Variable

For the primary efficacy variable, change from baseline HbA_{1c}, the least square means are displayed in Tables 13-15 by weeks and Figures 2 and 3 for the 3 studies, K, L, and M. The endpoint analysis is on the last-observation-carried-forward (LOCF) dataset of the ITT population.

Table 13 LSM Change from Baseline in HbA_{1c}(%): Intent-to-Treat Population, Study K

Week	Ergoset				Placebo				Difference A_{1c} Change Ergo-Plb	p-value
	n	A_{1c}	A_{1c} Change	SE	n	A_{1c}	A_{1c} Change	SE		
Baseline	122	9.30	-	0.12	123	9.39	-	0.12	-0.10	0.556
4	113	8.87	-0.36	0.06	121	9.17	-0.21	0.05	-0.15	0.045
8	102	8.78	-0.41	0.09	114	9.17	-0.14	0.08	-0.27	0.018
12	97	8.74	-0.47	0.10	108	9.18	-0.11	0.09	-0.36	0.005
16	94	8.88	-0.32	0.10	107	9.30	0.05	0.10	-0.37	0.006
20	93	9.06	-0.15	0.11	107	9.56	0.31	0.11	-0.45	0.002
24	93	9.23	0.03	0.13	104	9.74	0.50	0.12	-0.48	0.004
Endpoint	114	9.23	-0.01	0.11	122	9.85	0.48	0.11	-0.49	0.001

Table 14 LSM Change from Baseline in HbA_{1c}(%): Intent-to-Treat Population, Study L

Week	Ergoset				Placebo				Difference A_{1c} Change Ergo-Plb	p-value
	n	A_{1c}	A_{1c} Change	SE	n	A_{1c}	A_{1c} Change	SE		
Baseline	122	9.32	-	0.11	127	9.49	-	0.11	-0.17	0.237
4	114	8.86	-0.42	0.06	120	9.17	-0.24	0.06	-0.18	0.010
8	101	8.59	-0.72	0.09	114	9.15	-0.27	0.08	-0.46	0.000
12	94	8.52	-0.79	0.10	112	9.28	-0.14	0.09	-0.65	0.000
16	93	8.72	-0.62	0.11	111	9.47	0.03	0.10	-0.66	0.000
20	90	8.82	-0.52	0.12	109	9.58	0.15	0.11	-0.67	0.000
24	90	8.92	-0.43	0.13	108	9.64	0.19	0.12	-0.62	0.000
Endpoint	114	8.93	-0.37	0.11	123	9.66	0.23	0.10	-0.59	0.000

Table 15 LSM Change from Baseline in HbA_{1c}(%): Intent-to-Treat Population, Study M

Week	Ergoset				Placebo				Difference A_{1c} Change Ergo-Plb	p-value
	n	A_{1c}	A_{1c} Change	SE	n	A_{1c}	A_{1c} Change	SE		
Baseline	80	9.01	-	0.15	79	8.80	-	0.15	0.22	0.204
4	74	8.84	-0.19	0.08	73	8.65	-0.06	0.08	-0.13	0.160
8	68	8.84	-0.19	0.12	68	8.77	0.01	0.12	-0.20	0.138
12	64	8.69	-0.26	0.14	64	8.76	0.03	0.13	-0.28	0.073
16	61	8.45	-0.42	0.17	63	8.67	-0.03	0.16	-0.40	0.031
20	60	8.61	-0.30	0.19	62	8.75	0.07	0.18	-0.36	0.073
24	60	8.68	-0.22	0.21	62	8.96	0.26	0.20	-0.48	0.033
Endpoint	74	8.99	-0.03	0.17	74	9.09	0.35	0.17	-0.38	0.052

Fig 2: A_{1c} - Studies K, L, & M –

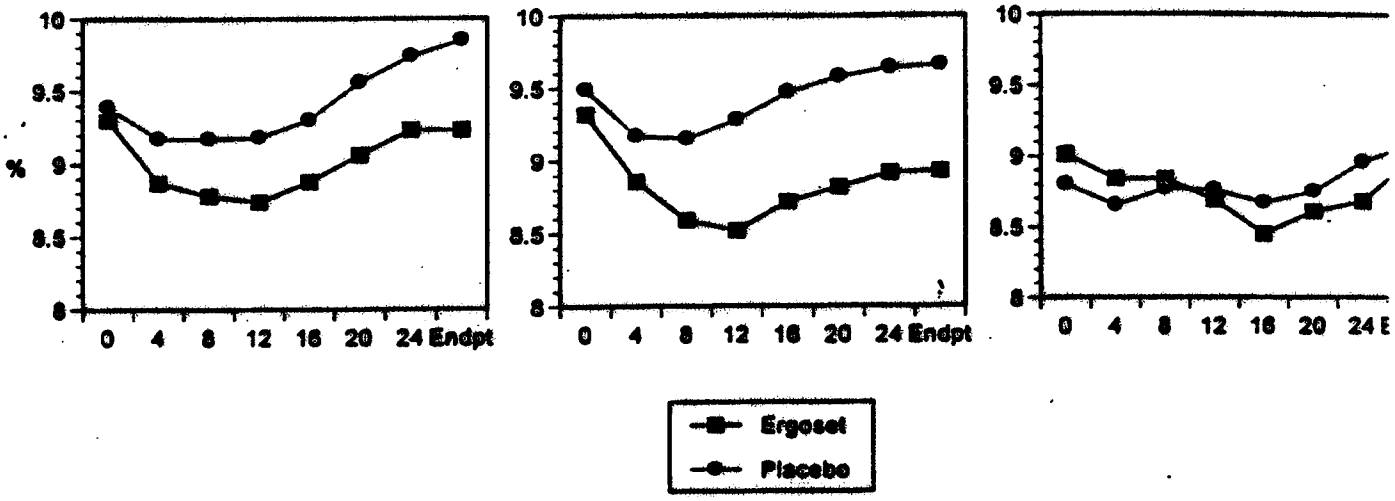
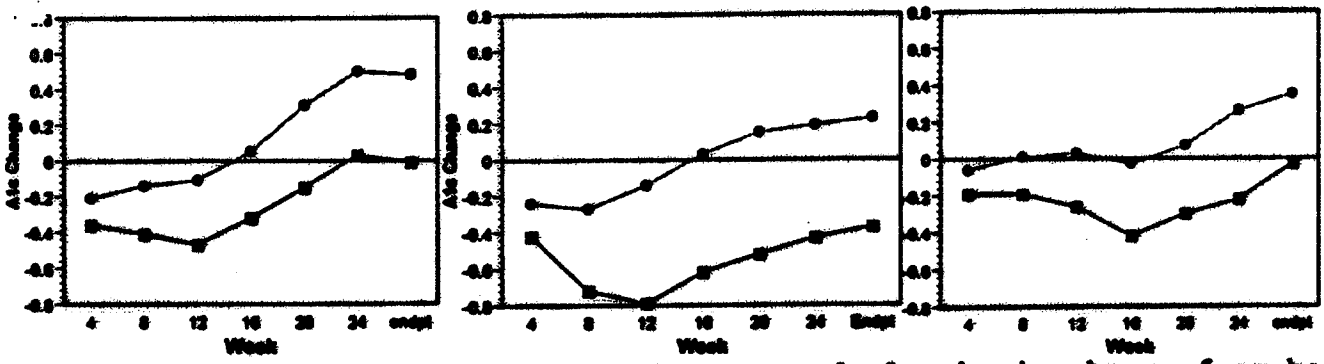


Fig 3: A_{1c} Change from Baseline - Studies K, L, & M



The LSM differences between Ergoset and placebo in change from baseline A_{1c} at week 24 are displayed in Figures 4 & 5 with 95% confidence intervals for the 3 studies.

Fig 4 Week 24 Change from Baseline A1c - Difference between Ergoset and Placebo with 95% C.I.

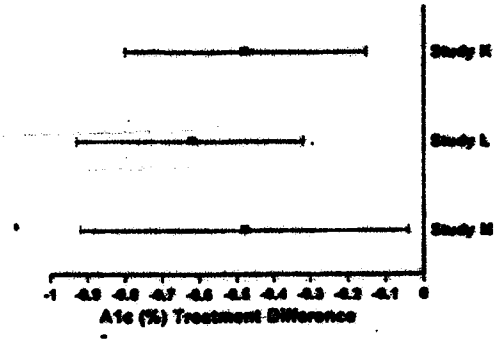
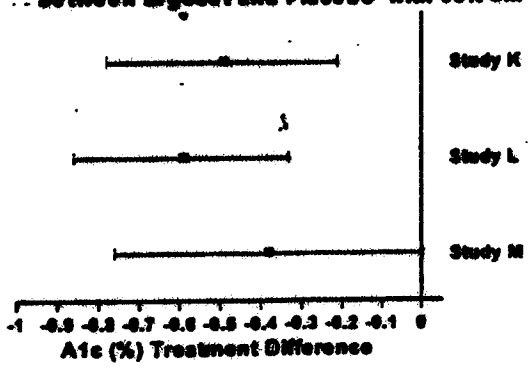


Fig 5: Endpoint Change from Baseline A1c - Difference between Ergoset and Placebo with 95% C.I.



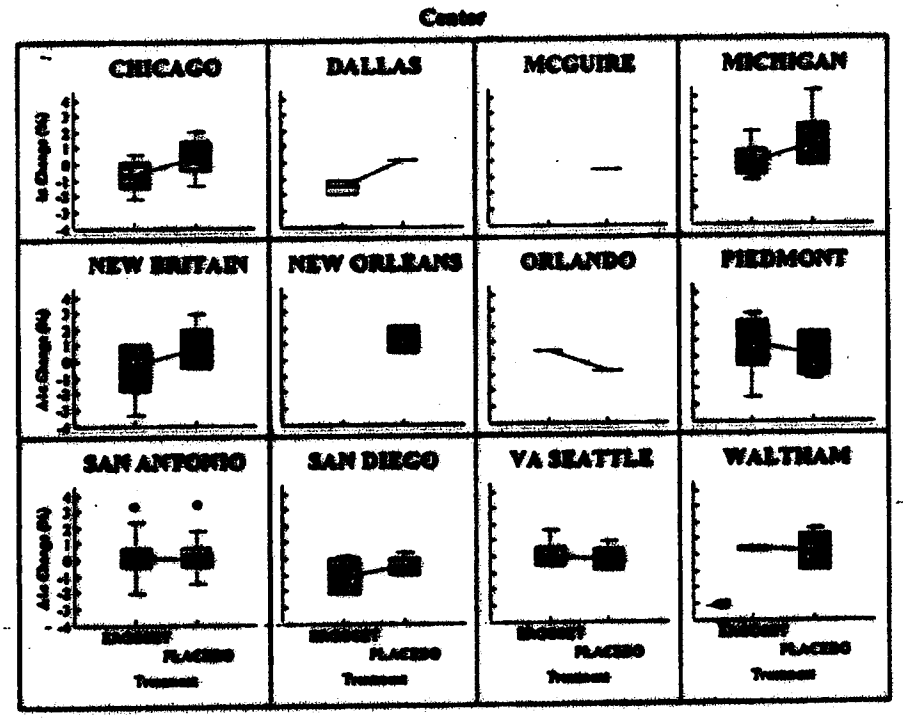
Further Analysis on HbA_{1c} - Study M

For study M, the number of patients enrolled in 5 smaller centers was ranged from 2 to 5 (Table 8). In the Week 24 analysis, centers McGuire Orlando, Dallas, and New Orleans had only 1, 2, 3, 3, patients, respectively (Fig 6). When those 4 centers were combined as one center, the analysis of variance results on change from baseline HbA_{1c} with treatment and center (9) in the model were as follows:

Table 16 ANOVA on Change from Baseline HbA_{1c} combining 4 smaller centers – Study M

		Ergoset	Placebo	Difference Ergoset-Placebo	p-value
Week 24	n	60	62		
	LSM	-0.16 (0.17)	0.38 (0.17)	-0.56	0.016
Endpoint	n	74	74		
	LSM	-0.05 (0.15)	0.37 (0.15)	-0.44	0.031

Fig. 6 Box Plot: A_{1c} Change from Baseline at Week 24 by Center, Study M



In the Orlando center with only 1 patient in each treatment group, the placebo patient is doing better than the Ergoset patient but it weighed equally as the other larger centers. When the smaller centers were

combined, the size of the center is more comparable and the data from those centers with patients in only one treatment group will not be excluded from the analysis. The results showed more significant difference between the Ergoset and placebo patients.

Repeated measures analysis on A_{1c}

The repeated measures analysis was performed on change of A_{1c} from baseline to examine the overall treatment effect from weeks 12 to 24 and also if the treatment effect varies from time to time. The results of the repeated measurement analysis are displayed in Table 17. It shows that the treatment effect is consistent from time to time (no treatment by week interaction).

Table 17 Repeated Measures Analysis on Change from Baseline of HbA_{1c} from Weeks 12 to 24

Study	LSM		Difference (C.I.)	p-value	
	Ergoset	Placebo	Ergoset - Placebo	Trt	Trt-by-Week Interaction
K	-0.26 (0.11)	0.20 (0.10)	-0.46 (-0.75, -0.17)	0.002	0.21
L	-0.51 (0.13)	0.02 (0.11)	-0.54 (-0.87, -0.20)	0.002	0.90
M	-0.17 (0.16)	0.19 (0.15)	-0.35 (-0.70, -0.005)	0.0469	0.48
M*	-0.19 (0.13)	0.23 (0.14)	-0.42 (-0.77, -0.07)	0.0195*	0.48

*Centers McGuire, Orlando, Dallas and New Orleans were combined

Categorical Analysis on A_{1c}

Based on the change from baseline of HbA_{1c} at endpoint, patients were classified as HbA_{1c} decreased by ≥0.3, no change, and increase by ≥0.3. Tables 18 & 19 and Figure 7 display the percentages of HbA_{1c} categories at endpoint for the three studies.

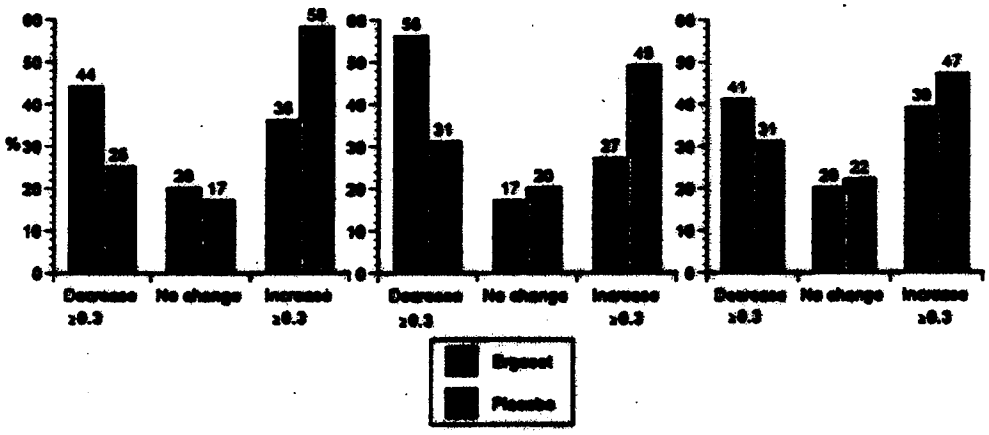
Table 18 Percentages of Patients by Change from Baseline in HbA_{1c} at Week 24

Change in HbA_{1c} (%)	Study K		Study L		Study M	
	Ergoset n=93	Placebo n=104	Ergoset n=90	Placebo n=108	Ergoset n=60	Placebo n=62
Decrease by ≥0.3	37 (40%)	25 (24%)	54 (60%)	34 (32%)	26 (43%)	19 (31%)
No Change	20 (22%)	19 (18%)	12 (13%)	24 (22%)	13 (22%)	14 (23%)
Increased by ≥0.3	36 (39%)	60 (58%)	24 (27%)	50 (46%)	21 (35%)	29 (47%)
	p=0.006		p=0.001		p=0.127	

Table 19 Percentages of Patients by Change from Baseline in HbA_{1c} at Endpoint: Intent-to-Treat Population

Change in HbA_{1c} (%)	Study K		Study L		Study M	
	Ergoset n=114	Placebo n=122	Ergoset n=114	Placebo n=123	Ergoset n=74	Placebo n=74
Decrease by ≥0.3	50 (44%)	30 (25%)	64 (56%)	38 (31%)	30 (41%)	23 (31%)
No Change	23 (20%)	21 (17%)	19 (17%)	25 (20%)	15 (20%)	16 (22%)
Increased by ≥0.3	41 (36%)	71 (58%)	31 (27%)	60 (49%)	29 (39%)	35 (47%)
	p=0.001		p=0.001		p=0.229	

Fig. 7 Percent of Patients by Changes from Baseline in A_{1c} (%) at Endpoint - Studies K, L, & M



This reviewer also performed a categorical analysis to compare the percent of patients who had a 1.0% reduction of HbA_{1c} at Week 24 between the two treatment groups.

Table 20 Percent of Patients with ≥1% Reduction in HbA_{1c} at endpoint from baseline – Patients Who Completed 24 Weeks of Treatment

Study	Treatment	# (%) with HbA_{1c} Reduction			
		≥1.0 %	<1.0 %	n	p-value
K	Ergoset	19 (20%)	74 (80%)	93	0.032
	Placebo	10 (10%)	94 (90%)	104	
L	Ergoset	25 (28%)	65 (72%)	90	0.001
	Placebo	8 (7%)	100 (93%)	108	
M	Ergoset	17 (28%)	43 (72%)	60	0.004
	Placebo	5 (8%)	57 (92%)	62	

Predictive Responder

The predictive responder was defined as patients who had a ≥0.3 reduction in HbA_{1c} (%) by week 8. The sponsor performed analyses on the predictive responders from the Ergoset group to the entire placebo group.

Reviewer's Comment on the Sponsor's Predictive Responder Analysis

The sponsor's comparison between the predictive responders from the Ergoset group and the entire placebo group is not a valid comparison even if it had been prospectively defined; actually the protocol called for a comparison between Ergoset predictive responders and Ergoset predictive non-responders (also an invalid comparison). The purpose of conducting a double-blind, randomized, placebo-controlled study is to make unbiased estimates of differences between randomized groups. There is statistical evidence that Ergoset is better than placebo in reduction of HbA_{1c} at Week 24 analysis with a treatment difference of 0.5%. Specification of a specific response by week 8 as a condition for continued treatment may be made based on clinical judgement but we cannot derive a valid treatment difference for this subpopulation. A trial to derive a valid estimate could have been an enrichment trial with qualified patients taking Ergoset for 8 weeks and then randomizing those patients who have a 0.3% reduction in HbA_{1c} to either Ergoset or placebo.

The sponsor preformed an analysis to compare the difference of the Kappa statistics between Ergoset (Kappa=0.496) and placebo (Kappa=0.314). The Kappa statistics examined agreement between predictive responders at Week 8 and responders (≤-0.3% change from baseline) at the end of study. The difference was not statistically significant at p=0.123.

The HbA_{1c} descriptive statistics of the predictive responders are displayed in Tables 21-23 and Figures 8-13 with A_{1c} levels over time and the box plots of Week 24 change from baseline A_{1c}.

Table 21 Descriptive Statistics of Predictive Responders (Reduction of HbA_{1c} from Baseline at Week 8 ≥ 0.3%) – Study K

		Predictive Non-responder		Predictive Responder	
		Ergoset	Placebo	Ergoset	Placebo
A_{1c} (%)	n	39	60	54	44
Baseline					
Mean (SD)		9.18 (1.27)	9.28 (1.27)	9.42 (1.30)	9.38 (1.24)
Range		7.2 – 12.3	7.3 – 11.8	7.3 – 12.5	6.8 – 11.9
Week 24					
Mean (SD)		9.72 (1.59)	10.10 (1.36)	8.96 (1.54)	9.34 (1.42)
Range		7.0 – 12.7	6.4 – 14.3	5.4 – 12.2	6.5 – 13.5
Change from Week 24					
Mean (SD)		0.53 (1.05)	0.84 (1.16)	-0.45 (0.89)	-0.87 (1.13)
Range		-2.1 – 3.5	-3.0 – 4.3	-2.3 – 2.0	-4.2 – 2.6

Table 22 Descriptive Statistics of Predictive Response (Reduction of HbA_{1c} from Baseline at Week 8 ≥ 0.3%) – Study L

		Predictive Non-responder		Predictive Responder	
		Ergoset	Placebo	Ergoset	Placebo
A_{1c} (%)	n	25	59	65	48
Baseline					
Mean (SD)		9.07 (1.10)	9.31 (1.17)	9.40 (1.18)	9.58 (1.03)
Range		7.7 – 12.1	7.3 – 12.9	7.2 – 11.7	7.7 – 11.8
Week 24					
Mean (SD)		9.70 (1.40)	9.93 (1.42)	8.63 (1.19)	9.33 (1.23)
Range		7.9 – 14.0	7.4 – 13.2	6.7 – 11.7	6.8 – 11.4
Change from Week 24					
Mean (SD)		0.63 (0.93)	0.61 (0.85)	-0.77 (0.93)	-0.25 (1.04)
Range		-0.6 – 3.9	-1.3 – 2.7	-3.6 – 1.7	-2.9 – 2.6

Table 23 Descriptive Statistics of Predictive Responders (Reduction of HbA_{1c} from Baseline at Week 8 ≥ 0.3%) – Study M

		Predictive Non-responder		Predictive Responder	
		Ergoset	Placebo	Ergoset	Placebo
A_{1c} (%)	n	23	38	37	24
Baseline					
Mean (SD)		8.93 (1.33)	8.95 (0.99)	8.91 (0.98)	8.42 (1.02)
Range		6.8 – 11.3	7.2 – 11.1	6.8 – 11.1	6.7 – 10.7
Week 24					
Mean (SD)		9.54 (1.76)	9.68 (1.27)	8.26 (1.27)	8.27 (1.26)
Range		6.3 – 12.8	7.4 – 12.4	5.3 – 10.7	6.3 – 11.2
Change from Week 24					
Mean (SD)		0.61 (1.05)	0.73 (1.21)	-0.65 (1.18)	-0.15 (0.71)
Range		-1.2 – 3.2	-1.5 – 4.3	-3.3 – 2.7	-1.4 – 1.7

Fig 8: A_{1c} Week 24 Change from Baseline by Predictive Response & Treatment - Study K

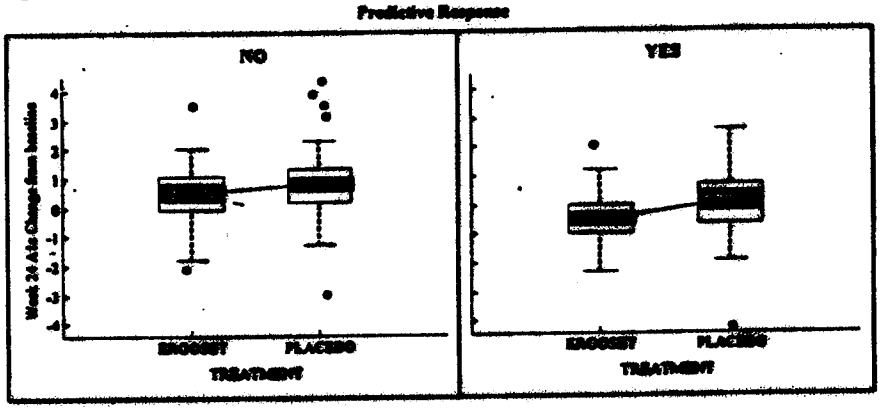


Fig 9: A_{1c} Week 24 Change from Baseline by Predictive Response & Treatment - Study L

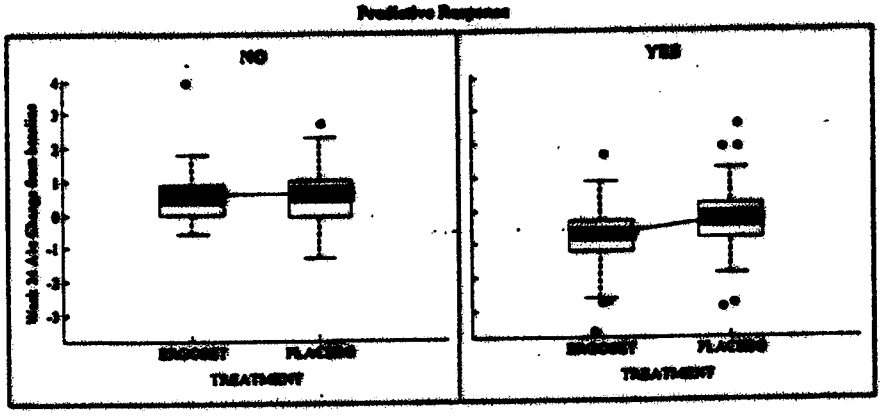


Fig 10: A_{1c} Week 24 Change from Baseline by Predictive Response & Treatment - Study M

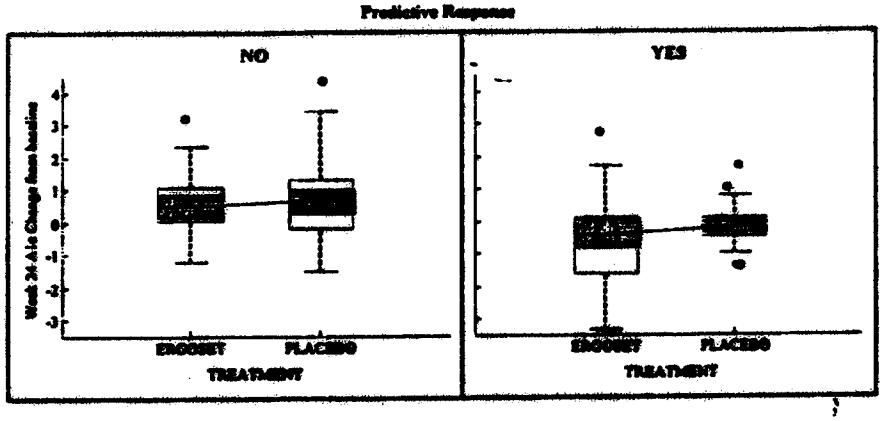


Fig. 11: A_{1c} Mean Change from Baseline by Predictive Response and Treatment - Study K

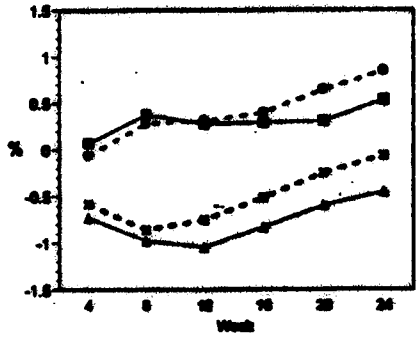
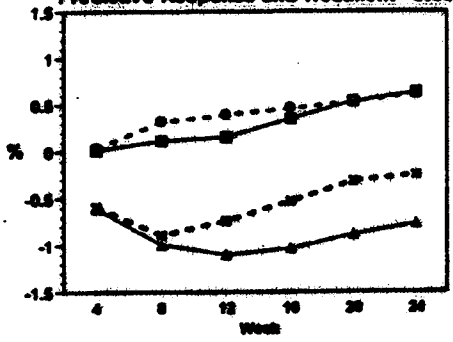


Fig. 12: A_{1c} Mean Change from Baseline by Predictive Response and Treatment - Study L



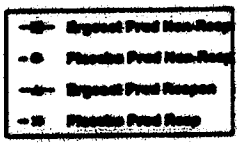
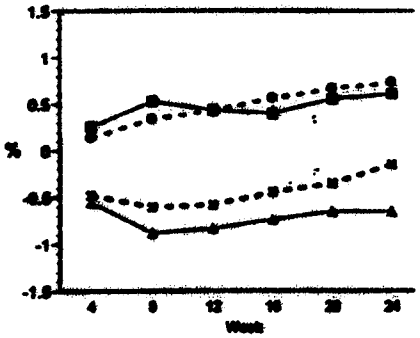


Fig. 13: A_{1c} Mean Change from Baseline b Predictive Response and Treatment - Study

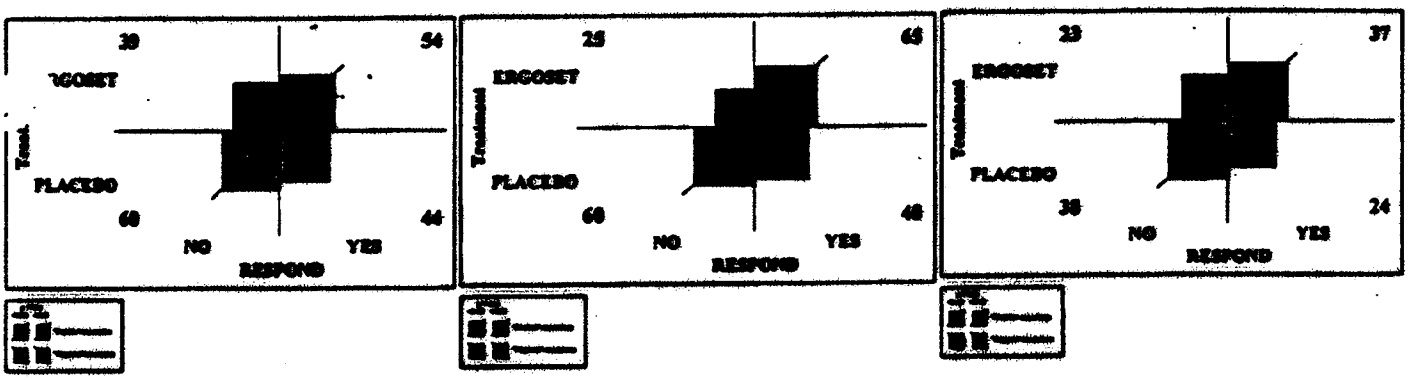


Categorical Analysis of the Predictive Response

The categorical analysis is applied to the predictive responders at week 8. The 2 by 2 table for treatment by predictive response is in Table 24 and the graphs that follows.

Table 24 Percent of Patients with Loss of HbA_{1c} (≥0.3%) from Baseline at Week 8

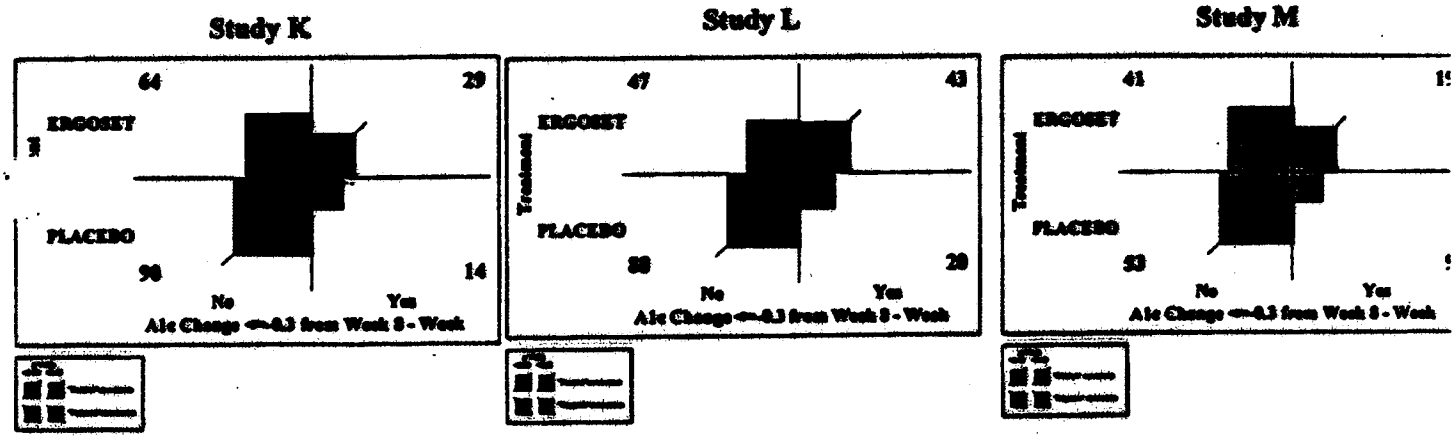
Study	Treatment	# (%) ≥0.3% Loss at Week 8 (Predictive Response)		n	p-value
		Yes	No		
K	Ergoset	54 (58%)	39 (42%)	93	0.027
	Placebo	44 (42%)	60 (58%)	104	
L	Ergoset	65 (72%)	25 (28%)	90	0.001
	Placebo	48 (44%)	60 (56%)	108	
M	Ergoset	37 (62%)	23 (38%)	60	0.011
	Placebo	24 (39%)	38 (61%)	62	



Patients with HbA_{1c} reduction greater than 0.3 from week 8 to week 24 were compared between the treatment groups (Table 25) with the corresponding graphs display the proportion of sustained ≥0.3 HbA_{1c} loss

Table 25 Percent of Patients with Sustained Loss of HbA_{1c} (≥0.3%) from Baseline Weeks 8, 12, 16, 20, & 24

Study	Treatment	# (%) Patients with ≥0.3% Loss			
		Yes	No	n	p-value
K	Ergoset	29 (31%)	64 (69%)	93	0.003
	Placebo	14 (13%)	90 (87%)	104	
L	Ergoset	43 (48%)	47 (52%)	90	0.001
	Placebo	20 (19%)	88 (81%)	108	
M	Ergoset	19 (32%)	41 (68%)	60	0.024
	Placebo	9 (15%)	53 (85%)	62	



The descriptive statistics for the sustained responders are displayed in Tables 26, 27 and 28 for the three studies.

Table 26 Descriptive Statistics of Sustained Responders – Study K

		Sustained Responder		Not Sustained Responder	
		Ergoset	Placebo	Ergoset	Placebo
A_{1c} (%)	n	29	14	64	90
Baseline					
Mean (SD)		9.42 (1.38)	9.77 (1.45)	9.27 (1.25)	9.25 (1.21)
Range		7.3 – 12.5	6.8 – 11.9	7.2 – 12.3	7.3 – 11.8
Change from Baseline Week 24					
Mean (SD)		-1.08 (0.57)	-1.24 (1.00)	0.43 (0.91)	0.72 (1.03)
Range		-2.3 – -0.4	-4.2 – -0.3	-2.1 – 3.5	-3 – 4.3

Table 27 Descriptive Statistics of Sustained Responders – Study L

		Sustained Responder		Not Sustained Responder	
		Ergoset	Placebo	Ergoset	Placebo
A_{1c} (%)	n	43	20	47	88
Baseline					
Mean (SD)		9.54 (1.19)	9.73 (0.90)	9.09 (1.11)	9.36 (1.15)
Range		7.3 – 11.7	7.9 – 11.3	7.2 – 12.1	7.3 – 12.9
Change from Baseline Week 24					
Mean (SD)		-1.22 (0.72)	-1.09 (0.74)	0.38 (0.85)	0.55 (0.87)
Range		-3.6 – -0.4	-2.9 – -0.3	-1.0 – 3.9	-1.3 – 3.1

Table 28 Descriptive Statistics of Sustained Responders – Study M

		Sustained Responder		Not Sustained Responder	
		Ergoset	Placebo	Ergoset	Placebo
A_{1c} (%)	n	19	9	41	53
Baseline					
Mean (SD)		9.00 (1.02)	8.01 (0.98)	8.88 (1.16)	8.87 (0.99)
Range		6.8 – 11.0	6.7 – 9.7	6.8 – 11.3	7.2 – 11.1
Change from Baseline Week 24					
Mean (SD)		-1.52 (0.76)	-0.68 (0.44)	0.46 (0.95)	0.57 (1.11)
Range		-3.3 - -0.3	-1.4 – -0.3	-1.2 – 3.2	-1.5 – 4.3

Secondary Efficacy Variables

The secondary efficacy variables were blood glucose, insulin, serum lipids, and blood pressure. For glucose, insulin, free fatty acids, and triglycerides, the effects of treatment were analyzed at selected time points: in the fasting state and after breakfast, lunch, and dinner. A fasting blood sample was drawn at 7 am after an overnight fast from 9:30 pm. Meals were scheduled at 7:00 to 7:30 am (breakfast), 12:00 to 12:30 pm (lunch), and 5:00 to 5:30 pm (dinner). Other additional blood samples for postprandial measurements were drawn at 8 and 9 am (postbreakfast samples), 1 and 2 pm (postlunch samples), and 6 and 7 pm (postdinner samples). The two postprandial values for each meal were averaged for each patient, and the means of the individual patient averages were calculated. An overall mean value for all six postprandial values was also calculated and compared between treatment groups. In the tabulated data to follow, the calculation of the difference from baseline to Week 24 or endpoint used only the baseline values for those patients who had values at those time points.

1. Glucose

The fasting plasma glucose of the Studies K, L, and M are displayed in Tables 29 - 31. At endpoint there is statistically difference between Ergoset and placebo treated patients in changes from baseline of fasting plasma glucose levels.

Table 29 LSM Change from Baseline in Fasting Plasma Glucose (mg/dL) – Study K

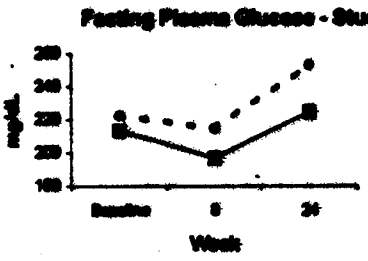
	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset-Placebo	
Baseline	102	213.22	5.81	114	222.36	5.5	-9.14	0.2311
Week 8		196.81	6.33		214.55	6	-17.74	
Week 8 -Baseline		-16.41	5.08		-7.81	4.81	-8.6	0.1979
Baseline	93	216.41	5.88	104	220.21	5.52	-3.81	0.6203
Week 24		224.63	6.84		253.18	6.46	-28.54	
Week 24- Baseline		8.3	6.41		33.01	6.05	-24.71	0.0037
Baseline	116	214.49	5.42	119	224.94	5.33	-10.46	0.1514
Endpoint		225.06	6.35		253.75	6.27	-28.69	
Endpoint-Baseline		10.58	5.84		28.81	5.76	-18.23	0.0206

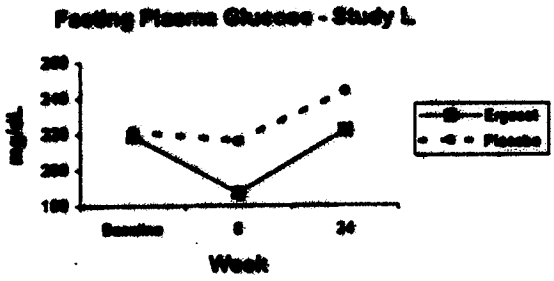
Table 30 LSM Change from Baseline in Fasting Plasma Glucose (mg/dL) – Study L

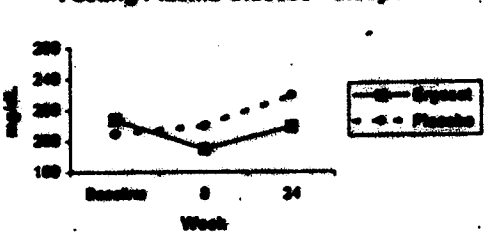
		Ergoset			Placebo		Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	99	218.74	6.19	115	221.5	5.73	-2.77	0.7023
Week 8		186.93	5.87		215.73	5.44	-28.79	
Week 8 -Baseline		-31.8	5.3		-5.78	4.9	-26.03	<0.01
Baseline	90	219.51	6.4	109	222.08	5.85	-2.57	0.7321
Week 24		221.87	7.37		243.71	6.75	-21.84	
Week 24- Baseline		2.36	6.49		21.63	5.94	-19.27	0.012
Baseline	113	218.3	5.42	123	222.4	5.19	-4.09	0.5496
Endpoint		223.84	6.45		248.15	6.18	-24.31	
Endpoint-Baseline		5.53	5.67		25.75	5.43	-20.22	0.0051

Table 31 LSM Change from Baseline in Fasting Plasma Glucose (mg/dL) – Study M

		Ergoset			Placebo		Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	68	213.49	6.37	68	204.49	6.58	8.99	0.3029
Week 8		194.85	7.15		209.61	7.38	-14.76	
Week 8 -Baseline		-18.63	4.49		5.12	4.64	-23.75	0.0002
Baseline	60	211.83	6.56	62	202.47	6.72	9.36	0.2975
Week 24		209.21	8.2		229.46	8.4	-20.25	
Week 24- Baseline		-2.61	6.4		26.99	6.55	-29.6	0.0009
Baseline	76	215.65	6.02	75	205.21	6.17	10.45	0.2036
Endpoint		216.03	7.46		228.41	7.64	-12.39	
Endpoint-Baseline		0.37	5.89		23.2	6.04	-22.83	0.005







2. Insulin

The baseline, week 8, week 24 and endpoint insulin levels and changes from baseline of fasting insulin are displayed in Tables 32 - 34. There is no statistically significant difference between Ergoset and placebo in change from baseline of fasting insulin levels.

Table 32 LSM Change from Baseline in Fasting Insulin (micro U/mL) – Study K

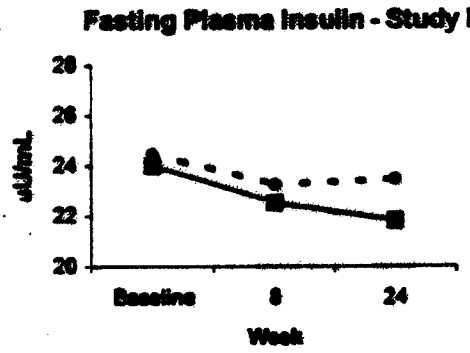
	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	102	24	1.63	114	24.45	1.55	-0.46	
Week 8		22.52	1.38		23.23	1.31	-0.72	
Week 8 -Baseline		-1.48	1.59		-1.22	1.51	-0.26	0.9009
Baseline	93	23.15	1.49	104	23.67	1.4	-0.51	
Week 24		21.81	1.47		23.46	1.39	-1.66	
Week 24- Baseline		-1.38	1.35		-0.01	1.27	-1.37	0.4377
Baseline	116	23.81	1.49	119	24.58	1.47	-0.77	
Endpoint A_{te}		23.19	1.4		23.61	1.38	-0.43	
Endpoint-Baseline		-0.63	1.42		-0.97	1.4	0.34	0.8574

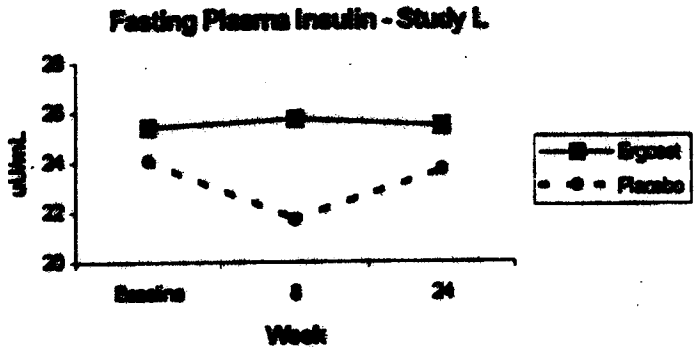
Table 33 LSM Change from Baseline in Fasting Insulin (micro U/mL) – Study L

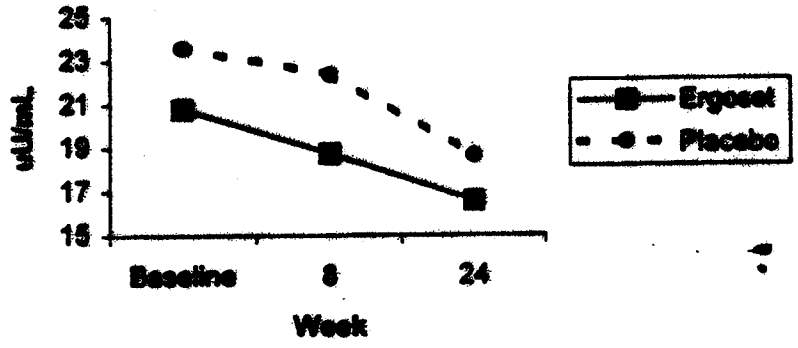
	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	99	25.41	1.85	115	24.07	1.71	1.33	
Week 8		25.75	1.52		21.7	1.41	4.04	
Week 8 -Baseline		0.34	1.79		-2.37	1.66	2.71	0.1968
Baseline	90	23.39	1.65	109	24.66	1.51	-1.27	
Week 24		25.46	1.88		23.72	1.72	1.74	
Week 24- Baseline		2.07	2.07		-0.93	1.89	3.01	0.2157
Baseline	113	25.11	1.64	123	24.14	1.57	0.97	
Endpoint		27.58	1.7		23.49	1.63	4.09	
Endpoint-Baseline		2.47	1.95		-0.65	1.87	3.12	0.2059

Table 34 LSM Change from Baseline in Fasting Insulin (micro U/mL) – Study M

	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	68	20.77	1.34	68	23.58	1.38	-2.82	
Week 8		18.74	1.42		22.36	1.46	-3.63	
Week 8 -Baseline		-2.03	1.49		-1.22	1.53	-0.81	0.6899
Baseline	60	20.68	1.44	62	23.2	1.48	-2.53	
Week 24		16.58	1.25		18.65	1.28	-2.07	
Week 24- Baseline		-4.1	1.36		-4.55	1.39	0.45	0.8065
Baseline	76	21.39	1.34	75	22.56	1.38	-1.16	
Endpoint		17.34	1.35		20.86	1.38	-3.52	
Endpoint-Baseline		-4.05	1.34		-1.69	1.37	-2.36	0.198







3. Free Fatty Acid

The fatty acid data are not valid for study K because of a laboratory assay error. For study L, the week 8 data were not analyzable. Therefore, there is no intent-to-treat endpoint analysis and only week 24 data are available as displayed in Table 35. Table 36 displays the week 24 and endpoint analysis for Study M.

Table 35 LSM Change from Baseline in Fasting Fatty Acid (mEq/L) at Week 24 – Study L

	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	86	0.84	0.06	107	0.85	0.05	-0.02	
Week 24		0.71	0.06		0.88	0.05	-0.16	
Week 24 - Baseline		-0.12	0.06		0.03	0.06	-0.15	0.0448

Table 36 LSM Change from Baseline in Fasting Fatty Acid (mEq/L) at Week 24 – Study M

	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	54	0.81	0.05	58	0.80	0.05	0.02	
Week 24		0.82	0.08		0.98	0.08	-0.16	
Week 24 - Baseline		0.01	0.08		0.19	0.08	-0.18	0.0959
Baseline	64	0.79	0.05	65	0.81	0.05	-0.02	
Endpoint		0.82	0.07		0.99	0.08	-0.18	
Endpoint-Baseline		0.03	0.07		0.18	0.07	-0.16	0.0997

4. Triglyceride

There is a significant difference at endpoint in changes from baseline of fasting triglyceride for Study L (p=0.02) and a trend for Studies K and M between Ergoset treated and placebo treated patients (Tables 37, 38, & 39).

Table 37 LSM Change from Baseline in Fasting Triglyceride (mg/dL) – Study K

		Ergoset			Placebo		Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	88	237.92	22.11	95	221.72	20.79	16.20	
Week 24		233.08	31.05		257.70	29.58	-24.62	
Week 24- Baseline		-4.01	27.27		41.79	26.05	-45.80	0.2037
Baseline	98	237.64	20.64	108	220.03	19.72	17.61	
Endpoint		231.49	28.26		261.32	27.01	-29.83	
Endpoint-Baseline		-6.15	24.16		41.29	23.08	-47.45	0.1388

Table 38 LSM Change from Baseline in Fasting Triglyceride (mg/dL) – Study L

		Ergoset			Placebo		Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	86	269.18	29.66	106	245.96	27.13	23.22	
Week 24		215.03	32.43		278.8	29.42	-63.77	
Week 24- Baseline		-60	26.1		29.01	23.67	-89.01	0.0039
Baseline	98	274.17	29.78	114	264.71	27.58	9.45	
Endpoint		218.29	29.87		278.88	27.67	-60.59	
Endpoint-Baseline		-55.87	24.62		14.17	22.81	-70.04	0.0161

Table 39 LSM Change from Baseline in Fasting Triglyceride (mg/dL) – Study M

		Ergoset			Placebo		Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	54	200.76	19.47	58	223.51	19.91	-22.75	
Week 24		168.15	23.06		217.78	23.51	-49.63	
Week 24- Baseline		-30.93	20.06		-3.63	20.35	-27.31	0.3198
Baseline	64	201.16	18.61	65	223.68	19.11	-22.52	
Endpoint		167.33	22.3		230.72	22.9	-63.39	
Endpoint-Baseline		-33.83	19.19		7.04	19.7	-40.87	0.1195

5. Cholesterol

The change from baseline cholesterol at endpoint in Study L is significantly different between Ergoset and placebo (p=0.04). There is a trend for Study K (p=0.09) and there is no difference between treatment groups for Study M (p=0.4).

Table 40 LSM Change from Baseline in Fasting Cholesterol (mg/dL) – Study K

	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	97	215.75	4.11	108	207.32	3.87	8.43	0.1197
Week 12		214.8	4.34		216.73	4.08	-1.93	
Week 12 -Baseline		-0.95	2.67		9.41	2.51	-10.36	0.0035
Baseline	93	215.91	4.23	104	207.05	4	8.86	0.1119
Week 24		215.11	4.75		214.65	4.48	0.46	
Week 24- Baseline		-0.8	2.91		7.59	2.74	-8.40	0.0287
Baseline	114	217.04	3.88	119	207.57	3.8	9.46	0.0697
Endpoint		217.08	4.12		213.65	4.04	3.43	
Endpoint-Baseline		0.04	2.64		6.07	2.58	-6.03	0.0885

Table 41 LSM Change from Baseline in Fasting Cholesterol (mg/dL) – Study L

	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	94	212.97	5.2	112	211.04	4.81	1.93	
Week 12		215.2	5.39		221.14	4.99	-5.94	
Week 12 -Baseline		2.23	3.38		10.1	3.12	-7.87	0.0488
Baseline	90	214.21	5.27	109	210.4	4.82	3.81	
Week 24		211.38	5.22		217.27	4.77	-5.89	
Week 24- Baseline		-2.83	3.54		6.88	3.23	-9.71	0.02
Baseline	113	214.81	4.45	122	212.46	4.29	2.35	
Endpoint		213.58	4.37		218.82	4.22	-5.24	
Endpoint-Baseline		-1.23	2.91		6.35	2.81	-7.58	0.0402

Table 42 LSM Change from Baseline in Fasting Cholesterol (mg/dL) – Study M

	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	64	214.85	5.55	64	208.73	5.74	6.12	
Week 12		217.64	5.53		212.6	5.71	5.04	
Week 12 -Baseline		2.79	3.68		3.87	3.8	-1.08	0.8299
Baseline	60	214.3	5.56	62	209.4	5.69	4.9	
Week 24		214	5.85		213.18	5.99	0.81	
Week 24- Baseline		-0.3	3.76		3.78	3.85	-4.08	0.4265

		Ergoset			Placebo		Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	74	214.94	5.2	75	210.85	5.27	4.09	
Endpoint		213.04	5.37		212.75	5.44	0.29	
Endpoint-Baseline		-1.91	3.68		1.9	3.72	-3.81	0.4453

6. Blood Pressure

For systolic blood pressure, the sponsor indicated that there is no meaningful difference between treatment groups for all three studies. The between treatment difference in change from baseline of diastolic blood pressure is statistically significant at Week 24 of Study K (p=0.04) and Study M (p=0.01).

Table 43 LSM Change from Baseline in Diastolic Blood Pressure (mm Hg) -- Study K

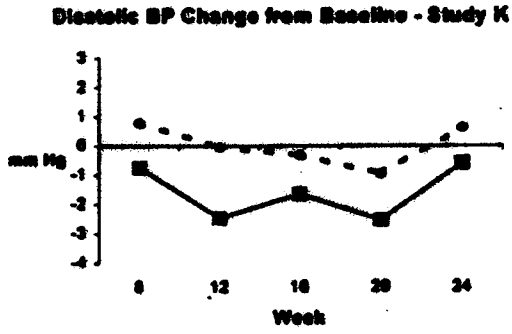
		Ergoset			Placebo		Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	107	81.05	0.88	117	79.65	0.85	1.4	
Week 8		78.52	0.84		78.68	0.81	-0.16	
Week 8 -Baseline		-2.53	0.82		-0.97	0.78	-1.56	0.1531
Baseline	99	81.42	0.92	112	79.73	0.87	1.69	
Week 12		80.68	0.88		80.5	0.83	0.18	
Week 12 -Baseline		-0.74	0.97		0.77	0.92	-1.51	0.2391
Baseline	95	81.55	0.93	109	79.62	0.87	1.93	
Week 16		80.96	0.82		80.21	0.77	0.74	
Week 16- Baseline		-0.59	0.9		0.6	0.84	-1.19	0.3148
Baseline	92	81.44	0.94	107	79.7	0.88	1.73	
Week 20		79.08	0.91		79.56	0.85	-0.48	
Week 20- Baseline		-2.35	0.88		-0.14	0.82	-2.22	0.0537
Baseline	93	81.37	0.94	106	79.71	0.88	1.65	
Week 24		78.9	0.9		79.65	0.84	-0.75	
Week 24- Baseline		-2.46	0.87		-0.06	0.82	-2.4	0.0369
Baseline	119	80.57	0.83	122	79.74	0.82	0.83	
Endpoint		78.92	0.78		79.42	0.77	-0.5	
Endpoint-Baseline		-1.65	0.81		-0.32	0.8	-1.33	0.2238

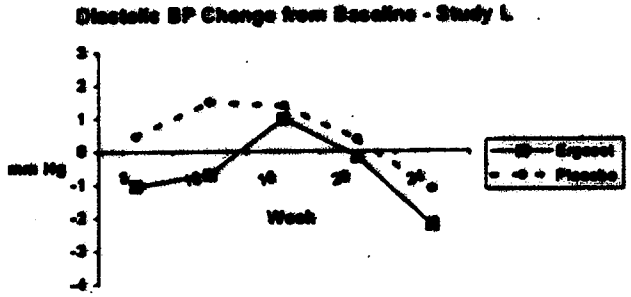
Table 44 LSM Change from Baseline in Diastolic Blood Pressure (mm Hg) – Study L

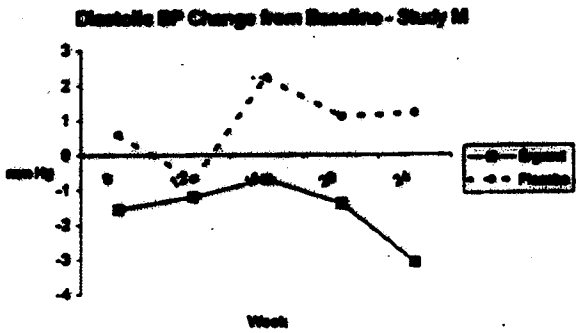
	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	104	78.69	0.94	117	79.58	0.89	-0.89	
Week 8		77.64	0.88		80.03	0.84	-2.39	
Week 8 -Baseline		-1.05	0.96		0.45	0.91	-1.5	0.2024
Baseline	100	79.52	1	112	80.14	0.94	-0.62	
Week 12		78.83	0.89		81.64	0.83	-2.82	
Week 12 -Baseline		-0.7	1.01		1.5	0.95	-2.2	0.0666
Baseline	94	79.12	1	109	80.27	0.93	-1.15	
Week 16		80.1	0.93		81.64	0.87	-1.53	
Week 16- Baseline		0.99	1.02		1.37	0.95	-0.38	0.7532
Baseline	90	78.78	1.03	109	80.17	0.94	-1.39	
Week 20		78.59	1.06		80.51	0.97	-1.92	
Week 20- Baseline		-0.18	1.22		0.35	1.11	-0.53	0.7088
Baseline	90	78.6	1.01	108	80.19	0.92	-1.59	
Week 24		76.37	0.98		79.05	0.9	-2.68	
Week 24- Baseline		-2.23	1.03		-1.14	0.94	-1.09	0.3664
Baseline	118	78.8	0.85	124	79.75	0.83	-0.94	
Endpoint		77.16	0.82		79.14	0.79	-1.98	
Endpoint-Baseline		-1.64	0.84		-0.61	0.82	-1.03	0.3319

Table 45 LSM Change from Baseline in Diastolic Blood Pressure (mm Hg) – Study M

	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	68	78.03	0.99	71	78.65	0.98	-0.62	
Week 8		76.47	1.08		79.22	1.08	-2.76	
Week 8 -Baseline		-1.56	1.11		0.58	1.11	-2.14	0.155
Baseline	65	78.12	1.02	66	78.69	1.05	-0.57	
Week 12		76.92	1.13		77.99	1.16	-1.08	
Week 12 -Baseline		-1.21	1.02		-0.7	1.05	-0.5	0.7178
Baseline	61	78.34	1.05	64	78.44	1.07	-0.1	
Week 16		77.63	1.05		80.65	1.06	-3.01	
Week 16- Baseline		-0.7	1		2.21	1.02	-2.91	0.0335
Baseline	61	78.2	1.04	61	78.21	1.08	-0.01	
Week 20		76.8	1.02		79.29	1.05	-2.49	
Week 20- Baseline		-1.4	1.17		1.08	1.21	-2.48	0.1238
Baseline	60	78.16	1.04	62	78.14	1.07	0.03	
Week 24		75.07	1.12		79.33	1.15	-4.25	
Week 24- Baseline		-3.09	1.17		1.19	1.19	-4.28	0.0081
Baseline	78	77.75	0.89	77	78.65	0.91	-0.9	
Endpoint		75.82	0.98		79.12	1	-3.31	
Endpoint-Baseline		-1.93	1.03		0.47	1.05	-2.4	0.0882







Additional Outcome Variables

In studies K and L, patients in the Ergoset group had a small but statistically significant weight gain compared to placebo (~ 2 lbs.) at endpoint. The weight was not statistically different in Study M at endpoint.

Table 46 LSM Change from Baseline Weight (lbs) – Study K

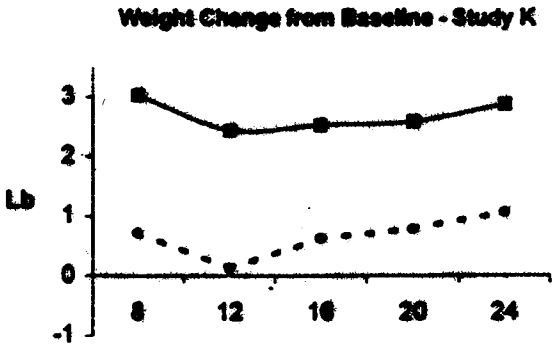
	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	107	213.39	3.16	115	215.07	3.07	-1.68	
Week 8		216.41	3.22		215.78	3.13	0.63	
Week 8 -Baseline		3.03	0.4		0.71	0.39	2.31	0
Baseline	99	212.36	3.3	110	215.81	3.15	-3.45	
Week 12		214.79	3.39		215.93	3.23	-1.14	
Week 12 -Baseline		2.44	0.47		0.12	0.45	2.31	0.0002
Baseline	95	212.17	3.4	108	216.15	3.2	-3.98	
Week 16		214.7	3.54		216.77	3.33	-2.07	
Week 16- Baseline		2.53	0.53		0.62	0.5	1.91	0.0065
Baseline	93	211.84	3.47	106	215.47	3.27	-3.63	
Week 20		214.44	3.61		216.25	3.41	-1.82	
Week 20- Baseline		2.59	0.55		0.78	0.52	1.81	0.013
Baseline	93	211.84	3.47	105	215.15	3.29	-3.31	
Week 24		214.71	3.68		216.21	3.49	-1.5	
Week 24- Baseline		2.88	0.69		1.06	0.66	1.82	0.0465
Baseline	119	212.62	2.95	120	215.6	2.95	-2.99	
Endpoint		215.33	3.12		216.33	3.12	-0.99	
Endpoint-Baseline		2.71	0.59		0.72	0.59	1.99	0.0134

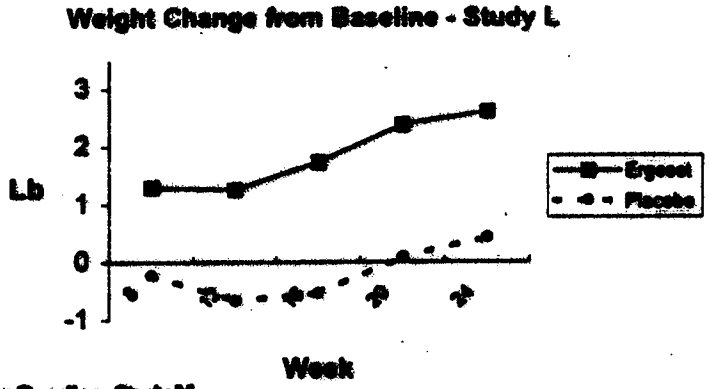
Table 47 LSM Change from Baseline Weight (lbs) – Study L

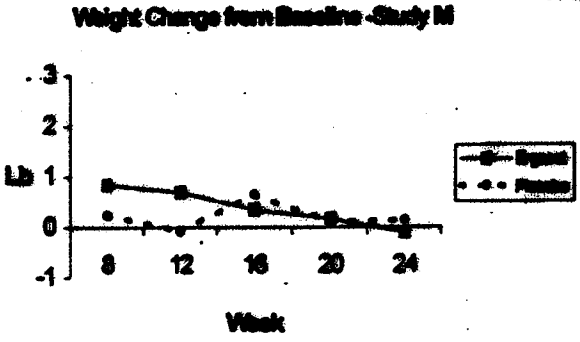
	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	106	202.64	3.55	119	204.36	3.38	-1.71	
Week 8		203.93	3.6		204.12	3.43	-0.19	
Week 8 -Baseline		1.29	0.4		-0.23	0.38	1.52	0.0021
Baseline	100	204.99	3.78	113	205.72	3.55	-0.73	
Week 12		206.25	3.83		205.05	3.59	1.2	
Week 12 -Baseline		1.26	0.48		-0.67	0.46	1.93	0.0008
Baseline	94	205.18	3.91	109	205.57	3.64	-0.39	
Week 16		206.91	3.98		205.02	3.7	1.88	
Week 16- Baseline		1.73	0.53		-0.54	0.49	2.27	0.0003
Baseline	90	205.65	3.99	110	205.06	3.63	0.59	
Week 20		208.03	4.08		205.13	3.72	2.89	
Week 20- Baseline		2.38	0.55		0.08	0.5	2.3	0.0004
Baseline	90	204.36	3.96	109	205.16	3.63	-0.8	
Week 24		206.97	4.04	.	205.58	3.69	1.38	
Week 24- Baseline		2.61	0.57	.	0.42	0.52	2.19	0.0011
Baseline	118	202.35	3.28	125	203.24	3.19	-0.89	
Endpoint		204.52	3.33		203.59	3.23	0.92	
Endpoint-Baseline		2.17	0.47		0.35	0.46	1.82	0.0026

Table 48 LSM Change from Baseline Weight (lbs) – Study M

	Ergoset			Placebo			Difference	p-value
	n	LSM	SE	n	LSM	SE	Ergoset - Placebo	
Baseline	68	208.31	3.83	71	213.1	3.83	-4.79	
Week 8		209.16	3.95		213.34	3.95	-4.18	
Week 8 -Baseline		0.84	0.56		0.23	0.56	0.61	0.4232
Baseline	65	210.08	3.88	66	212.94	3.98	-2.86	
Week 12		210.76	3.98		212.86	4.08	-2.1	
Week 12 -Baseline		0.69	0.67		-0.08	0.68	0.77	0.3998
Baseline	61	212.32	4.04	64	214.11	4.11	-1.79	
Week 16		212.66	4.22		214.75	4.3	-2.09	
Week 16- Baseline		0.34	1.02		0.64	1.04	-0.3	0.8293
Baseline	61	212.26	4.05	61	213.32	4.18	-1.06	
Week 20		212.42	4.21		213.41	4.34	-0.99	
Week 20- Baseline		0.16	0.92		0.09	0.95	0.07	0.9544
Baseline	60	210.85	3.94	62	213.45	4.03	-2.6	
Week 24		210.75	4.11		213.59	4.21	-2.84	
Week 24- Baseline		-0.11	0.98		0.13	1	-0.24	0.8576
Baseline	78	207.88	3.53	77	213.21	3.6	-5.32	
Endpoint		207.91	3.69		212.99	3.76	-5.08	
Endpoint-Baseline		0.03	0.82		-0.22	0.84	0.24	0.8265







Prolactin Levels

Patients with normal diurnal prolactin profiles at baseline were excluded from the study. A normal diurnal prolactin profile was characterized as levels at 7:00 am, 8:00 am, 9:00 am, 5:00 pm, 6:00 pm, and 7:00 pm that were all ≤5.5 ng/ml for men or ≤7.0 ng/ml for women. The fasting (7:00 am) prolactin was not normally distributed ($p<0.01$), therefore, the median is also displayed in the following table for descriptive statistics of prolactin.

Table 49 Descriptive Statistics of Prolactin (ng/ml) – Study K

Fasting Prolactin		Ergoset			Placebo	
7:00 am	n	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	122	9.5 (4.6)	8.8	123	9.5(6.0)	8.4
Week 8	102	4.0 (3.8)	2.4	114	9.1(3.9)	8.6
Final	92	4.6 (4.2)	2.4	102	9.3(4.9)	8.4
Change from Baseline						
Week 8	102	-5.5 (5.5)	-4.9	114	-0.44(5.4)	0.39
Final	92	-4.8 (5.6)	-4.5	102	-0.32(5.3)	-0.07

Table 50 Descriptive Statistics of Prolactin (ng/ml) – Study L

Fasting Prolactin		Ergoset			Placebo	
7:00 am	n	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	122	9.2 (3.6)	8.5	127	9.6 (5.6)	8.1
Week 8	99	4.0 (3.0)	2.5	115	9.6 (5.4)	8.0
Final	86	4.4 (3.4)	2.2	108	10.2 (5.3)	9.0
Change from Baseline						
Week 8	99	-5.1 (4.4)	-5.0	115	-0.15 (4.9)	-0.32
Final	86	-4.6 (4.6)	-4.5	108	-0.51 (3.5)	0.64

Table 51 Descriptive Statistics of Prolactin (ng/ml) – Study M

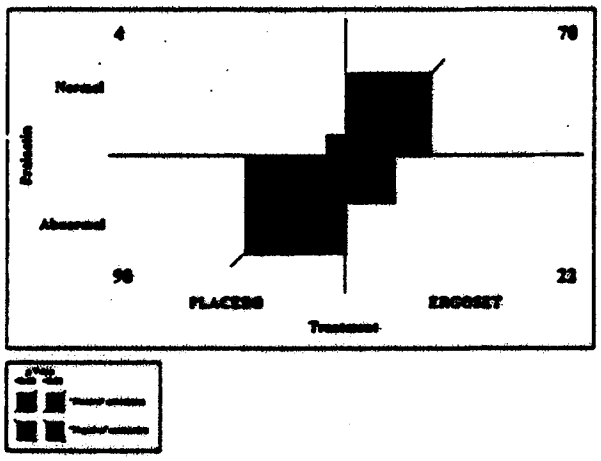
Fasting Prolactin		Ergoset			Placebo	
7:00 am	n	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	80	10.0 (9.5)	8.4	79	9.7 (4.0)	9.1
Week 8	68	3.9 (2.9)	2.1	68	9.5 (4.5)	8.9
Final	57	5.3 (4.2)	2.6	62	10.1 (6.2)	8.7
Change from Baseline						
Week 8	68	-6.00 (9.7)	-4.88	68	0.29 (3.3)	-0.24
Final	57	-4.9 (11.1)	-4.45	62	1.00 (4.7)	0.33

The proportion of patients who had a final normal prolactin profile (as defined in p. 3) was compared between the Ergoset and placebo groups in Table 52 and the graph that follows.

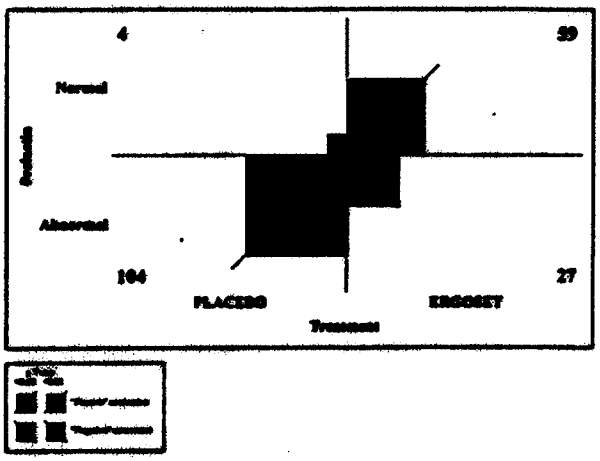
Table 52 Percent of Patients with Final Normal Prolactin Profile - Week 24 Completers

Study	Treatment	# (%) Patients			
		Normal	Abnormal	n	p-value
K	Ergoset	70 (76%)	22 (24%)	92	0.001
	Placebo	4 (4%)	98 (96%)	102	
L	Ergoset	59 (69%)	27 (31%)	86	0.001
	Placebo	4 (5%)	104 (95%)	108	
M	Ergoset	36 (63%)	21 (37%)	57	0.001
	Placebo	1 (2%)	61 (98%)	62	

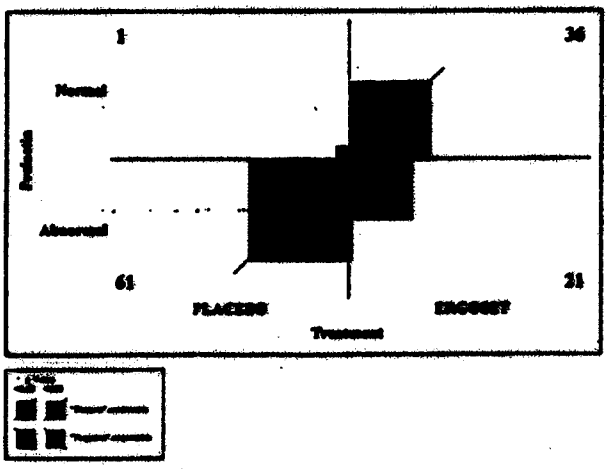
2 X 2 Table Plot: Treatment by Prolactin, Study K



2 X 2 Table Plot: Treatment by Prolactin, Study L

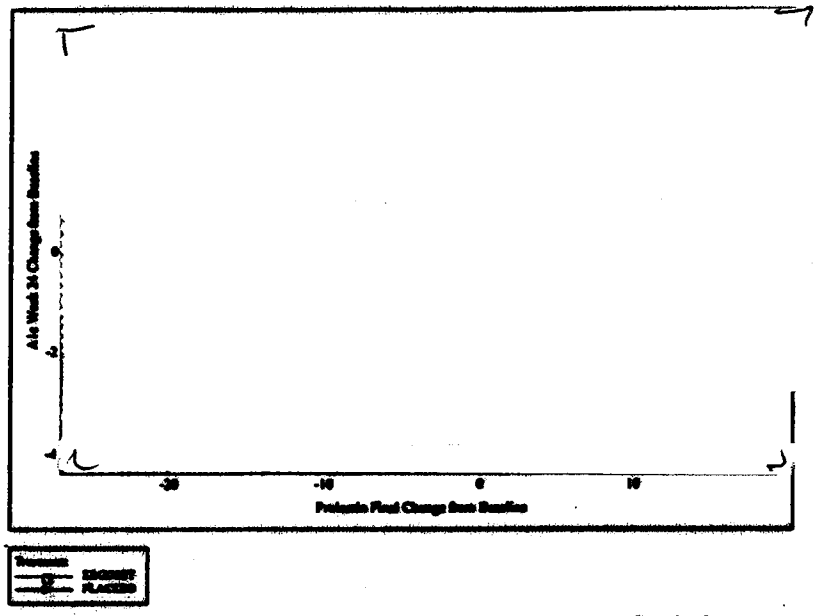


2 X 2 Table Plot: Treatment by Prolactin, Study M



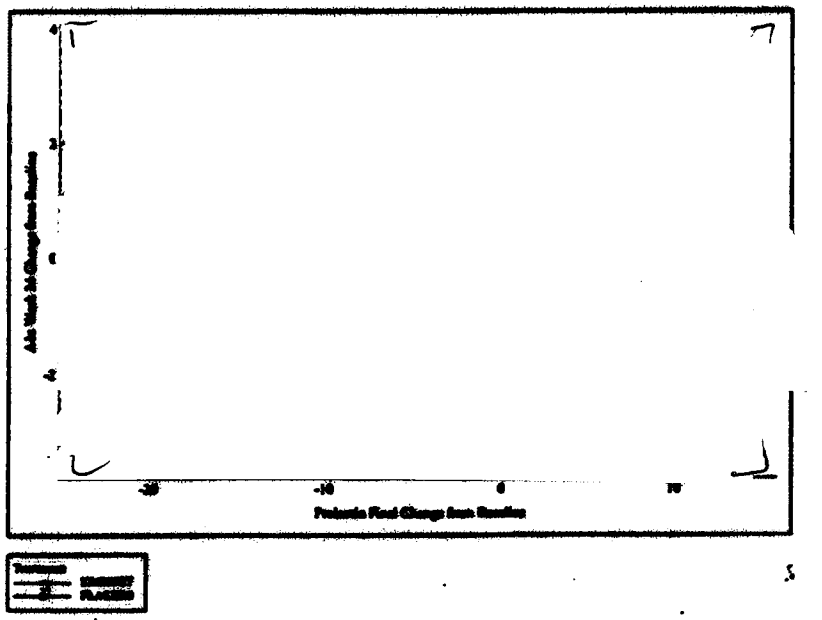
The correlation between change from baseline of A_{1c} and change from baseline of fasting prolactin is not established in Studies K and L but the correlation in Study M is 0.3 (p=0.03) for the Ergoset group and -0.2 (p=0.2) in the placebo group.

Change from Baseline at Week 24: Prolactin vs. A1c, Study K



b(4)

Change from Baseline at Week 24: Prolactin vs. A1c, Study L



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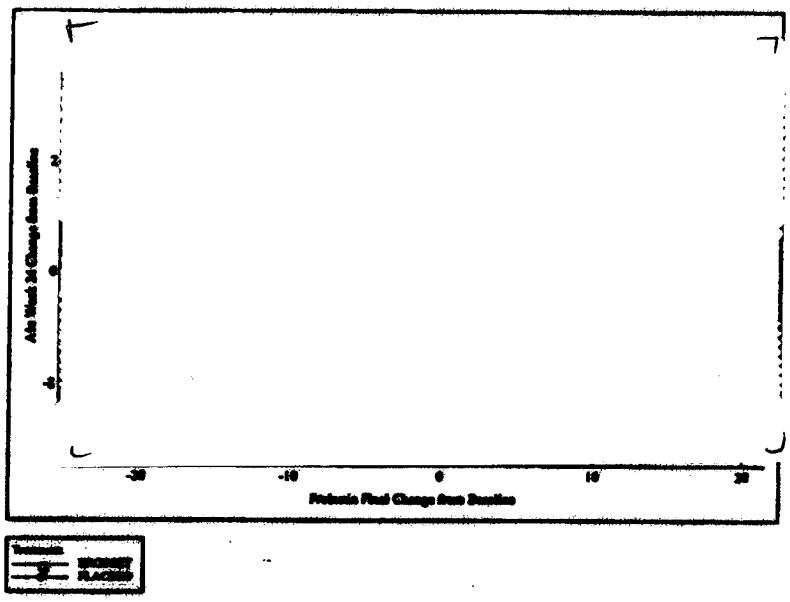
Change from Baseline at Week 24: Prolactin vs. A_{1c}, Study M



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Study G

Study Population

Patients in the study were type II NIDDM patients 30 to 80 years of age with a BMI of ≥26 (kg/m^2) and a glycated hemoglobin A_{1c} ≥7.5%. Patients were stable for 1 month before Week -4 with treatment of standard diet therapy and/or a SOHA. Patients with normal prolactin diurnal profile were excluded from the study.

Patient Disposition

A total of 99 patients were randomized at 2 centers, 48 to the bromocriptine group and 51 to the placebo group. In the Ergoset group, 19 of the 48 patients were assigned to maintain an isocaloric diet and 29 were assigned a hypocaloric diet. In the placebo group, 23 of the 5 patients were assigned to the isocaloric diet and 28 were assigned a hypocaloric diet. The Waltham center enrolled 71 (72%) patients, and the Hartford center enrolled 28 (28%) patients. Forty-two patients (87.5%) in the bromocriptine group and 47 patients (92.2%) in the placebo group completed the study. Reasons of premature withdraw from the study are displayed in Table 53.

Table 53: Disposition of Patients

Patient Status	Ergoset	Placebo	Total
Randomized	48	51	99
Intent to Treat	48	51	99
Completed	42 (87.5%)	47 (92.2%)	89 (89.9%)
Withdrawn	6 (12.5%)	4 (7.8%)	10 (10.1%)
Protocol violation	3	2	5
Adverse events	2	1	3
Intercurrent illness	1	1	2

For protocol violations, 3 Ergoset and 2 placebo patients, did not meet inclusion/exclusion criteria. One of the Ergoset patient withdrawn fro the study because his physician prescribed a beta blocker. The other tw patients were unable to comply with the protocol or commit sufficient time. One of placebo patient withdrew due to side-effect; the other patient was unable to comply with the study visits.

Demographic and Baseline Characteristics

The demographic and baseline characteristics are displayed in Table 5 for the intent-to-treat population.

Table 54: Demographic and Baseline Characteristics - Study G

	Ergoset (n=48)	Placebo (n=51)
Age (years)		
Mean (SD)	55.7 ± 8.8	54.9 ± 8.3
Race		
White	46 (95.8%)	48 (94.1%)
Black	1 (2%)	3 (5.9%)
Hispanic	1 (2%)	-
Sex		
Male	40 (83.3%)	44 (86.3%)
Female	8 (16.7%)	7 (13.7%)
Weight (lbs)		
Mean ± SD	208.3 ± 33.8	222.6 ± 41.8

There is no baseline significant difference between treatment groups with respect to age, race, sex, height, baseline body weight, duration of NIDDM, number of patients per center, concurrent SOHA use, or assignment to an isocaloric or a hypocaloric diet.

Efficacy analyses

There was no statistically significant difference between treatment groups in mean changes from baseline to endpoint HbA_{1c} (%) or any of the secondary outcome variables; glucose (p=0.51), insulin (p=0.28), total cholesterol (p=0.63), triglycerides (p=0.52), systolic blood pressure (p=0.06), diastolic blood pressure (p=0.55), body weight and body density (p=0.09). The HbA_{1c} mean change from baseline at endpoint for the intent-to-treat population is in Table 55.

Table 55: Mean Change from Baseline in Glycated Hemoglobin A_{1c} (%) at Endpoint

Time point	Ergoset n	Ergoset	Change from baseline	Placebo n	Placebo	Change from Baseline	Treatment Difference	p-value
Baseline	48	9.3 (1.5)		51	9.4 (1.6)			
Endpoint	48	9.2 (1.6)	-0.1 (0.9)	51	9.7 (2.1)	0.3 (1.4)	-0.4	0.10

Safety evaluation

No patients died during the study. Two Ergoset patients and one placebo patient were prematurely withdrawn from the study because of adverse events. Two Ergoset patients and one placebo patient had a serious adverse event. The two serious adverse events in Ergoset were carcinoma liver (#245) and atrial flutter (#258). For the placebo patient, the serious adverse event was polyp colon (#246).

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Integrated Efficacy

Disposition of Patients

In Studies K, L, and M, a total of 324 patients were randomized to the Ergoset group and 329 to the placebo group. Table 56 displays patient disposition. Approximately 25% (81) of the Ergoset patients and 16% (52) of the placebo patients did not complete the study.

Table 56: Patient Disposition – Studies K, L, and M

Patient Status	Ergoset	Placebo
Randomized	324	329
Efficacy populations		
Intent-to-treat	314	325
Efficacy evaluable	295	315
Completed study	243	277
Withdrawn from study	81 (25.2%)	52 (15.8%)
Reasons for withdrawal		
Protocol violation	15 (5%)	7 (2%)
Adverse events	41 (13%)	11(3%)
Laboratory abnormality	1 (<1%)	1 (<1%)
Request to withdraw	9 (3%)	19 (6%)
Noncompliance	14 (4%)	12 (4%)
Other	1 (<1%)	2 (<1%)

Demographic and baseline characteristics

There were no significant differences between the two treatment groups in any of the demographic or baseline characteristics (Table 57). Overall, patients were white (75%), male (73%), and obese (mean BMI 32.(kg/m^2) with a mean age of 55.1 years (30 - 73 years).

Table 57: Integrated Patient Demographic Characteristics

Variable	Ergoset (n=314)	Placebo (n=325)	p-value
Age (yrs)			
Mean (SEM)	55.3 (0.51)	54.6 (0.50)	0.32
Range	30 – 72	33 – 73	
Sex			
Male	225 (72%)	243 (75%)	0.42
Female	89 (28%)	82 (25%)	
Race			
White	230 (73%)	249 (77%)	0.37
Black	26 (8%)	15 (5%)	
Hispanic	47 (15%)	52 (16%)	
Other	11 (4%)	9 (3%)	
Weight (lbs)			
Mean (SEM)	207.1 (1.81)	209.6 (1.75)	0.27
Range	142 – 311	136 – 300	
Height (in)			
Mean (SEM)	67.6 (0.21)	67.7 (0.20)	0.51
Body Mass Index (kg/m^2)			
Mean (SEM)	31.9 (0.21)	32.1 (0.21)	0.34
Range	25.0 – 40.7	25.4 – 40.4	

Table 58: Integrated Baseline Diabetic Status: Studies K, L, and M

Variable	Ergoset (n=314)	Placebo (n=325)	p-value
HbA_{1c}			
Mean (SEM)	9.21 (0.068)	9.27 (0.065)	0.0001
Range	6.8 – 12.5	6.7 – 12.9	
NIDDM Duration (yrs)			
Mean (SEM)	5.5 (0.3)	6.0 (0.31)	0.73
Range	0 – 35	0 - 28	
Fasting Glucose (mg/dL)			
Mean (SEM)	217 (3.0)	221 (3.0)	0.60
Range	90 – 383	101 – 408	
Fasting Insulin (μU/dL)			
Mean (SEM)	23.7 (0.82)	24.1 (0.85)	0.68
Fasting Triglycerides (mg/dL)			
Mean (SEM)	273 (10.8)	272 (8.3)	0.82
Fasting Fatty Acids (mEq/L)[1]			
Mean (SEM)	0.76 (0.036)	0.78 (0.031)	0.50
Total Cholesterol (mg/dL)			
Mean (SEM)	215 (2.5)	210 (2.1)	0.13
SOHA Use[2]			
Diabeta	33 (14%)	33 (13%)	0.45
Glipizide	26 (11%)	38 (15%)	
Glucotrol	22 (9%)	21 (9%)	
Glyburide	83 (35%)	71 (29%)	
Glynase	23 (10%)	33 (13%)	
Micronase	30 (13%)	26 (11%)	
Others[3]	20 (8%)	26 (11%)	

[1] Data from Studies L and M

[2] Data from Studies K and L

[3] Others includes Chlorapropamide, Diabinese, Dymelor, Glucotrolix, Glucotrolext, Glucotrolxl, Tolazamide, and Tolbutamide.

Table 59 is a summary of the three Phase III studies.

Table 59: Summary of Studies K, L, and M

Design	K	L	M	
Completion	1/3/95, 3/29/96	1/17/95, 4/23/96	1/16/95, 10/19/96	
Location	United States			
Design Indication	Adjunct to SOHAs		Monotherapy	
Multicenter	8	10	13	
Treatment Duration	2 4 weeks			
Dosage	Timed (8 AM ± 30 mins) Dose titration over 6 weeks from 0.8 mg to 4.8 mg with increment of 0.8 mg (1 to 6 tablets			
n				Total
Ergoset	122	122	80	324
Placebo	123	127	79	329
Age Range (Mean)				
Ergoset	31 – 72 (54.5)	30 – 70 (55.8)	32 – 72 (54.9)	
Placebo	33 – 73 (54.3)	38 – 71 (55.5)	36 – 69 (53.8)	
% Male/Female				
Ergoset	72/28	70/30	71/29	
Placebo	78/22	69/31	80/20	
% B/W/O				
Ergoset	9/79/12	8/67/25	10/73/17	
Placebo	6/79/15	4/72/24	4/81/15	
Primary Efficacy Change from Baseline HbA_{1c} at Endpoint	-0.49 (p=0.004)	-0.59 (p≤.001)	-0.38 (p=0.052) -0.44 (p=0.03) (combining 4 smaller centers)	

Subgroup analysis

Table 60 displays the mean change from baseline to Week 24 in glycated hemoglobin A_{1c} by age group for Studies K, L, and M combined. HbA_{1c} decreased in all Ergoset age groups except for patients 30-45 years of age. P-value for the treatment by age interaction was 0.28.

Table 60: Week 24 Mean Change from Baseline in HbA_{1c} by Age Group

Age (years)	n	Ergoset	n	Placebo	Treatment Difference
30-45	36	0.17 (0.20)	45	0.79 (0.18)	-0.62
46-50	52	-0.31 (0.14)	56	0.50 (0.15)	-0.81
51-55	42	-0.10 (0.20)	52	0.29 (0.16)	-0.39
56-60	51	-0.12 (0.15)	59	0.40 (0.11)	-0.52
61-65	53	-0.20 (0.17)	44	0.16 (0.15)	-0.36
>65	42	-0.40 (0.14)	44	-0.14 (0.20)	-0.54
Total	276	-0.17 (0.07)	300	0.34 (0.07)	-0.51

Race

Table 61 displays the mean change from baseline at endpoint of HbA_{1c} by racial groups. The p-value for treatment-by-race interaction is 0.17. If the 'Other' race is not included in the analysis, there is no treatment-by-race interaction (p=0.7).

Table 61: Mean Change from Baseline at Endpoint in HbA_{1c} by Race – Studies K, L, and M

Race	n	Ergoset Mean (SD)	n	Placebo Mean (SD)	Treatment Difference
Caucasian	223	-0.19 (1.06)	245	0.33 (1.53)	-0.52
Hispanic	42	-0.17 (1.11)	51	0.22 (1.03)	-0.39
Afro American	26	0.12 (1.31)	14	0.78 (1.28)	-0.66
Asian	5	0.18 (0.53)	3	0.33 (1.53)	-0.15
Other	6	-1.65 (1.17)	6	0.73 (1.76)	-2.38
Total	302	-0.18 (1.11)	319	0.34 (1.11)	-0.51

Gender

Table 62 displays the endpoint mean change from baseline in HbA_{1c} by gender. The treatment-by-gender interaction was not statistically significant (p=0.55).

Table 62: Mean Change from Baseline at Endpoint in HbA_{1c} by Gender – Studies K, L, and M

Gender	n	Ergoset Mean (SD)	n	Placebo Mean (SD)	Treatment Difference
Male	218	-0.17 (1.12)	217	0.32 (1.18)	-0.49
Female	84	-0.22 (1.07)	81	0.40 (0.92)	-0.62
Total	302	-0.18 (1.11)	319	0.34 (1.11)	-0.51

Safety Evaluation

Adverse Events

Overall Incidence of Adverse Events

Summary of adverse events is displayed in Table 63 for studies K, L, and M. The drug related adverse events were statistically significantly greater ($p<0.0001$) in the Ergoset patients than the placebo patients (53% vs. 22%, 58% vs. 30% & 56% vs. 24%, respectively for studies K, L, & M). The adverse events that lead to treatment discontinuation were statistically significantly higher in the Ergoset patients (12% vs. 2%, 14% vs. 3%, & 13% vs. 5%, respectively).

Table 63: Summary of Adverse Events

Adverse Event	Study K		p-value	Study L		p-value	Study M		p-value
	Ergoset n=122	Placebo n=123		Ergoset n=122	Placebo n=127		Ergoset n=80	Placebo n=79	
Any	112 (92%)	101 (82%)	0.036	101 (83%)	105 (83%)	1.000	72 (90%)	63 (80%)	0.080
Drug related	64 (53%)	27 (22%)	<0.0001	71 (58%)	38 (30%)	<0.0001	45 (56%)	19 (24%)	<0.0001
Deaths	0	0	-	0	0	-	0	0	-
Treatment discontinuation	14 (12%)	3 (2%)	0.006	17 (14%)	4 (3%)	0.003	10 (13%)	4 (5%)	0.160
Serious	4 (3%)	3 (2%)	0.722	2 (2%)	1 (1%)	0.616	0	2 (3%)	0.245
Severe	16 (13%)	7 (6%)	0.051	8 (7%)	7 (6%)	0.794	0	2 (3%)	0.245

Frequent Adverse Events

The incidence of adverse events that occurred more frequent in the Ergoset group (except hyperglycemia) than the placebo group is displayed in Table 64.

Table 64: Frequent Adverse Events – Studies K, L, & M

Adverse Event	Study K Ergoset n=122	Study K Placebo n=123	p-value	Study L Ergoset n=122	Study L Placebo n=127	p-value	Study M Ergoset n=80	Study M Placebo n=79	p-value
Nausea	35 (29%)	4 (3%)	<0.0001	27 (22%)	8 (6%)	<0.0001	26 (33%)	6 (8%)	<0.001
Asthenia	22 (18%)	8 (7%)	0.006	24 (20%)	12 (10%)	0.03	10 (13%)	5 (6%)	0.278
Rhinitis	13 (11%)	5 (4%)	0.054	13 (11%)	7 (6%)	0.164	11 (14%)	3 (4%)	0.047
Sinusitis	11 (9%)	5 (4%)	0.129	7 (6%)	11 (9%)	0.466	8 (10%)	2 (3%)	0.098
Hypoglycemia	10 (8%)	1 (1%)	0.005	11 (9%)	12 (10%)	1.000	2 (3%)	1 (1%)	-
Hyperglycemia	13 (11%)	15 (12%)	0.841	1 (1%)	8 (6%)	0.036	10 (13%)	9 (11%)	1.000
Dizziness	10 (3%)	4 (3%)	0.107	19 (16%)	10 (8%)	0.075	10 (13%)	6 (8%)	0.430
Constipation	14 (12%)	7 (6%)	0.116	10 (8%)	4 (3%)	0.102	9 (11%)	3 (4%)	0.131
Amblyopia	6 (4.9%)	3 (2.4%)	-	7 (5.7%)	3 (2.4%)	-	6 (7.5%)	1 (1.3%)	0.117
Somnolence	5 (4.1%)	2 (1.6%)	-	11 (9.0%)	3 (2.4%)	0.028	3 (3.8%)	-	-
Vomit	5 (4.1%)	3 (2.4%)	-	8 (6.6%)	5 (3.9%)	-	5 (6.3%)	1 (1.3%)	0.210
Pain Abdominal	7 (5.7%)	3 (2.4%)	0.216	5 (4.1%)	5 (3.9%)	-	3 (3.8%)	3 (3.8%)	-

In Studies K, L, & M, the most frequent adverse event was nausea in the Ergoset group (29%, 22%, 33%) compared with the placebo group (3%, 6%, 8%) which was statistically significant ($p<0.001$). Nausea was the reason cited for 6, 5, and 1 Ergoset patients, respectively, in studies K, L, and M who discontinued prematurely.

Adverse Events by Subgroups

Age

Of the 324 patients receiving Ergoset, 93 (29%) were 30-49 years old, 175 (54%) were 50-64 years old, and 56 (17%) were 65 years of age or older. Of the 329 patients receiving placebo, 103 (32%) were 30-49 years old, 170 (52%) were 50-64 years old, and 56 (17%) were 65 years of age or older.

Table 65 displays the four adverse events that occurred at a relatively higher incidence in older Ergoset-treated patients than in older patients receiving placebo or in younger Ergoset patients.

Table 65: Adverse Events Incidence by Age Group

Adverse Event	Ergoset Age group				Placebo Age group			
	30-49 (n=93)	50-64 (n=175)	≥65 (n=56)	Total (n=324)	30-49 (n=103)	50-64 (n=170)	≥65 (n=56)	Total (n=329)
Asthenia	11 (14%)	35 (20%)	10 (18%)	56	9 (10%)	12 (7%)	4 (7%)	25
Nausea	26 (28%)	43 (25%)	19 (34%)	88	6 (7%)	9 (5%)	3 (5%)	14
Dizziness	8 (10%)	20 (11%)	11 (20%)	39	7 (7%)	10 (6%)	3 (5%)	20
Rhinitis	11 (12%)	17 (10%)	9 (16%)	37	6 (7%)	6 (4%)	3 (5%)	15

Race

The sponsor's subgroups were white and nonwhite (blacks, Hispanics, Asians and other races). Nausea occurred more frequently in white Ergoset patients (30%) than in nonwhite Ergoset patients (21%). Somnolence was more frequent in nonwhite than in white Ergoset patients (10% vs. 4%, respectively).

Table 66 Adverse Events Incidence by Race

Adverse Event	Ergoset (n=324)		Placebo (n=329)	
	White n=236	Nonwhite n=88	White n=252	Nonwhite n=77
Nausea	70 (30%)	18 (21%)	14 (6%)	4 (5%)
Somnolence	10 (4%)	9 (10%)	3 (1%)	2 (3%)

Gender

In the pooled phase III studies (K, L, & M), the incidence of vomiting was seven times higher in women than men for the Ergoset group compared with twice as high in women than men receiving placebo (Table 67).

Table 67 Adverse Event Incidence by Gender

Adverse Event	Ergoset (n=324)		Placebo (n=329)		Test for Homogeneity
	Men n=231 (71%)	Women n=93 (29%)	Men n=247 (75%)	Women n=82 (25%)	p-value
Vomit	5 (2%)	13 (14%)	6 (2%)	3 (4%)	0.07
Nausea	54 (23%)	34 (37%)	10 (4%)	8 (10%)	0.58
Constipation	26 (11%)	7 (8%)	9 (4%)	5 (6%)	0.17

Adverse Events of Particular Concern

Symptomatic hypoglycemia

In the adjunctive therapy studies K and L, 21 of 244 (8.6%) Ergoset treated patients and 13 of the 250 (5.2%) placebo treated patients experienced the incidence of hypoglycemia. In the monotherapy study M, the incidence was lower with 2 of 80 (2.5%) in Ergoset patients and 1 of 79 patients (1.3%) in the placebo group.

The myocardial infarction is another adverse event of concern. The incidence of myocardial infarction in Ergoset patients excluding the pharmacokinetic studies was 1.9 per 100 patient exposure years compared with 0.6 per 100 patient exposure years in placebo patients. When combined with angina pectoris, the total incidence rate is 3.4 per 100 patient years for Ergoset patients and 2.4 per 100 patient years for patients in the placebo group. For studies K, L, & M, Table 67 displays the incidence rates for myocardial infarction and angina pectoris.

Table 68: Incidence for Myocardial Infarction and Angina Pectoris

Cardiovascular System	Study K		Study L		Study M	
	Ergoset n=122	Placebo n=123	Ergoset n=122	Placebo n=127	Ergoset n=80	Placebo n=79
Infarction myocardial	3 (2.5%)	-	-	1 (0.8%)	-	-
Angina pectoris	2 (1.6%)	2 (1.6%)	1 (0.8%)	-	-	1 (1.3%)

Table 69 is a list of patients who discontinued or experienced a cardiovascular related adverse events for both controlled and non-controlled studies.

Table 69 Patients who discontinued or experienced a serious (bold) vascular-related Adverse Event

Patient # Age, Race, Gender	COSTART Code	Treatment Dose Group	Drop Out Day	Severity	Relationship to Study Drug	Outcome
Study K						
1311509 63 White Female	**infarct myocardial**	**Ergo 4.8 mg**	**55**	**Severe**	**Possible**	**Resolved**
1311543 54 White Male	**infarct myocardial**	**Ergo 1.6 mg**	**43**	**Mild**	**Remote**	**Resolved**
1312511 73 White Male	**Infarct myocardial**	**Ergo 4.8 mg**	**178**	**Severe**	**None**	**Resolved**
1311058 57 Hispanic Male	**Pain chest**	**Placebo**	**157**	**Mild**	**None**	**Resolved**
1311290 56 White Male	**Cerebrovascular accident (mild CVA)**	**Placebo**	**14**	**Severe**	**None**	**Improved**
1311325 .8 White Male	**Angina pectoris**	**Placebo**	**189**	**Severe**	**None**	**Resolved**
Study L						
1324806 53 White Female	**Thrombosis (TKR)**	**Ergo 1.6 mg**	**44**	**Severe**	**None**	**Resolved**
1326019 62 White Female	**Angina pectoris (required beta blocker after angioplasty)**	**Ergo 4.8 mg**	**51**	**Moderate**	**Remote**	**Resolved**
1323509 51 White Female	**Pain Chest**	**Placebo**	**62**	**Severe**	**Possible**	**Improved**
1326528 50 Hispanic Male	**Infarction myocardial (chest pain, CABG X6)**	**Placebo**	**168**	**Severe**	**None**	**Unchanged**
Study M						
1339028 49 White Female	**Angina pectoris (required beta blocker for angina)**	**Placebo**	**39**	**Mild**	**Remote**	**Improved**
Study KX						
1311065 72 White Male	**Heart failure right (congestive heart**	**Ergo 3.2 mg**	**26**	**Severe**	**None**	**Improved**

Patient # Age, Race, Gender	COSTART Code	Treatment Dose Group	Drop Out Day	Severity	Relationship to Study Drug	Outcome
	failure)					
1311104 56 White Male	Tachycardia (rapid heart beat)	Ergo 4.8 mg	35	Mild	Possible	Resolved
1311281 57 White Male	Angina pectoris (angina)	Ergo 4.8 mg	130	Moderate	None	Resolved
1311341 55 White Man	Infarction myocardial (MI)	Ergo 2.4 mg	11	Moderate	None	Resolved
1311501 44 White Male	Coronary artery disorder (right coronary artery disease)	Ergo 2.4 mg	157	Severe	Remote	Resolved
1312274 46 White Male	Infarction myocardial (MI)	Ergo 4.8 mg	94	Severe	Remote Possible?	Resolved
1312508 53 White Male	Coronary artery disorder (coronary artery blockage)	Ergo 4.8 mg	104	Severe	Remote	Unchanged
1312529 [illegible]8 White Male	Infarction myocardial (MI)	Ergo 0.8 mg	2	Severe	None	Resolved
Study LX						
1324792 65 White Male	Cardiovascular disorder	Ergo 0.8 mg	7	Severe	None	Worsened
Study MX						
1338259 67 White Male	Infarction myocardial (heart attack)	Ergo 4.8 mg	45	Severe	None	Death
1338765 70 White Man	Pain Chest (chest pain)	Ergo 4.8 mg	137	Severe	Remote	Resolved
Study H						
206 52 White Female	206 pain chest (aching chest)	Ergo 3.2 mg	6	Mild	Possible	Resolved
409 54 White Female	Pain chest (weight on chest)	Ergo 1.6 mg	1	Mild	Probable	Resolved
Study KXX						
1311515 69 White Male	Pain chest	Ergo4.8 mg	5	Mild	Remote	Unchanged
1312017 49 White Male	Infarct myocardial (Acute)	Ergo 4.8 mg	131	NA	Remote	Resolved

Serious Adverse Events

A serious adverse event is defined as any event that is fatal or life threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital abnormality, cancer, or overdose.

A total of 29 of the 1096 patients (2.6%) had serious adverse events 22 of 894 (2.5%) Ergoset patients and 7 of 416 (1.7%) placebo patients had adverse events. These events are listed by frequency in Table 70.

Table 70 Serious Adverse Events in All Studies in NDA Combined

Adverse Event	Ergoset (n=894)	Placebo (n=416)
Infarction myocardial	7 (0.8%)	1(0.2%)
Carcinoma	2 (0.2%)	0
Coronary artery disorder	2 (0.2%)	0
Liver function abnormal	2 (0.2%)	0
Angina pectoris	1 (0.1%)	1 (0.2%)
Cerebrovascular accident	0	1 (0.2%)
Cholelithiasis	1 (0.1%)	0
Flutter atrial	1 (0.1%)	0
Heart failure right	1 (0.1%)	0
Lymphoma-like reaction	1 (0.1)	0
Nausea	1 (0.1)	0
Neoplasm	0	1 (0.2%)
Neoplasm mouth	0	1 (0.2%)
Pain chest	1 (0.1%)	1 (0.2%)
Peptic ulcer	0	1 (0.2%)

Myocardial infarction was the most frequent serious adverse event in all the NDA studies combined. Seven (0.8%) of the 894 patients treated with Ergoset and 1 (0.2%) out of the 416 patients treated with placebo had a serious myocardial infarction. Myocardial infarction was the most frequently serious adverse event occurring in the phase III studies (K, L, and M): in 3 of 324 (0.9%) Ergoset patients and in 1 of 329 (0.3%) placebo patients (Table 67).

Conclusions:

All three studies, K, L, and M demonstrated at Week 24 from randomization a small but statistically significant difference in mean change from baseline in glycated hemoglobin A_{1c} comparing Ergoset with placebo. The difference in mean change from baseline at endpoint (LOCF) between Ergoset and placebo treated patients was -0.49%, -0.59% for the

two adjunctive studies K and L, respectively. For the monotherapy study, the difference was -0.38%. The comparison of the predictive responders from the Ergoset group to the totality of the placebo patients is a biased comparison, therefore all the predictive responders analysis should be removed from the annotated package insert.

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cc: Arch NDA 20-866
HFD-510
HFD-510/SSobel/AFleming
HFD-510/JGueriguian
HFD-510/EGalliers
HFD-510/MJohnston
HFD-715/Division file, LPian, MNg, Chron
Chron.

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