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APPLICATION NUMBER:

20-866

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Trade Name	Cycloset
Therapeutic Class	Antidiabetic
Applicant	Veroscience
Priority Designation	Standard
Formulation	oral
Indication	Hyperglycemia
Intended Population	Type 2 Diabetes

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATION ON REGULATORY ACTION

Cycloset (bromocriptine) is effective in lowering HbA1c across a wide spectrum of patient with type 2 diabetes. FDA's earlier concern about cardiovascular safety has been satisfied. Given its modest efficacy, it is likely that Cycloset will be used primarily as an adjunct to other antidiabetic agents. Nausea will limit its acceptability. In addition to reducing HbA1c, bromocriptine treatment led to small but consistent decreases in systolic and diastolic blood pressure. Taken together, these effects would be expected to decrease the long term risk of the complications of diabetes, particularly retinopathy and nephropathy. An unexpected finding from the recently completed safety trial was an apparent decrease in serious cardiovascular events, especially in patients with HbA1c of 7% or less at baseline. The Sponsor should be encouraged to attempt to replicate this finding.

The NDA should be approved assuming that satisfactory changes are made to the proposed label.

1.2 SUMMARY OF CLINICAL FINDINGS

Development of bromocriptine (using the Tradename Ergoset) for treatment of type 2 diabetes (T2DM) was undertaken by Ergo Science in the mid 1990's. Results of three, 24 week comparisons of bromocriptine to placebo were put forth as a basis for approval. The NDA was discussed on May 14, 1998 at a meeting of the Endocrine and Metabolic Drugs Advisory Committee, which voted unanimously that Ergoset should not be approved.

Ergoset was better than placebo with respect to change in HbA1c in all three studies, but the treatment difference, approximately 0.5% units was small. With respect to safety, it was noted that bromocriptine had lost the indication to suppress postpartum lactation in 1994 because of reports of myocardial infarction and stroke in otherwise healthy young women. Although there were few serious cardiovascular adverse events in diabetes trials of Ergoset, the possibility of an imbalance in the risk of myocardial infarction was also cause for concern

A complete response to FDA's approvable letter, submitted by the Sponsor Dec 27, 2007, contained the results of a 12 month safety trial (165-AD-04-03-US-1). In this trial, patients were randomized 2:1 to bromocriptine or placebo. The primary endpoint was occurrence of serious adverse events (SAE). There were 176/2054 (8.6%) SAE's on Cycloset and 98/1016 (9.6%) on placebo. Cycloset met the test of noninferiority set forth in the protocol and statistical plan. Although there was no difference in occurrence of

SAE's, there was a statistically significant reduction in the composite cardiovascular endpoint among patients receiving Cycloset (table 18).

Table 18. Composite and Individual Cardiovascular Serious Adverse Events (ITT Population)

	Cycloset (N=2054) n (%)	Placebo (N= 1016) n (%)	Hazard Ratio (95% CI)[1] n (%)
Composite Cardiovascular Endpoint	31 (1.5%)	30 (3.0%)	0.58 (0.35 – 0.96)
Individual Cardiovascular Endpoints[2]			
Myocardial Infarction	6 (0.3%)	8 (0.8%)	0.44 (0.15 – 1.26)
Stroke	4 (0.2%)	6 (0.6%)	0.37 (0.10 – 1.32)
Inpatient Hospitalization for Angina	9 (0.4%)	9 (0.9%)	0.55 (0.22 – 1.38)
Inpatient Hospitalization for Heart Failure	7 (0.3%)	5 (0.5%)	0.81 (0.26 – 2.57)
Coronary Revascularization Surgery	9 (0.4%)	6 (0.6%)	0.85 (0.30 – 2.40)
Coronary revascularization following primary event	9 (0.4%)	10 (1.0%)	0.50 (0.20 – 1.24)

[1] From the Cox regression, 95% two sided hazard ratio confidence limits

[2] For individual cardiovascular endpoints — individuals may appear in multiple categories if they experience more than one event (i.e. individual that experienced both a stroke and a MI would appear in both categories)

Source: Table 14.2.2.1

Nausea was reported by 32.2% of patients on Cycloset and 7.6% on placebo. Dizziness was reported by 14.8% of patients on Cycloset and 9.2% on placebo. There were small but statistically significant decreases in systolic and diastolic blood pressure, Cycloset vs placebo, throughout the trial. The difference appeared greatest at week 12 (Systolic bp: Cycloset -2.0 mm Hg placebo -0.5 mmHg, p=0.0003).

The specified efficacy subgroup consisted of patients with HbA1c greater than 7.5% at baseline while talking at least one oral hypoglycemic agent. This consisted of 559 subjects, 376 on Cycloset and 183 on placebo. Efficacy changes are summarized in Table 20. The mean HbA1c fell approximately -0.6% units with Cycloset and changed little with placebo. Glucose levels fell with Cycloset as well. There was little change in lipid or insulin levels, and no statistically significant difference in these parameters between Cycloset and placebo. Mean body weight changed little in either arm.

Table 20 Glycemic Parameters in Cycloset Safety Study among Patients with Type 2 Diabetes Poorly Controlled on Oral Diabetes Agents

	24 – Week ITT[1,2] Completers		24 – Week[3] Evaluable per Protocol	
Adjunct to Metformin+/- other diabetes oral agent	**Cycloset**	**Placebo**	**Cycloset**	**Placebo**
HbA1c (%)	N = 181	N = 101	N = 166	N = 100
Baseline mean	8.3	8.4	8.3	8.3
Change from baseline (adjusted mean)	-0.6	0.1	-.6	0.1
Difference from placebo (adjusted mean) p-value	-0.7 <0.0001		-0.7 <0.0001	
% Subjects achieving A1c of ≤ 7.0 p-value	36 <0.0001	10	36 <0.0001	9
Adjunct to Sulfonylurea +/- other oral diabetes agent				
HbA1c (%)	N = 176	N = 106	N = 162	N = 106
Baseline mean	8.3	8.3	8.3	8.3
Change from baseline (adjusted mean)	-0.6	0.02	-0.6	0.02
Difference from placebo (adjusted mean) p-value	-0.6 <0.0001		-0.6 0.0002	
% Patients achieving HbA1c of ≤ 7.0 p-value	34 0.0001	10	35 0.0001	10
Adjunct to Metformin + Sulfonylurea				
HbA1c (%)	N = 121	N = 71	N = 110	N = 71
Baseline mean	8.3	8.3	8.3	8.3
Change from baseline (adjusted mean)	-0.7	0.01	-0.7	0.01
Difference from placebo (adjusted mean) p-value	-0.7 0.0002		-0.7 0.0005	
% Patients achieving HbA1c of ≤ 7.0 p-value	39 0.0004	11	40 0.0005	11

[1] Intent to treat population that completed 24 weeks of treatment.

[2] Analyses of the ITT population using the last observation carried forward yielded significant reductions in the differences in the mean changes in HbA1c across all groups in favor of CYCLOSET (-0.5% HbA1c for adjunct to metformin +/- oral agent, -0.4%for adjunct to sulfonylurea +/- oral agent, -0.5% HbA1c for adjunct to metformin and sulfonylurea).

[3] Evaluable per protocol population where patients completing 24 weeks of treatment without major protocol violations and at least 80% compliant with study drug dosing.

2 INTRODUCTION AND BACKGROUND

2.1 Background

Type 2 diabetes results when the beta cells of the pancreas are unable to secrete enough insulin to overcome insulin resistance. In the past, development of new drugs to treat type 2 diabetes has targeted the beta cells themselves, and insulin-sensitive tissues (muscle, liver and fat). Because it acts directly on the brain, bromocriptine is a step in a different direction. This approach has been a long time in coming. As we are reminded by Schwartz and Porte (1), Claude Bernard anticipated in 1854 that the brain played an important role in the development of diabetes. It is now believed that the brain is the control center of a feed back system that has evolved over time to promote energy storage during times of plenty. This system involves insulin, leptin and various neurotransmitters, including dopamine (1,2).

A mechanism to store fat during periods of famines used to be important for survival. But the cycle of seven fat years and seven lean years foretold by Joseph in ancient Egypt has been replaced in modern Western society by uninterrupted abundance of calorie-rich food that can be obtained with little expenditure of energy. Under these conditions, efficiency of energy utilization and storage is no longer advantageous, but instead leads to obesity and diabetes (3-6).*

Bromocriptine is a dopamine receptor agonist that was approved in 1977. Its labeling includes treatment of hyperprolactinemia syndromes, prolactinomas, acromegaly and Parkinson's disease. The rationale for use of bromocriptine for treatment of type 2 diabetes comes largely from experiments in animals. Many vertebrate species develop hyperinsulinemia and obesity in preparation for periods of food deprivation such as hibernation or seasonal migration. When administered systemically or into the cerebral ventricle during the early hours of the light cycle, bromocriptine has been reported to prevent or reverse this seasonally related fat deposition and hyperinsulinemia (7).**

* References 3-6 provide a brief overview of the "thrifty gene" hypothesis first put forth by Neel in 1962.
** Reference 7 gives an authoritative discussion of this topic with many references.

2.2 Regulatory History

Development of a quick release formulation of bromocriptine (using the Tradename Ergoset) for treatment T2DM was undertaken by Ergo Science in the mid 1990's. Results of three pivotal trials were put forth as a basis for approval. Two trials were 24 week comparisons of bromocriptine to placebo in patients on sulfonylureas (trial K and L). One trial (trial M) was a 24 week comparison of bromocriptine to placebo in patients who were not taking other antidiabetic medications. The NDA was discussed on May 14, 1998 at a meeting of the Endocrine and Metabolic Drugs Advisory Committee; which voted unanimously that Ergoset not be approved.

Although bromocriptine beat placebo with respect to change in HbA1c in three phase 3 studies, the treatment difference, approximately 0.5% units, was small. The clinical significance of these results was suspect because of a consistent rise in glucose and HbA1c in placebo-treated subjects. Bromocriptine prevented this rise but did not appear to lower levels of glucose and HbA1c from baseline. Given the need to treat hyperglycemia in patients with diabetes, it was not clear what role could be played by bromocriptine.

The sense of the committee is largely captured by the observation of committee member, Dr Jaime Davidson, who noted (pages 261/262 of the transcript) that:

"In study L, the A1c at 24 weeks was the same as baseline. In every other study the A1c at 24 weeks is higher than baseline."

With respect to safety, it was noted that bromocriptine had lost the indication to suppress postpartum lactation in 1994 because of reports of myocardial infarction and stroke in otherwise healthy young women. Although there were few serious cardiovascular adverse events in trials of Ergoset, the possibility of imbalance in the risk of myocardial infarction was cause for concern.

In accordance with the recommendation of the advisory committee, FDA issued a "Not Approvable letter" on November 20, 1998. The Sponsor appealed this action, noting that efficacy had been established in all three phase 3 trials. In response to this appeal, FDA issued an "approvable letter" on October 15, 1999, stating that approval requires a favorable balance of benefit vs risk and that the risk of bromocriptine treatment had not been shown to outweigh the benefit. In a meeting on April 6, 2000, FDA stated that approval would require the Sponsor to perform a safety study which compared bromocriptine to placebo with ascertainment of myocardial infarction, stroke and death.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

See Section 5 for findings from the clinical pharmacology review. There were no approvability issues identified by the Chemistry and Pharmacology-Toxicology reviewers.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data and Review Strategy

Studies K and L were 24 week comparisons of bromocriptine to placebo in patients taking sulfonylureas. Study M was a 24 week comparison of bromocriptine to placebo in treatment naive patients. As noted above, FDA acknowledged in the "approvable" letter that these trials had established the efficacy of bromocriptine for treatment of type 2

diabetes. I have not rereviewed these trials but present the summary results for the sake of completion and to provide context.

The major focus of this review is the safety trial (165-AD-04-03-US-1). This trial was performed as required by FDA to provide assurance that bromocriptine did not increase the risk of serious adverse events, particularly events related to myocardial ischemia. This trial was conducted in a broad population of patients, that is much more representative than were the type 2 diabetes trials (K , L and M) in the original NDA. Efficacy data from this trial were reviewed to determine if the finding in the original trials was reconfirmed. Special attention was paid to subsets of patients taking metformin or metformin plus a sulfonylurea. Metformin is generally considered to be initial treatment of patients with type 2 diabetes. Because it was approved in 1995, metformin-treated patients were not studied in the original NDA. Because the safety trial (165-AD-04-03-US-1) is pivotal to approvability of the application, three clinical sites were inspected.

In this review, I use the term **Cycloset** to refer to the formulation of bromocriptine used in the safety trial (165-AD-04-03-US-1) and to the to-be-marketed formulation. The term **Ergoset** is used to refer to the formulation of bromocriptine used in trials in the original NDA.

4.2 Data Quality and Integrity

Three sites from the Safety Study (165-AD-04-03-US-1) were inspected. No important violations were found.

4.3 Compliance with Good Clinical Practices

A statement was signed 4/13/2008 by Dr Cincotta certifying that the Sponsor did not and will not use the services of any person debarred under section 306.

Patients received a standard of care that was consistent with what FDA has accepted in other programs for development of new oral antidiabetic drugs.

4.4 Financial Disclosures

Form 910-0396 was signed 4/13/2008 by Dr Cincotta certifying that he has not entered into a financial arrangement with the listed investigators and that the listed investigators did not disclose any propriety interest of receipt of significant payment as defined in 21 CFR 54.2(b). The list of investigators was appended.

5 CLINICAL PHARMACOLOGY:

Cycloset (bromocriptine mesylate tablets) is an immediate release formulation of bromocriptine mesylate. NDA 20-866 was originally filed by ErgoScience Corp in 1997. ErgoScience transferred the NDA to Pliva in 2003. Pliva then transferred the ownership of the NDA to VeroScience in May 2006. VeroScience collaborated with Pliva on the study design and execution of the safety study (# 165-AD-04-03-US-1) which started in July 2004.

Three different formulations were used in this NDA and are described in Table 1 below:

Table 1: Formulations used in development of Cycloset™

Sponsor	*Manufacturer of Cycloset™ Tablets*	*Formulation used in Clinical Trials*
ErgoScience	Geneva Pharmaceuticals, Broomfield, CO	Studies submitted with the originally filed NDA in 1999
Transferred to Pliva	Pliva, Croatia	Subsequent clinical studies, including safety trial (# 165-AD-04-03-US-1)
VeroScience	Patheon Inc, Cincinnati, Ohio	To-be-marketed formulation

The table and preceding text were taken from Clinical Pharmacology Review by Dr Vaidyanathan.

The Sponsor performed a study that established bioequivalence between the Pliva formulation (used in the safety trial) and the Pantheon (to be marketed) formulation. Supplies of the formulation (Geneva Pharmaceuticals) used in the original trials are no longer available, so bridging to the original trials cannot be done. For this reason, it is important that efficacy be demonstrated for the Pliva preparation. Although a rigorous comparison is not possible, the efficacy of the Pliva formulation appears to be similar to that of the Geneva formation. In sulfonylurea-treated patients, for example, the mean placebo-subtracted change in HbA1c was -0.55% at 24 weeks with the Geneva preparation (the original trials K and L) and -0.60% with the Pliva formulation (safety trial). As will be discussed in detail in section 6, there is little doubt that the Pliva

preparation is efficacious. Thus, the bioequivalence trial bridging the Pliva formulation and the Pantheon formulation is adequate for marketing of the Pantheon formulation.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Finding from the original NDA

6.1.1 Studies K and L combination with sulfonylureas

Studies K and L had the same trial design. They were comparisons of bromocriptine to placebo in patients on sulfonylureas.

Patients were age 30-72, BMI 26-40 for men and 28-40 for women, HbA1c 8.8-12.5% on a stable dose of oral agent other than metformin. Patients were given 0.8 mg tablet of Ergoset or placebo at 8:00 am with breakfast. The dose was increased by one tablet weekly until the sixth week when the maximum allowable dose, 4.8 mg , was attained. This dose was continued throughout the remaining 18 weeks. Patients unable to achieve 4.8 mg were allowed to remain in the study at their maximum tolerated dose provided it was at least 2 tablets (1.6 mg)

Because the studies had the same trial design, I have used the pooled results in the following text. Subjects in the ITT were 74% Caucasian and 72% male. The mean age was 54 year, mean BMI 32 kg/m2 and mean duration of T2DM 6 years. 71% of patients on Ergo and 90% on placebo achieved the maximal dose of 6 tablets (4.8 mg).

Mean HbA1c at baseline was 9.3% (n=237) for Ergo and 9.4% (n=248) for placebo. Mean change at final visit (LOCF) was -0.21 for Ergo (n=228) and +0.34 (n=245) for placebo. Mean change at 24 weeks (completers) was -0.21 for Ergo (n=183) and +0.35 (n=215) for placebo. A statistically significant difference was achieved by week 4 and remained throughout.

There were significant decreases in fasting and postprandial glucose, FFA and triglycerides with Ergoset. The mean change in body weight was +2.6 lbs with Ergo and +0.6 with placebo ($p<0.0002$).

Time courses of change in HbA1c for studies K and L are shown in the next two tables, These tables were taken from the 1998 review by FDA statistician Lee Pian

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	9.83	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

Changes in lipids for studies K and L are shown in table 25. There were reductions in triglyceride and total cholesterol relative to placebo.

Table 25. Plasma Triglyceride and Free Fatty Acid Level Changes in 24-Week Placebo Controlled Study of Cycloset in Patients with Type 2 Diabetes

	Study L		Study L		Study K		Study K	
	Fasting		Post Prandial[2]		Fasting		Post Prandial[2]	
	Cycloset	Placebo	Cycloset	Placebo	Cycloset	Placebo	Cycloset	Placebo
Triglycerides (mg/dl)[1]	N = 86	N = 106	N = 87	N = 106	N = 88	N = 95	N = 91	N = 100
Baseline triglyceride level	273	245	289	268	251	233	292	261
Change from baseline	-54.7	36.8	-44.3	31.5	-19.0	33.8	-30.5	21.0
Difference from placebo P value	-91.5 0.003		-75.8 0.0002		-52.8 0.20		-51.5 .06	
Free Fatty Acids (uEq/ml)[1]	N = 86	N = 107	N = 87	N = 106	NA	NA	NA	NA
Baseline free fatty acid	840	850	830	810				
Change from baseline	-140	10	-130	40				
Difference from placebo p-value	-150 0.04		-170 0.02					
Total Cholesterol (mg/dl)[1]	N = 113	N = 122	-	-	93	104	-	-
Baseline total cholesterol	215	211	-	-	216	207	-	-
Change from baseline	-1.5	6.5	-	-	-1.3	7.0	-	-
Difference from placebo p-value	-8.0 0.04		-	-	-8.3 0.03		-	-
LDL Cholesterol (mg/dl)[1]	N = 111	N = 120			90	101		
Baseline LDL cholesterol	133	133			138	132		
Change from baseline	-1.0	-3.0			0.3	1.6		
Difference from placebo p-value	1.9 0.4				-1.2 0.55			
HDL Cholesterol (mg/dl)[1]	N = 111	N = 120	-	-	90	101	-	-
Baseline HDL cholesterol	34.7	33.6	-	-	34.1	34.9	-	-
Change from baseline	-1.0	-0.9	-	-	0.1	-0.6	-	-
Difference from placebo p-value	-0.1 0.9		-	-	0.7 0.38		-	-

[1] Intent to treat population completing treatment course

[2] Represents the combined average of the one hour and two hour post meal (breakfast, lunch and dinner) free fatty acid and triglyceride levels (average of six measurements).Total and HDL cholesterol were not measured in the post-prandial state

P-value calculated by ANOVA

Source Study L and Study K (page 38) (page 37 & 39) Study Reports NDA 20866

6.1.2 Study M – Ergoset Monotherapy

The study population was treatment naïve with HbA1c of 7.5-11% at baseline

Subjects in the ITT were 80% Caucasian and 76% male. The mean age was 55 year, mean BMI 32 kg/m2 and mean duration of DM 4 years. 69% of patients on Ergo and 90% on placebo achieved the maximal dose of 6 tablets (4.8 mg).

Time courses of change in HbA1c for study M is shown in the next tables. This table was taken from the 1998 review by FDA statistician Lee Pian.

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

Week	Ergoset				Placebo				Difference	p-value
	n	A_{1c}	A_{1c} Change	SE	n	A_{1c}	A_{1c} Change	SE	A_{1c} Change Ergo-Plb	
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

There were significant decreases relative to placebo in fasting and postprandial glucose of 31 mg/dl and 37 mg/d; respectively. Changes in FFA, total cholesterol, and triglycerides were not statistically significant. The mean change in body weight was -0.2 lbs with Ergo and +0.6 with placebo (NS).

6.1.3 Other Efficacy results:

A subgroup analysis in Dr Lee Pian's statistical review indicates no major effect of age, gender or ethnicity in the change in HbA1c associated with Ergoset (trials K, L, and M combined)

Changes in insulin for studies K, L and M are shown in table 28. Treatment with Ergoset was associated with little change in insulin levels relative to placebo.

Table 28. Changes in Fasting and Post Meal Insulin Levels Following Treatment with Cycloset

Week	Placebo	Cycloset	Difference	95% Confidence Interval	P - Value
Fasting (average of two values) µU/mL					
24	-1.82	-1.32	-0.50	-3.06, 2.07	Treatment = 0.65
24 (completers)	-1.53	-0.90	-0.64	-3.04, 1.77	Treatment = 0.83
Postbreakfast (average of two values) µU/mL					
24	-2.71	0.05	-2.76	-6.29, 0.77	Treatment = 0.051
24 (completers)	-1.91	1.23	-3.14	-6.54, 0.27	Treatment = 0.48
Postlunch (average of two values) µU/mL					
24	-1.47	-2.71	1.24	-2.41, 4.90	Treatment = 0.19
24 (completers)	-1.23	-2.22	0.99	-2.32, 4.30	Treatment = 0.009
Postdinner (average of two values) µU/mL					
24	-1.01	1.97	-2.98	-6.40, 0.44	Treatment = 0.028
24 (completers)	-0.57	2.69	-3.25	-6.78, 0.27	Treatment = 0.57
Postprandial (average of six values) µU/mL					
24	-1.77	-0.27	-1.50	-4.15, 1.16	Treatment = 0.22
24 (completers)	-1.27	0.50	-1.77	-4.28, 0.74	Treatment = 0.57

Source ISS Section 8 NDA 20-866 Vol. 69 page 27

Insulin-treated patients

The original NDA contained a 12 week study of Ergoset vs placebo in insulin treated patients. There were 23 patients on Ergoset and 15 on placebo. The median insulin dose was 55 units. When compared to placebo, there was a significant reduction in HbA1c of 0.7% at 12 weeks. There was a mean decrease in insulin dose of about 6 units.

6.2 Efficacy results from the Safety Study (165-AD-04-03-US-1)

6.2.1 Study design

This was a 12 month, double blind outpatient study in patients with type 2 diabetes for at least six months, on a stable regimen (at least four weeks) of either, diet, one or two oral agents, or insulin, alone or with one oral agent. Noteworthy exclusion criteria were seizure disorder, gastroparesis, orthostatic hypotension, cerebrovascular accident or acute myocardial infarction within six months, hospital visit for ischemic heart disease within three months, congestive heart failure NYHA class 111 or 1V, systolic BP. 160 mm Hg, diastolic BP > 100 mm Hg, serum creatinine greater than 1.4 mg/dl, ALT or AST > 3 x ULN, use of other ergots , zolmitripan or sumatriptin (anti-migraine medications).Patients were instructed to continue their usual antidiabetic medications. Additional antidiabetic therapy could be added beyond week 12 if needed to control hyperglycemia. In accordance with recommendations of the American Diabetes Association, the goal of treatment was HbA1c < 7%.

Details of the protocol as well as demographics and baseline data are given in section 7. A brief summary of changes in HbA1c, FPG, lipids are presented here for the ITT patient population at 52 weeks and specified subsets at 24 weeks. The treatment effect at 52 weeks is probably an underestimation because of unequal intensification (Cycloset vs placebo) of concomitant antidiabetic therapy, which was allowed beyond 12 weeks (see discussion below). Because this was a safety trial, intensification of antidiabetic treatment was felt to be appropriate in order to eliminate the effects of hyperglycemia per se on the safety variables. In order to evaluate the efficacy of Cycloset, an efficacy subgroup was specified in the protocol. This subset consisted of patients with HbA1c greater than 7.5% at baseline while talking at least one oral hypoglycemic agent. The efficacy variable was change in HbA1c at 24 weeks (see below)

6.2.2 Changes at 52 weeks

Efficacy data for completers at 52 weeks are presented below. As noted above, the treatment effect at 52 weeks is probably an underestimation because of unequal intensification (15% for Cycloset vs 24.5% for placebo) of concomitant antidiabetic therapy. Changes in concomitant antidiabetic therapy are shown in the three tables below. (These tables were submitted by the Sponsor, Nov 14, 2008 and by email Nov 11, 2008 in response to a request by FDA).

Table 1. Intensified Diabetes Therapies

	ITT pop. N = 2054 Cycloset	ITT pop N = 1016 Placebo
Total no. of people that intensified diabetes therapy	300 (15%)	248 (24%)
Total no. of people that intensified diabetes therapy (excluding insulin therapy)*	224(11%)	191(19%)
Subjects that intensified by adding an OHA	98 (5%)	93 (9%)
Subjects that intensified by increasing the dose of existing OHA	126 (6%)	98 (10%)
Total no. of people that intensified diabetes therapy by adding insulin or increasing insulin dose**	76 (4%)	57 (6%)
Subjects that intensified by adding insulin therapy	21 (1%)	14 (1%)
Subjects that intensified by increasing their insulin dose	55 (3%)	43 (4%)

*either added or increased dose of baseline DM therapy but not subjects that intensified their DM therapy by adding insulin or increasing insulin dose

**Among subjects that intensified by adding insulin therapy, six subjects on Cycloset and one subject on placebo also added an OHA (Cycloset: 3 metformin, 1 acarbose, 1 pioglitazone, 1 sulfonylurea; Placebo: 1 sulfonylurea) and four subjects on Cycloset and two subjects on placebo also increased the dose of an existing OHA. Among subjects that intensified by increasing their insulin dose from their baseline dose, three subjects on Cycloset and four subjects on placebo also added an OHA (Cycloset: 1 rosiglitazone, 1 acarbose, 1 metformin; Placebo: 1 acarbose, 2 metformin, 1 sulfonylurea) and one subject on placebo also increased the dose of an existing OHA.

Table 2. Intensified Diabetes Therapy by Adding a Diabetes Medication (*excluding subjects initiating insulin or increasing insulin dose*)

	Cycloset N = 2054	Placebo N = 1016
	No. (% of population)	
Intensified DM therapy by adding an OHA †	98 (5%)	93 (9%)
Added a sulfonylurea*	34 (2%)	26 (3%)
Added metformin	47 (2%)	44 (4%)
Added a thiazolidinedione		
Rosiglitazone	17 (0.8%)	25 (2.5%)
Pioglitazone	10 (0.5%)	13 (1%)
Added "Other" OHA ‡	5 (0.2%)	3 (0.3%)

† A subject may be included in multiple classes of diabetes therapies but are only counted once in this overall total of subjects that intensified diabetes therapy
* includes all classes of sulfonylurea and the insulin secretagogues nateglinide {Starlix} and repaglinide {Prandin}
‡Other OHA includes exenatide {Byetta} and acarbose {Precose}

Table 3. Intensified Diabetes Therapy by Increasing Dose of Baseline Diabetes Medications (*excluding subjects initiating insulin or increasing insulin dose*)

	Cycloset N = 2054	Placebo N = 1016
	No. (% of population)	
Intensified DM therapy by increasing dose of OHA†	126 (6%)	98 (10%)
Increased dose of sulfonylurea*	49 (2%)	44 (4%)

Increased dose of metformin	80 (4%)	60 (6%)
Increased dose of thiazolidinedione		
Rosiglitazone	10 (0.5%)	6 (0.6%)
Pioglitazone	5 (0.2%)	2 (0.2%)

HbA1c - The mean baseline was 7.0% in both groups. For patients at 52 weeks, 1212 patients on bromocriptine had a mean HbA1c of 7.0. 730 patients on placebo had a mean HbA1c of 7.2%. The mean change was +0.1 for bromocriptine and +0.2 for placebo ($p<0.002$).

Fasting plasma glucose - The mean baseline was 142 mg/dl in patients on bromocriptine and 141 in patients on placebo. For patients at 52 weeks, 1213 patients on bromocriptine had a mean FPG of 139 mg/dl. 725 patients on placebo had a mean FPG of 144 mg/dl. The mean change was -0.5 mg/dl for bromocriptine and +4.1 for placebo ($p=0.075$).

LDL cholesterol - The mean baseline was 98.4 mg/dl for patients on bromocriptine and 97.1 for patients on placebo. At patients at 52 weeks, 1130 patients on bromocriptine had a mean LDL of 94.3 mg/dl, 687 patients on placebo had a mean LDL of 94.8 mg/dl. The mean change was -1.7 for bromocriptine and -1.6 for placebo ($p=.81$).

HDL cholesterol - The mean baseline was 46.2 mg/dl for patients on bromocriptine and 46.1 for patients on placebo. For patients at 52 weeks, 1214 patients on bromocriptine had a mean HDL of 44.7 mg/dl. 728 patients on placebo had a mean HDL of 43.9 mg/dl. The mean change was -1.0 for bromocriptine and -1.5 for placebo ($p=.085$).

Triglyceride - The mean baseline was 181 mg/dl for patients on bromocriptine and 175 for patients on placebo. For patients at 52 weeks, 1214 patients on bromocriptine had a mean triglyceride of 175 mg/dl. 728 patients on placebo had a mean triglyceride of 181 mg/dl. The mean change was -0.8 for bromocriptine and +4.2 for placebo ($p=.43$).

6.2.3 Specified efficacy subgroups

The specified efficacy subgroup consisted of patients with HbA1c greater than 7.5% at baseline while talking at least one oral hypoglycemic agent. This group consisted of 559 subjects, 376 on Cycloset and 183 on placebo. Changes in HbA1c for patients taking metformin and/or sulfonylureas are summarized in Table 20. The three subsets shown in Table 20 overlap. The major finding is the treatment effect of -0.7% units in patients on a combination of metformin plus a sulfonylurea. For patients taking a thiazolidinedione, the placebo-subtracted change in HbA1c at 24 weeks was -0.46 ($p=0.01$). A discussion of

this analysis and other results for other subsets can be found in the FDA statistical review by Lee Pian.

Table 20 Glycemic Parameters in Cycloset Safety Study among Patients with Type 2 Diabetes Poorly Controlled on Oral Diabetes Agents

	24 – Week ITT[1,2] Completers		24 – Week [3] Evaluable per Protocol	
Adjunct to Metformin+/- other diabetes oral agent	**Cycloset**	**Placebo**	**Cycloset**	**Placebo**
HbA1c (%)	N = 181	N = 101	N = 166	N = 100
Baseline mean	8.3	8.4	8.3	8.3
Change from baseline (adjusted mean)	-0.6	0.1	-.6	0.1
Difference from placebo (adjusted mean) p-value	-0.7 <0.0001		-0.7 <0.0001	
% Subjects achieving A1c of ≤ 7.0 p-value	36 <0.0001	10	36 <0.0001	9
Adjunct to Sulfonylurea +/- other oral diabetes agent				
HbA1c (%)	N = 176	N = 106	N = 162	N = 106
Baseline mean	8.3	8.3	8.3	8.3
Change from baseline (adjusted mean)	-0.6	0.02	-0.6	0.02
Difference from placebo (adjusted mean) p-value	-0.6 <0.0001		-0.6 0.0002	
% Patients achieving HbA1c of ≤ 7.0 p-value	34 0.0001	10	35 0.0001	10
Adjunct to Metformin + Sulfonylurea				
HbA1c (%)	N = 121	N = 71	N = 110	N = 71
Baseline mean	8.3	8.3	8.3	8.3
Change from baseline (adjusted mean)	-0.7	0.01	-0.7	0.01
Difference from placebo (adjusted mean) p-value	-0.7 0.0002		-0.7 0.0005	
% Patients achieving HbA1c of ≤ 7.0 p-value	39 0.0004	11	40 0.0005	11

[1] Intent to treat population that completed 24 weeks of treatment.
[2] Analyses of the ITT population using the last observation carried forward yielded significant reductions in the differences in the mean changes in HbA1c across all groups in favor of CYCLOSET (-0.5% HbA1c for adjunct to metformin +/- oral agent, -0.4%for adjunct to sulfonylurea +/- oral agent, -0.5% HbA1c for adjunct to metformin and sulfonylurea).
[3] Evaluable per protocol population where patients completing 24 weeks of treatment without major protocol violations and at least 80% compliant with study drug dosing.

The treatment effect of about -0.7% units (baseline through week 24) shown in the above table may a slight underestimate because of a greater tendency for intensification of concomitant antidiabetic therapy among placebo patients (see table below).

Table 21. Change from Baseline to Week 24 in Concomitant Diabetes therapy (ITT Population)

	Metformin plus Sulfonylurea		Metformin ± diabetes oral agent		Sulfonylurea ± diabetes oral agent	
Intensity of Therapy	Cycloset	Placebo	Cycloset	Placebo	Cycloset	Placebo
No change	75%	72%	71%	62%	67%	64%
Increased	16%	22%	20%	29%	25%	29%
Decreased	6%	3%	5%	3%	4%	3%

Source: Clinical Study Report NDA Amend: 27

7 INTEGRATED REVIEW OF SAFETY

7.1 Findings from the original NDA

In the original NDA, a total of 845 patients had received Ergoset. In studies K, L, M there were a total of 385 patients, 288 over 24 weeks and 96 treated over 48 weeks. The following table shows adverse events that appeared to be associated with Ergoset. Nausea was the most common adverse events and lead to withdrawal in 5% of patients.

Adverse events in controlled studies K,L M

	Ergoset n=324	Placebo n=329
Nausea	88	18
Constipation	33	14
Vomiting	18	9
Anorexia	10	3
Dizziness	39	20
Somnolence	19	5
Amblyopia	19	7

There were no episodes of severe hypoglycemia. Hypoglycemia was reported as an AE in 8.6% on Ergoset and 5.2% on placebo in studies K/L and 2.5% on Ergoset and 1.3% in placebo in study M.

There were no deaths during the controlled studies but two during the extensions. One was a 67 year old man in study L who died following a cerebellar infarction 14 months after starting Ergoset. He had been on 3.2 mg for about one year. The second case was a 67 year old man who had been in study M and died "as a result of a sudden heart attack" seven months after starting Ergoset. He had been taking 4.8 mg for about six months.

The two tables that follow show summaries of cardiovascular adverse events from the original NDA. The first table compares bromocriptine to placebo in the three pivotal trials. The second table shows cardiac events in all bromocriptine patients from all trials in the original NDA. Although the numbers are very small, the findings were interpreted as showing a possible signal that bromocriptine may increase the risk of serious cv adverse events, particularly myocardial infarction.

Cardiovascular events in controlled studies K, L and M

	Ergoset	Placebo
Number of patients	324	329
Patients years	124	137
Total cv AE's	12	10
Serious cv AE's	4	3
cv SAE per patients years	0.0123	0.0091
Myocardial infarctions	3	1
MI per patients years	0.0242	0.0073

Cardiovascular events on Ergoset (all studies, all patients)

	Ergoset
Number of patients	746
Patients years	371
Total cv AE's	35
Serious cv AE's	14
cv SAE per patients years	0.0377
Myocardial infractions	8
MI per patients years	0.0216

Changes in blood pressure for studies K, L and M are shown in table 26. Treatment with Ergoset was associated with a mean fall in blood pressure of about 2 mm Hg with little change in placebo.

Table 26. Mean Changes in Systolic and Diastolic Blood Pressure: Studies K, L, and M

Week	Placebo	Cycloset	Difference	95% CI	P - Value
Systolic blood pressure					
04	0.5	-0.8	1.3	-0.8, 3.4	Treatment = 0.008
08	1.3	-2.6	3.9	1.6, 6.3	
12	0.3	-1.8	2.1	-0.3, 4.5	
16	1.5	-1.3	2.8	0.4, 5.2	
20	1.0	-0.8	1.8	-0.7, 4.4	
24	1.3	-1.7	3.0	0.5, 5.5	
24 (completers)	0.8	-1.6	2.5	-0.1, 5.0	Treatment = 0.21
Diastolic Blood Pressure					
04	0.1	0.5	-0.3	-1.6, 0.9	Treatment = 0.012
08	0.2	-1.6	1.8	0.4, 3.2	
12	0.5	-0.9	1.4	-0.1, 2.8	
16	0.9	-0.4	1.3	-0.1, 2.7	
20	0.4	-1.3	1.7	0.1, 3.2	
24	0.5	-1.9	2.5	1.0, 3.9	
24 (completers)	0.5	-1.7	2.2		Treatment = 0.002

Source ISS Section 8 NDA 20-866 Vol. 69 page 29

Changes in weight for studies K, L and M are shown in table 27. Treatment with Ergoset was associated with a mean increase in body weight relative to placebo of about 1.4 pounds.

Table 27. Changes in Weight (lbs) in Combined Studies (K, L, and M)

Week	Placebo	Cycloset	Difference placebo-Cycloset	95% Confidence Interval	P - Value
04	-0.1	1.0	-1.1	-1.6, -0.5	Treatment = 0.0001
08	0.2	1.6	-1.4	-2.1, -0.8	
12	-0.4	1.4	-1.7	-2.5, -1.0	
16	0.2	1.5	-1.3	-2.2, -0.4	
20	0.1	1.6	-1.5	-2.4, -0.6	
24	0.3	1.7	-1.4	-2.5, -0.4	
24 (completers)	0.4	1.9	-1.4	-2.4, -0.4	Treatment = 0.03

Source ISS Section 8 NDA 20-866 Vol. 69 page 31

7.2 Findings from the Safety Trial (165-AD-04-03-US-1)

7.2.1 Study design

This was a 12 month, double blind outpatient study in patients with type 2 diabetes. Patients were ages 30-80, inclusive, with type 2 diabetes for at least six months, on a stable regimen (at least four weeks) of either, diet, one or two oral agents, or insulin, alone or with one oral agent. Patients had HbA1c< 10% prior to screening, BMI<43. In females, precautions were taken to prevent pregnancy. Patients were excluded because of systolic BP >160, diastolic BP >100, coronary revascularization within three months or acute MI within six months, NYHA class 3/4 heart failure. Patient were instructed to continue their usual antidiabetic medications and were withdrawn for HbA1c>12, significant deterioration of glycemia, or inability to tolerate at least two tablets of study drug per day by the end of the third week. Additional antidiabetic therapy could be added after week 12 if needed to attempt to achieve a goal of HbA1c < 7%. The mean baseline was 7.0% in both groups. At 52 weeks, patients on Cycloset had a mean HbA1c of 7.0. Patients on placebo had a mean HbA1c of 7.2%. The mean change of +0.1 for Cycloset and +0.2 for placebo were different statistically ($p<0.002$)., but probably contributed little if at all to assessment of safety. As discussed earlier, there was greater intensification of concomitant antidiabetic medication with placebo (24.5%) than with Cycloset (15%).

An event adjudication committee, consisting of two cardiologists and an endocrinologist, adjudicated all serious adverse events while blinded to treatment. The responsibility of the committee was to confirm that the event was serious and to determine if it met the protocol specified criteria for myocardial infarction, stroke, inpatient hospitalization for heart failure, angina or coronary revascularization.

Statistical plan, primary/secondary endpoints, subgroups analyses, etc are discussed by FDA reviewer Lee Pian.

Patients were randomized 2:1 to 0.8 mg bromocriptine or placebo. Study drugs were given daily at 8:00 am with breakfast. The initial dose was one tablet per day. The dose was increased by one tablet per day weekly as tolerated until the maximum tolerated dose of 6 tablets (4.8 mg) was achieved. The average dose was 4.4 tablets per day for Cycloset and 5.0 for placebo.

7.2.2 Study population

The ITT population consisted of 2054 for Cycloset and 1016 for placebo. The two arms were well matched. Approximately 56% male, 68% Caucasian, mean age 59.7 years, mean BMI 32.4, mean HbA1c 7%, mean FPG 142 mg/dl, mean LDL cholesterol 98 mg/dl. 12% were on diet only, 40% on one oral agent, 33% on two oral agents, 9% on insulin plus an oral agent, and 7% on insulin only.

The two arms were well matched with respect to CV risk factors. (Table 10). HMG CoA reductase inhibitors were used by approximately 61%, ACE inhibitors by 50% and antiplatelet drugs by 48%. (Table 14.5.4).

Table 10. Medical, Cardiovascular and Diabetes Baseline History (ITT Population)

	Cycloset n (%)	Placebo n (%)	Total n (%)
Medical History (Select Body System/ Category)			
Renal (%)	460 (22.4)	242 (23.8)	702 (22.9)
Pulmonary (%)	604 (29.4)	304 (29.9)	908 (29.6)
Gastrointestinal (%)	1250 (60.9)	607 (59.7)	1857 (60.5)
Musculoskeletal (%)	1508 (73.4)	746 (73.4)	2254 (73.4)
Neurologic (%)	896 (43.6)	444 (43.7)	1340 (43.6)
Cardiovascular Medical History			
Myocardial Infarction (%)	186 (9.1%)	106 (10.4%)	292 (9.5)
Angina Pectoris (%)	214 (10.4)	101 (9.9%)	315 (10.3)
Stroke[1] (%)	86 (4.2)	63 (6.2)	149 (4.9)
Revascularization Surgery (%)	204 (9.9)	128 (12.6)	332 (10.8)
Hypertension (%)	1548 (75.4)	767 (75.5)	2315 (75.4)
Hypercholesterolemia (%)	1575 (76.7)	767 (75.5)	2342 (76.3)
Hypertriglyceridemia (%)	853 (41.5)	422 (41.5)	1275 (41.5)
Family History of Cardiovascular Disease (%)	651 (31.7)	323 (31.8)	974 (31.7)
History of Obesity (%)	1312 (63.9)	638 (62.8)	1950 (63.5)
History of Smoking (%)			
Current	306 (14.9)	133 (13.1)	439 (14.3)
Past	802 (39.0)	419 (41.2)	1221 (39.8)
Prescribed Anti-Diabetic Therapy Medication at Diagnosis (%)	1308 (63.7)	651 (64.1)	1959 (63.8)

Table 10. Medical, Cardiovascular and Diabetes Baseline History (ITT Population)

	Cycloset n (%)	Placebo n (%)	Total n (%)
Diabetes Therapeutic Regimen at Screening[2]			
Diet Only (%)	257 (12.5)	114 (11.2)	371 (12.1)
One Oral Hypoglycemic Agent (%)	806 (39.2)	403 (39.7)	1209 (39.8)
Two Oral Hypoglycemic Agents (%)	686 (33.4)	323 (31.7)	1009 (32.9)
Insulin Plus One or Two Oral Agents (%)	171 (8.2)	98 (9.7)	269 (8.8)
Insulin Only (%)	133(6.4)	78 (7.8)	211(6.9)

[1] Difference between groups P value = 0.01

[2] One subject not reported

Source: Tables 14.1.11.2, 14.1.12.2, 14.1.13.2, 14.1.14.2

From baseline to 52 weeks, lipid lowering therapy was intensified in 11% of placebo patients and 12% of Cycloset patients. Lipid lowering therapy was decreased in 3% of placebo patients and 5% of Cycloset patients. From baseline to 52 weeks, hypertension therapy was intensified in 11% of placebo patients and 10% of Cycloset patients. Hypertension therapy was decreased in 6% of placebo patients and 8% of Cycloset patients.

7.2.3 Primary and secondary (safety) endpoint.

There were 176/2054 (8.6%) SAE's with Cycloset and 98/1016 (9.6%) with placebo. Cycloset met the test of noninferiority set forth in the protocol and statistical plan.

Although there was no difference in occurrence of SAE's, there was a statistically significant reduction in the composite cardiovascular endpoint among patients receiving Cycloset (table 18).

Table 18. Composite and Individual Cardiovascular Serious Adverse Events (ITT Population)

	Cycloset (N=2054) n (%)	Placebo (N= 1016) n (%)	Hazard Ratio (95% CI)[1] n (%)
Composite Cardiovascular Endpoint	31 (1.5%)	30 (3.0%)	0.58 (0.35 – 0.96)
Individual Cardiovascular Endpoints[2]			
Myocardial Infarction	6 (0.3%)	8 (0.8%)	0.44 (0.15 – 1.26)
Stroke	4 (0.2%)	6 (0.6%)	0.37 (0.10 – 1.32)
Inpatient Hospitalization for Angina	9 (0.4%)	9 (0.9%)	0.55 (0.22 – 1.38)
Inpatient Hospitalization for Heart Failure	7 (0.3%)	5 (0.5%)	0.81 (0.26 – 2.57)
Coronary Revascularization Surgery	9 (0.4%)	6 (0.6%)	0.85 (0.30 – 2.40)
Coronary revascularization following primary event	9 (0.4%)	10 (1.0%)	0.50 (0.20 – 1.24)

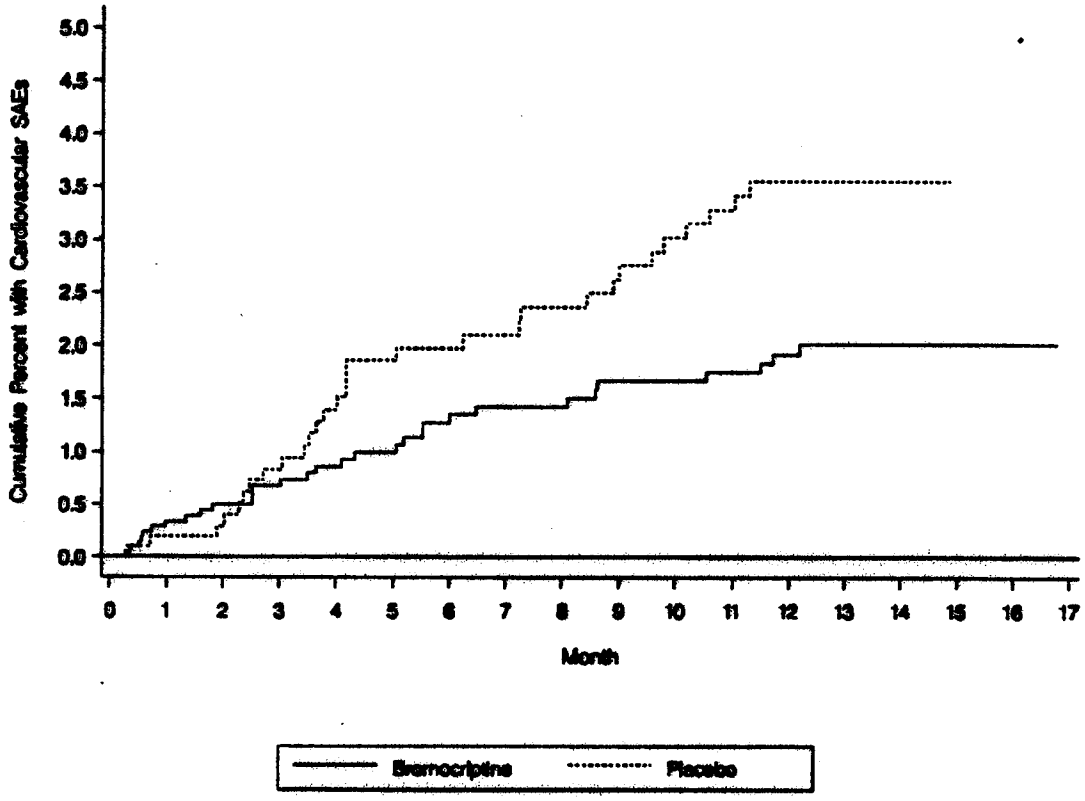
[1] From the Cox regression, 95% two sided hazard ratio confidence limits

[2] For individual cardiovascular endpoints — individuals may appear in multiple categories if they experience more than one event (i.e. individual that experienced both a stroke and a MI would appear in both categories)

Source: Table 14.2.2.1

From the Kaplan Meier plot shown below (fig 2), the separation in favor of Cycloset begins at about 3 months and persists through the end of the study.

Figure 2. Kaplan-Meier of Subjects with Cardiovascular Serious Adverse Events (ITT Population)



Subgroup analyses (table 20) suggests that greatest benefit from Cycloset appeared in subjects with baseline HbA1c of 7.0% or less.

Table 20. Subgroup Analyses of Secondary Endpoint Time to First Composite CVD Endpoint

Variable	Cycloset	Placebo	HR[1] (95% CI)[2]
	no. people with events/ no. of patients		
Secondary Endpoint – Composite CVD Endpoint[3]	31/2054	30/1016	0.58 (0.35 — 0.96)
Gender			
Male	26/1141	24/598	0.62 (0.36 — 1.08)
Female	5/913	6/418	0.47 (0.14 — 1.54)
Age			
≤ 65 years	14/1453	13/701	0.58 (0.27 — 1.23)
> 65 years	17/601	17/315	0.63 (0.32 — 1.23)
Race			
Caucasian	25/1381	24/698	0.61(0.35 — 1.07)
Non-Caucasian	6/673	6/318	0.52 (0.17 — 1.60)
Glycemic Control Baseline			
Hba1c > 7.0	16/830	12/400	0.74 (0.35 — 1.56)
Hba1c ≤ 7.0	15/1219	18/615	0.48 (0.24 — 0.95)

[1]This is the maximum (partial) likelihood estimate of the hazard ratio from Cox regression. The analysis is based on drug effect extending 30 days after last dose.

[2]From Cox regression, 95% Hazard Ratio Confidence Limits.)

[3]Serious Cardiovascular adverse events include myocardial infarction, stroke, inpatient hospitalization for heart failure or angina, and revascularization surgery.

Source: Table 14.2.3, 14.2.5.1, 14.2.5.2, 14.2.5.3, 14.2.5.4

Based on the signal in the original NDA, the comparison with respect to myocardial infarction (MI) is of particular interest. There were 6/2054 (0.3%) MI's in Cycloset treated patients compared to 8/1016 (0.8%) with placebo. The hazard ratio is 0.44. Because the 95% Confidence Interval (0.15-1.26) includes 1.00, one cannot conclude that Cycloset decreases the risk of MI. A post-hoc analysis restricting the composite to major adverse cardiac events (MACE) found 11 events on bromocriptine compared to 14 on placebo (table 19). The hazard ratio was 0.45 (95% CI 0.205-0.996).

Table 19. Analysis Based on First Composite CVD SAE including CVD Death and Time to First Myocardial Infarction, Stroke or CVD Death (ITT Population)

	Bromocriptine (N = 2054)	Placebo (N = 1016)
Serious Cardiovascular Adverse Events[1] including CVD Deaths[2]		
Number of Subjects with at Least One SAE	32	31
Hazard of All-Cause SAEs[3]	0.584	
95% two-sided CI of Rate Ratio[4]	(0.356 – 0.958)	
Myocardial Infarction (MI), Stroke or CVD Death[2]		
Number of Subjects with at Least One SAE	11	14
Hazard Ratio of All-Cause SAEs[3]	0.452	
95% two-sided CI of Rate Ratio[4]	(0.205 – 0.996)	

[1]Serious Cardiovascular Adverse Events include myocardial infarction, stroke, inpatient hospitalization for heart failure or angina, and revascularization surgery.

[2]CVD Deaths not included in Table 14.2.2.1 include subjects 8733 and 19231.

[3]This is the maximum (partial) likelihood estimate of the hazard ratio from Cox regression. The analysis is based on drug effect extending 30 days after last dose.

[4]From Cox regression, 95% Hazard Ratio Confidence Limits.

Source: Tables 14.2.3, 14.2.4

"Off treatment" cardiovascular events

The primary analysis consisted of events that occurred while patients were taking the study drug or up to 30 days after stopping the study drug. The Sponsor submitted a secondary safety analysis (submission #34) to include events that occurred greater than 30 days beyond cessation of study drug. This analysis is based on information obtained by telephone on the expected week 52 follow visit date. An additional 748 patients contributed person time in this analysis. As shown in the following table (table 5 from submission #34), there were 8 events "off treatment". Adding these events to the 61 "on treatment" events (see table 18 page 26) makes little difference to the overall finding. Details about these 8 "Off treatment" events are shown in the subsequent table. (table 4 from submission 34). For Cycloset, these events occurred 84 -292 days after the drug had been stopped.

Table 5. Cardiovascular Events by Person and Per 100 Person Years of "On, Off, or On plus Off" Study Treatment Exposure Time

	ON Treatment		Off Treatment		Combined ON and Off Treatment	
	# of people with an event	*Event per 100 person years*	*# of people with an event*	*Event per 100 person years*	*# of people with an event*	*Event per 100 person years*
Cycloset	31	1.89	6	2.16	37	1.93
Placebo	30	3.28	2	2.87	32	3.25

Table 4. Cardiovascular Events Reported on Week 52 Follow Up Phone Call

Subject ID	Treatment Assignment	Event description	Days on Study drug	Event – days from last dose of study drug
09317	Cycloset	Stroke	167	84
17402	Cycloset	Congestive heart failure	65	204
19801	Cycloset	Revascularization	44	292
27326	Cycloset	Congestive heart failure	69	205
28522	Cycloset	Revascularization	30	230
25559	Cycloset	Death*	90	208
15607	Placebo	Congestive heart failure	219	32
28517	Placebo	Myocardial infarction followed by revascularization	62	75

*Death event was adjudicated and the reviewers felt that the event did not meet the primary CVD endpoint criteria

Source: Listing 16.2.7.8 and Appendix 3

7.2.4 Other Adverse events

Nausea was reported by 32.2% of patients on Cycloset and 7.6% on placebo. Dizziness was reported by 14.8% of patients on Cycloset and 9.2% on placebo. Other adverse events are listed in table 21.

Table 21 Most Commonly Reported (≥5% in Any Treatment Group) Adverse Events (ITT Population)

	Cycloset (N=2054)	Placebo (N=1016)	Total (N=3070)
Total Number of Patients with at least one AE, n (%)	1832 (89.2)	840 (82.7)	2672 (87.0)
MedDRA SOC Preferred Term [1]	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal disorders			
Nausea	661 (32.2)	77 (7.6)	738 (24.0)
Diarrhea	167 (8.1)	81 (8.0)	248 (8.1)
Vomiting	167 (8.1)	32 (3.1)	199 (6.5)
Constipation	119 (5.8)	52 (5.1)	171 (5.6)
Infections and infestations			
Upper respiratory tract infection	92 (4.5)	66 (6.5)	158 (5.1)
Nasopharyngitis	101 (4.9)	55 (5.4)	156 (5.1)
Urinary Tract Infection	66 (3.2)	55 (5.4)	121 (3.9)
Nervous system disorders			
Dizziness	303 (14.8)	93 (9.2)	396 (12.9)
Headache	235 (11.4)	84 (8.3)	319 (10.4)
General disorders and administrative site conditions			
Fatigue	285 (13.9)	68 (6.7)	353 (11.5)
Musculoskeletal and connective tissue disorders			
Arthralgia	77 (3.7)	56 (5.5)	133 (4.3)
Endocrine disorders			
Hypoglycaemia	141 (6.9)	54 (5.3)	195 (6.4)

[1]Subjects may appear in more then one SOC or preferred term category
Source: Table 14.3.1.1

7.2.4 **Death.**— There were 12 deaths while on study drug or within 30 days of stopping, 9 on Cycloset and 3 on placebo. Three deaths on Cycloset were classified as cardiopulmonary arrest, not meeting Event Adjudication Committee criteria (19231, 25559, 27004). There was one suicide and one death from an MVA on Cycloset.

7.2.5 **Adverse events leading to discontinuation** As shown in table 31, nausea was the most common cause of discontinuation. This occurred during the initial six week titration period in half the cases.

Table 31. Most Common (≥ 2% in Any Treatment Group) Adverse Experiences Leading to Discontinuation by Symptom Intensity in Decreasing Frequency (ITT Population)

	Cycloset N=2,054			Placebo N= 1,016		
Subjects with at least one Adverse Event leading to DC n (%)	195 (9.5)	289 (14.1)	124 (0.6)	28 (2.8)	53 (5.2)	36 (3.5)
MedDRA System Organ Class[1]/ Preferred Term[2]	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Gastrointestinal						
Nausea	53 (2.6)	105 (5.1)	21 (1.0)	4 (0.4)	4 (0.4)	2 (0.2)
Vomiting	8 (0.4)	33 (1.6)	3 (0.1)	0	3 (0.3)	1
Nervous System disorders						
Dizziness	27 (1.3)	33 (1.6)	10 (0.5)	3 (0.3)	3 (0.3)	2 (0.2)
Headache	26 (1.3)	21 (1.0)	5 (0.2)	3 (0.3)	3 (0.3)	0
General disorders						
Fatigue	24 (1.2)	32 (1.6)	19 (0.9)	5 (0.5)	4 (0.4)	1

[1] System organ class as determined by MedDRA coding of preferred term provided by study investigator.
[2] Subjects reporting differing AE intensities or multiple AEs are included in multiple AE intensity and/or multiple preferred term categories.
Source: section 14.3 Table 14.3.5.1

7.2.6 Other findings of special interest

7.2.6.1
Weight

Mean change in weight at week 24 was -0.1 lb with Cycloset and +0.1 for placebo.
Mean change in weight at week 52 was +0.5 with Cycloset and +0.3 for placebo.

7.2.6.2
Blood pressure

There were small but statistically significant decreases in blood pressure, Cycloset vs placebo, throughout the trial. The difference appeared greatest at week 12 (Systolic bp - Cycloset -2.0 mm Hg placebo -0.5 mmHg, p=0.0003).

There were 45 hypotensive AE's on Cycloset (2.2%) compared to 8 events, 0.8% on placebo. The AE led to discontinuation in 9 patients on Cycloset and 2 on placebo. All but one of the Cycloset patients with hypotensive events were on antihypertensive medication(s).

7.2.6.3
Psychiatric adverse events

21/2054 (1.9%) on Cycloset and 5/1016 (0.5%) on placebo had a psychiatric AE leading to discontinuation of treatment. 4/2054 (0.2%) on Cycloset and 2/1016 (0.2%) on placebo discontinued because of depression. There was one completed suicide on Cycloset and there was one suicide attempt on placebo. 17/2054 (0.8%) on Cycloset discontinued because of disordered sleep (n=5), confusion/disorientation (n=3), anxiety/nervousness/stress (n=4), bipolar disorder (n=1) and other descriptive terms (mood swings, emotional disorder, etc). 3/1016 (0.3%) on placebo discontinued because of insomnia (1), anxiety (1) and mood swings (1). No patients on placebo withdrew because of confusion or disorientation.

The composite of depression, depressed mood, suicide, suicide attempt and bipolar disorder occurred in 17 (0.8%) patients on Cycloset and 16 (1.6%) patients on placebo.

Reviewer comment: That bromocriptine may have some positive effects in patients with depression is consistent with the literature about bromocriptine in psychiatric illness (9). Bromocriptine has also been reported to induce schizophrenia in a man with hyperprolactinemia (10).

7.2.6 **Laboratory Values: There were no noteworthy changes in laboratory values from baseline to endpoint in Cycloset treated patients relative to placebo. Selected values are shown in the table.**

	CYCLOSET			PLACEBO	
	Baseline	Endpoint	units	Baseline	Endpoint
Hemoglobin	42.4	41.1	g/dL	42.6	41.4
White cells	6.9	6.8	1000/uL	6.9	6.8
Platelets	249	242	1000/uL	246	246
Albumin	4.3	4.4	g/L	4.3	4.4
Bilirubin	0.6	0.6	mg/dL	0.6	0.6
BUN	17.5	18.7	mg/dL	17.5	18.5
Creatinine	1.1	1.1	mg/dL	1.1	1.1
Potassium	4.5	4.4	mmol/L	4.5	4.5
Phosphorous	3.5	3.4	mg/dL	3.5	3.5
ALT	27.7	24.3	U/L	27.7	23.8

7.3 Pharmacovigilance

In August 1994, FDA removed bromocriptine's indication to suppress postpartum lactation because of reports of myocardial infarction and stroke in otherwise healthy young women. A direct relationship was never established. But FDA's Fertility and Maternal Health Drugs Advisory Committee concluded that "the possibility that bromocriptine may cause serious events in some patients outweighs the limited benefits for its use in a temporary condition that can be managed by more conservative treatment."

Although there were few serious cardiovascular adverse events in original trials of Ergoset, the possibility of imbalance in the risk of myocardial infarction was cause for concern. In addition to requiring a safety study, FDA requested that the Sponsor review adverse events that have been reported with bromocriptine.

Based on data form IMS Health Inc, the Sponsor estimates the worldwide exposure to bromocriptine through 2006 has been ———— patient-years. Reviewing the worldwide literature they found 31 reports of cardiovascular disease, 30 reports of non-cardiac vascular disease, 69 reports of respiratory disease and 16 reports of retroperitoneal fibrosis. There have been 34 cases of myocardial infarction and/or stroke. There were 17 report of myocardial infarction, 94% were women age 18-44 (see table 23). There was one case of valvular heart disease. Results from FDA Medwatch (table 24) and WHO (table 25) are also shown. b(4)

Reviewer comments about Pharmacovigilance

As noted previously, it was never established that myocardial infarctions reported in otherwise healthy young women were due to the bromocriptine that they took to suppress postpartum lactation. From the Sponsor's review, there were 17 reports of myocardial infarction, 94% were women age 18-44. The Sponsor has attempted to explain these cases by citing the work of James et al (Circulation 2006;113;1564-1571, who found that there was 3 to 4 fold increase in risk of acute myocardial infarction during pregnancy and postpartum. Regardless whether one finds this argument convincing, it is noteworthy that there were few cases of myocardial infarction in patients over 44, the age group most relevant to type 2 diabetes.

The 16 reports of retroperitoneal fibrosis are of concern because retroperitoneal fibrosis has been linked to other ergot derivatives. This issue is dealt with adequately in the label the Sponsor has proposed and in their plan for post marketing pharmacovigilance.

That there was only one report of valvular heart disease is noteworthy, because valvular heart disease has been linked to other dopamine agonists (8). Valvular heart disease should be added to the pharmacovigilance plan.

As discussed in 7.2.6.3, there is literature about effects of bromocriptine in psychiatric illness. The plan for pharmacovigilance should include disorientation/confusion and schizophrenia.

Table 23. Published Adverse Events among Bromocriptine Users

Years 1960 – 2007

Key Words	Number of Reports	Preferred Term By Gender[a]		Preferred Term By Age Categories (years)[a]		
		Male	Female	18-44	45-64	≥65
Total	149	46% (50/109)	54% (59/109)	37% (46/124)	37% (46/124)	26% (32/124)
Cardiovascular Disorders	31	27% (8/30)	73% (22/30)	73% (22/30)	10% (3/30)	13% (4/30)
Hypertension	1	0	100% (1/1)	100% (1/1)	0	0
Hypotension	1	0	0	0	0	0
Pericarditis	4	100% (3/3)	0	0	0	100% (3/3)
Dilated Cardiomyopathy	1	0	100% (1/1)	100% (1/1)	0	0
Valvular Heart Disease	1	100% (1/1)	0	0	100% (1/1)	0
Arrythmia	4	25% (1/4)	75% (3/4)	100% (4/4)	0	0
Myocardial Infarction	17	6% (1/17)	94% (16/17)	94% (16/17)	6% (1/17)	0
Shock	2	50% (1/2)	50% (1/2)	0	50% (1/2)	50% (1/2)
Vascular (extracardiac) Disorders	30	0% (0/26)	100% (26/26)	91% (20/22)	9% (2/22)	0% (0/22)
Cerebral Angiopathy	5	0	100% (5/5)	100% (5/5)	0	0
Stroke	7	0	100% (6/6)	100% (2/2)	0	0
Intracranial/Intracerebral Hemorrhage	10	0	100% (10/10)	100% (10/10)	0	0
Pituitary Apoplexy	6	0	100% (3/3)	33% (1/3)	66% (2/3)	0
Thrombosis	2	0	100% (2/2)	100% (2/2)	0	0
Respiratory System Disorders	69	89% (33/37)	11% (4/37)	2% (1/54)	56% (30/54)	43% (23/54)
Pleuropulmonary Disease	33	90% (19/21)	10% (2/21)	0	64% (14/22)	36% (8/22)
Pulmonary Infiltrate	1	0	0	0	0	100% (1/1)
Pleural Thickening	5	100% (4/4)	0	0	60% (3/5)	40% (2/5)
Interstitial Pneumonitis	1	100% (1/1)	0	0	100% (1/1)	0
Pleural Effusion	3	100% (3/3)	0	0	67% (2/3)	33% (1/3)
Pleurisy	2	50% (1/2)	50% (1/2)	0	0	100% (2/2)
Pleuropulmonary Fibrosis	23	100% (5/5)	0	0	53% (10/19)	47% (9/19)
Pulmonary Edema	1	0	100% (1/1)	100% (1/1)	0	0
Retroperitoneal Fibrosis	16	69% (9/13)	31% (4/13)	0% (0/15)	66% (10/15)	33% (5/15)
Death	3	0% (0/3)	100% (3/3)	100% (3/3)	0% (0/3)	0% (0/3)

[a] Not all reports provide an age or gender.
Source Pharmacovigilance report Section 8

Table 23 (above) IMS Health Care Inc

Reporting from FDA Medwatch is shown in table 24 (below)

Table 24. FDA MedWatch Reporting of Bromocriptine for Selected Preferred Terms by Age and Gender

Select Preferred Terms [a]	Number of Reports [b]	Preferred Term By Gender [c]		Preferred Term By Age Categories [c]		
		Male	Female	18-44 years	45-64 years	≥65 years
Total	135	30.2% (39/129)	69.8% (90/129)	52.5% (64/122)	18.0% (22/122)	29.5% (36/122)
Cardiovascular Disorders Myocardial Infarction Myocardial Ischaemia Cardiac Failure Coronary Artery Disorder Angina Pectoris	38	36.8% (14/38)	62.2% (24/38)	41.7% (15/36)	22.2% (8/36)	36.1% (13/36)
Vascular (extracardiac) Disorders Cerebrovascular Disorder Cerebral Infarction Hemorrhage Intracranial Cerebral Hemorrhage Subarachnoid Hemorrhage	43	9.5% (4/42)	90.5% (38/42)	86.8% (33/38)	7.9% (3/38)	5.3% (2/38)
Respiratory System Disorders Pleural Fibrosis Pulmonary Fibrosis	14	61.5% (8/13)	38.5% (5/13)	7.7% (1/13)	38.5% (5/13)	53.8% (7/13)
Retroperitoneal Fibrosis	6	33.3% (1/3)	66.7% (2/3)	33.3% (1/3)	33.3% (1/3)	33.3% (1/3)
Death	34	36.4% (12/33)	63.6% (21/33)	43.8% (14/32)	15.6% (5/32)	40.6% (13/32)

[a] Listings are limited to preferred terms where at least one report was provided.
[b] For a given report there may be multiple system organ classes associated.
[c] Not all reports provide an age or gender.
Source Pharmacovigilance report Section 8

Table 25. WHO Reporting of Bromocriptine by Selected Preferred Terms by Age and Gender

Select Preferred Terms [a]	Number of Reports [b]	Years 1977-2006				
		Preferred Term By Gender [c]		Preferred Term by Age Categories [c]		
		Male	Female	18-44 years	45-64 years	≥65 years
Cardiovascular Disorders	395					
Hypertension	149	4.2% (6/142)	95.8% (136/142)	95.2% (118/124)	4.8% (6/124)	--
Hypotension	145	26.6% (37/139)	73.3% (102/139)	67.5% (81/120)	8.3% (10/120)	24.2% (29/120)
Pericarditis	9	56.6% (5/9)	44.4% (4/9)	--	25.0% (2/8)	75% (6/8)
Cardiomegaly	2	--	100% (2/2)	100% (2/2)	--	--
Arrhythmia, Atrial or Ventricular	24	39.1% (9/23)	60.9% (14/23)	66.7% (14/21)	19.0% (4/21)	14.0% (3/21)
Myocardial Infarction	38	5.4% (2/37)	94.6% (35/37)	85.3% (29/34)	8.8% (3/34)	5.9% (2/34)
Thrombosis Coronary	5	--	100% (5/5)	100% (5/5)	--	--
Angina Pectoris	8	33.3% (2/6)	66.7% (4/6)	66.7% (4/6)	16.7% (1/6)	16.7% (1/6)
Coronary Artery Disorder	5	--	100% (5/5)	100% (5/5)	--	--
Cardiac Failure	10	10% (1/10)	90% (9/10)	87.5% (7/8)	--	12.5% (1/8)
Vascular (extracardiac)	101					
Disorders	49	2.1% (1/47)	97.9% (46/47)	95.1% (39/41)	--	4.9% (2/41)
Cerebrovascular Disorder	13	--	100% (13/13)	100.0% (13/13)	--	--
Cerebral Infarction	14	--	100% (14/14)	100.0% (13/13)	--	--
Hemorrhage Intracranial	24	18.2% (4/22)	81.8% (18/22)	81.0% (17/21)	9.5% (2/21)	9.5% (2/21)
Cerebral Hemorrhage	1	--	100% (1/1)	100.0% (1/1)	--	--
Subarachnoid Hemorrhage						
Respiratory System Disorders	254					
Pulmonary Infiltrate	18	50.0% (9/18)	50% (9/18)	17.6% (3/17)	52.9% (9/17)	29.4% (5/17)
Pleural Fibrosis	43	87.8% (36/41)	12.2% (5/41)	--	41.5% (17/41)	58.5% (24/41)
Pulmonary Fibrosis	34	81.3% (26/32)	18.8% (6/32)	--	26.7% (8/30)	73.3% (22/30)
Pleural Effusion	61	82.8% (48/58)	17.2% (10/58)	13.2% (7/53)	37.7% (20/53)	49.1% (26/53)
Pleurisy	86	83.5% (71/85)	16.5% (14/85)	2.4% (2/84)	44.0% (37/84)	53.6% (45/84)
Pulmonary Hemorrhage	1	--	100% (1/1)	100% (1/1)	--	--
Pulmonary Edema	11	--	100% (11/11)	100% (10/10)	--	--
Retroperitoneal Fibrosis	26	62.5% (15/24)	37.5% (9/24)	4.3% (1/23)	43.5% (10/23)	52.1% (12/23)
Death	55	16.7% (9/54)	83.3% (45/54)	75% (30/40)	10% (4/40)	15% (6/40)

[a] Only preferred terms where there was at least one report provided are listed.
[b] For a given report there may be multiple system organ classes associated.
[c] Not all reports provide an age or gender. (Source Pharmacovigilance report Section 8)

8. ADDITIONAL CLINICAL ISSUES.....

8.1 Pediatric plan - The Sponsor has requested a waiver of studies in patients [redacted] years old and under because type 2 diabetes is rare at this age. The have requested a deferral in patients [redacted] pending approval of the NDA in adults. Both requests are reasonable. b(4)

8.2 Proposal for postapproval pharmacovigilance (submitted Sep 4, 2008) –

1 Claims Database study:

The Sponsor proposes to employ an outcomes research group such as [redacted] to conduct studies using two databases – [redacted] database. For the period September 2002 through June 2007, there were [redacted] in the Market scan data base with an ICD-9 diagnosis code of type 2 diabetes. For the period September 2006 through June 2007, there were [redacted] patients. Assuming that 1% of patients these patients are started on Cycloset, the Sponsor estimates that [redacted] will be in the MarketScan database at the end of one year. The database will be scanned for adverse events 6-12 months before the Index prescription and up to 12 months post index. Adverse events of particular interest are: b(4) b(4)

1 Hypotension and syncope,
2 Fibrotic complication including retroperitoneal fibrosis, pleural effusion or thickening, pulmonary infiltrates, pericarditis
3 Liver or renal impairment

2 The Sponsor is in discussions with [redacted] to establish a patient registry b(4)

3 The Sponsor will establish a Call-in Center for adverse Events

8.3 Comments on insulin clamp study - As a supplement to the original NDA, the Sponsor submitted a study designed to investigate the mechanism of action of bromocriptine. This study utilized the glucose clamp technique to investigate the effect of bromocriptine on insulin action. It was originally reviewed by Dr Bruce Schneider, who was then a Medical Officer in DMEDP. Dr Schneider now works in CBER but agreed to rereview this study. A summary of his finalized Oct 2008 review is shown below:

REVIEWER'S SUMMARY COMMENTS

This small study demonstrated mean decreases in fasting plasma glucose and HbA1c levels, compared to baseline, in 15 patients treated with bromocriptine for 16 weeks. Increases in FPG and a small, non-significant change in HbA1c were noted in a group of seven PBO patients. In addition, during OGTT, the mean plasma glucose concentration fell following Cycloset treatment, compared to a small, non-significant elevation in the PBO patients. The between-group differences were statistically significant. There were no between-group differences in plasma insulin, C-peptide, or FFA concentrations during an OGTT.

Euglycemic clamp studies showed no changes in basal endogenous glucose production rates in patients treated with either Cycloset or PBO, or in oxidative or non-oxidative glucose disposal rates or endogenous glucose production during the first stage of the clamp.

During the second stage of the clamp study, the rate of total glucose disposal was increased by 24% in the Cycloset group (from 6.8 +/- 0.8 to 8.4 +/- 0.6 mg/min/kg FFM (p=0.01), but decreased by 27% in PBO (from 8.7 +/- 1.0 to 6.4 +/- 0.7 mg/min/kg FFM (p=0.02). The difference between the groups was significant (p=0.001).

This increase was almost entirely accounted for by the 32% gain in non-oxidative glucose disposal. NOGD increased from 3.3 +/-0.8 to 4.3 +/- 0.5 mg/min/kg FFM (p<0.05) in the Cyclo group and decreased 52%, from 4.6 +/- 0.8 to 2.2 +/- 0.7 mg/min/kg FFM in PBO (p=0.01). The between group difference was significant (p<0.002).

The rate of glucose oxidation was not affected by treatment. Also, suppression of endogenous glucose production by insulin during the second stage was similar in both groups and was not affected by treatment.

Based on these data, the sponsor proposes [redacted] b(4)

I recommend that the results of this study should not be included in the product label, for multiple reasons.

First, changes in non-oxidative glucose disposal rates under hyperinsulinemic conditions do not represent a known clinical benefit in themselves. Such changes may conceivably be related to drug-induced increases in insulin sensitivity, but it remains to be established how the effects of bromocriptine on blood glucose are linked to this single parameter that emerged from a one glucose clamp study.

There were no changes in basal glucose production rates, or in endogenous glucose production, total glucose disposal rates, oxidative glucose metabolism, or non-oxidative glucose disposal during the first phase of the insulin clamp study. During the second phase, when insulin was delivered at a rate of 160mU/min/kg FFM, there was no treatment-related difference in suppression of endogenous glucose production, but there was an increase over baseline in NOGD.

The quantitative relationship between the changes in NOGD and effects on any of the multiple parameters carbohydrate metabolism are unclear from the study. In this regard, it should be noted that, although the changes from baseline were in accord with the sponsor's objectives, the baseline levels themselves were lower in the Cycloset group compared to PBO, although not significantly so. The 16-week NOGD rate in the Cycloset group was about the same as the baseline rate in PBO. (Fig.3 pg 52 of the submission). Thus it is difficult to assign meaning to these changes in NOGD, based on the magnitude of the responses, irrespective of directionality. Of greater importance, correlation analyses among all individuals failed to show any association between increases in NOGD on the one hand and decreases in fasting plasma glucose, HbA1c, or mean glucose during OGTT on the other (Appendix 1).

For these general reasons based on the results, I would recommend excluding the relevant sections from the label.

However, the study *itself* was inadequate to justify including such information about the pharmacodynamic properties of bromocriptine.

As noted above, this investigation was intended by the sponsor as a pilot study, "...the results of which may be used to design a future larger study. Sample size was not calculated to achieve statistical significance for anticipated end results." There was no stated hypothesis.

Furthermore, there was a decided imbalance at randomization. The sponsor presents data on 22 completers, which is appropriate as the primary analytical population for this type of study. Since data are compared within- and between groups, it is important to re-analyze baseline characteristics for each treatment group.
On closer analysis there were differences, some quite large, between treatment groups at baseline (in age, gender distribution, sulfonylurea use, and duration of diabetes). Whether or not these dissimilarities are "statistically significant," they can potentially translate into significant differences in outcome. In the present case, the role, if any, of each of these factors, either alone or in combination, in determining metabolic responses to bromocriptine is unclear. However, this substantial imbalance at randomization can invalidate comparison of mean differences between groups in determining efficacy or in demonstrating any pharmacodynamic action of the drug.

Bruce S. Schneider, MD
Division of Clinical Evaluation and Pharm/Tox Review
Office of Cellular, Tissue, and Gene Therapies
CBER/FDA

9 OVERALL ASSESSMENT AND RECOMMENDATION

The original application was rejected because of the small imbalance in reports of myocardial infarction in the original trials, together with the lingering concern about myocardial infarction in otherwise healthy young women who used bromocriptine to suppress lactation.

The results of the Safety Study (165-AD-04-03-US-1) have adequately addressed these concerns. There was no increase in risk of serious cardiovascular AE's or myocardial infarction in patients treated with Cycloset. If anything, Cycloset appeared to be protective, with a hazard ratio of 0.58 (95% CI 0.35-0.96). Given the large number of patients who did not complete the study, FDA statistician Lee Pian has questioned the validity of the Sponsor's estimate of the hazard ratio. Her point is well-taken; and I agree that a Cycloset label should not contain statistical inferences about the risk of cardiovascular events. On the other hand, inclusion of the cardiovascular events that occurred after withdrawal of test drug did not materially affect the results. In addition, the Kaplan Meier plot (section 7.2.3) showed separation in favor of Cycloset after only about 3 months. Thus, I am persuaded that the effect is more likely than not to be real.

It is worth noting that the greatest "protection" was found in patients with HbA1c of 7% or less at baseline. It would be desirable if the Sponsor attempted to reproduce this finding in a post marketing trial. However, I am not recommending that such a trial be required for approval. The Sponsor has already demonstrated to my satisfaction that use of Cycloset does not increase the risk of serious adverse events. I am also mindful that the availability of generic bromocriptine may pose an obstacle to recruiting patients for a placebo controlled trial, and in addition will likely limit the Sponsor's ability to recoup the costs of additional research.

The Sponsor should be requested to reexamine the cardiovascular safety data to determine what patient characteristics may have contributed to the favorable finding. As noted above, the greatest "protection" appeared to be in patients with HbA1c of 7% or less at baseline. Age, gender and race appeared to play little role. It would be of interest to know if a history of previous cardiovascular disease, or the presence or absence of certain concomitant medications contributed to the effect.

The approvable letter indicated that the efficacy of bromocriptine, small as it was, had been established for monotherapy and for combination with sulfonylureas. However, not many patients in the safety trial received [redacted] Most patients received the test drug in combination with metformin, a sulfonylurea, or a combination of oral agents. Some also received insulin. There were several reasons why the safety trial was conducted in a different population of patients from the original efficacy trials. Feasibility was one reason. Given the other drugs, especially metformin, which have become available since

b(4)

the original trials, few patients would start Cycloset as initial treatment, or even as add-on to sulfonylureas. In addition, naïve patients would be expected to have a lower risk of cardiovascular events so a much larger number would have been required to provide enough statistical power to detect a difference. The most important reason for using a broader population in the safety trial is that the broader population better reflects the population that would likely use Cycloset if it were approved. Although there is no head to head comparison, metformin is almost certainly more effective than Cycloset and will continue to be initial therapy for most patients with type 2 diabetes. Cycloset will likely be added to metformin, or be the third drug in combination with metformin and a sulfonylurea or TZD.

Despite the approvable letter issued by FDA, October 15, 1999, it would not be appropriate (in my judgment) to approve Cycloset relying solely on the efficacy data in the original trials. As noted in the preceding paragraph, the face of diabetes has changed substantially since when these trials were done. In addition, the formulation of bromocriptine used in the original trials is no longer available, so bridging to the "to be marketed" formulation cannot be done. For these reasons, it is important that efficacy was demonstrated in the "safety trial'. Although a rigorous comparison is not possible, the efficacy of bromocriptine in the original trials appears to be similar to that observed in the safety trial. In sulfonylurea-treated patients, for example, the mean placebo-subtracted change in HbA1c was -0.55 at 24 weeks in the original trials and -0.60 in the safety trial.

In conclusion, Cycloset is effective in lowering HbA1c across a wide spectrum of patients with type 2 diabetes. FDA's earlier concern about cardiovascular safety has been satisfied. Given its modest efficacy, it is likely that Cycloset will be used primarily as an adjunct to other antidiabetic agents. Nausea will limit its acceptability. The most important unanswered question is whether or not the apparent protection from serious cardiovascular adverse events observed in the safety study is real. In addition to reducing HbA1c, Cycloset treatment leads to small but consistent deceases in systolic and diastolic blood pressure. Taken together, these effects would be expected to decrease the long term risk of the complications of diabetes, particularly retinopathy and nephropathy. But one would not expect to see changes in complications of diabetes during the course of a 12 month study. Furthermore, addition of antidiabetic medications beyond week 12 minimized differences in glycemia between Cycloset and placebo (section 6.2.2). Thus, the apparent protection from serious cardiovascular events with Cycloset (section 7.2.3) is not easily explained. .

Recommendation: Pending satisfactory revisions to the label, Cycloset should be approved for treatment of type 2 diabetes

In addition to revising the Cycloset label as requested by FDA, the Sponsor should be asked to:

1. Reexamine the cardiovascular safety data to determine what patient characteristics may have contributed to the favorable finding. It would be of particular interest to know if a history of previous cardiovascular disease, or the presence or absence of certain concomitant medications contributed to the effect.
2. Add valvular heart disease to the Claims Database Study
3. Psychiatric diagnoses should be added to the Claims Database Study
4. [redacted]

b(4)

Labeling of drugs for diabetes is in a state of flux. For this reason, I am not making specific labeling recommendations in this review.

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NDA 20866,
Addendum

In the body of my review, I recommended that the Sponsor should be asked to:

Reexamine the cardiovascular safety data to determine what patient characteristics may have contributed to the favorable finding. It would be of particular interest to know if a history of previous cardiovascular disease, or the presence or absence of certain concomitant medications contributed to the effect.

This request was made to the Sponsor on Dec 29, 2008. The Sponsor submitted adequate responses January 8 and 9, 2009.

1 Previous cardiovascular disease

As described in the Clinical Study Report, the interaction terms of stroke by treatment and coronary revascularization by treatment were added to the Cox regression model. Neither interaction term was significant, indicating that the Cycloset treatment effect does not differ according to whether or not the subject had a history of stroke or coronary revascularization. The table below depicting the % Event Reduction is supportive of these prior conclusions.

Table 1

	Baseline Study Population		Subjects that Experienced a CVD Event by Baseline History of Either Stroke or Coronary Revascularization		% CVD Event by Baseline History of Either Stroke or Coronary Revascularization		Placebo-Cycloset % CVD Event Reduction
	Cycloset N = 2054	Placebo N = 1016	Cycloset N = 32*	Placebo N = 31*	Cycloset	Placebo	
History of Stroke	86 (4.2%)	63 (6.2%)	6 (18.8%)	5 (16.1%)	7.0%	7.9%	12%
History of Coronary Revascularization	210 (10.2%)	128 (12.6%)	13 (40.6%)	13 (41.9%)	6.2%	10.2%	39%

*The analyses in the Cycloset Safety Trial – Clinical Study Report (Amendment 27 to the NDA) on stroke and coronary revascularization interaction by treatment were conducted on the composite of the CVD endpoint (MI, stroke, coronary revascularization surgery, hospitalization for angina or CHF) and including death from CVD causes. This explains why the event numbers of 32 and 31 for Cycloset and placebo, respectively, in the table above are different from the previously submitted tables of baseline cardioprotective and diabetes medications and CVD event reduction wherein the N numbers were of the composite CVD endpoint only (i.e., 30 and 31, respectively).

2 Cardioprotective medications

As might be expected, a large proportion of patients were using the cardioprotective medications shown in the table below. Statins were taken by two thirds of patients and and platelet aggregation inhibitors by nearly half. Greater than 70% were using two or more medications. Four or more medications were used by 33% of patients on Cycloset and 34% on placebo. Cycloset appeared to reduce the proportion of patients who experienced a cardiovascular adverse event endpoint (CVD) irrespective of the use of concomitant cardioprotective medication.

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Table 2 Cardioprotective Medications at Baseline and Among Subjects That Experienced a CVD Endpoint with Determination of the Proportion of CVD Events by Baseline Cardioprotective Medication and Percentage Event Reduction

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Table 2

	Subjects on CV-MED at Baseline within the Study Population		Subjects that Experienced a CVD Event by CV-MED		% of subjects experiencing a CVD Event By CV-MED		Cycloset vs. Placebo % CVD Event Reduction
Cardioprotective Medication by class and sub-class	**Cycloset N = 2054**	**Placebo N = 1016**	**Cycloset N = 31**	**Placebo N = 30**	**Cycloset**	**Placebo**	
ACE Inhibitors							
ACE Inhibitors, plain	966 (47%)	492 (48%)	17 (55%)	12 (40%)	1.8%	2.4%	28%
Fixed ACE plus diuretic	66 (3%)	28 (3%)	1	0	-	-	-
Angiotensin Inhib							
Angiotensin II Inhibitors, plain	302 (15%)	163 (16%)	6 (19%)	5 (17%)	2.0 %	3.1 %	35 %
Fixed AII plus diuretic	105 (5%)	66 (6%)	2 (6.5%)	2 (7%)	1.9 %	3.0 %	37 %
Beta Blockers							
Beta Blockers, selective	458 (22%)	257 (25%)	12 (39%)	10 (33%)	2.6%	3.9%	33%
Alpha-beta blockers	39 (2%)	27 (3%)	2 (6.5%)	0	-	-	-
Diuretics							
Thiazide, plain	336 (16%)	188 (19%)	4 (13%)	8 (27%)	1.2%	4.3%	72%
Fixed Thiazide plus ACE	66 (3%)	28 (3%)	1	0	-	-	-
Fixed Thiazide, plus AII Inhib.	105 (5%)	66 (6%)	2 (6.5%)	2 (7%)	1.9%	3.0%	37%
Sulfamides, plain (loop diuretics)	213 (10%)	98 (10%)	8 (26%)	5 (17%)	3.8%	5.1%	26%
Other diuretic, (aldosterone inhib., low ceiling diuretics)	74 (4%)	55 (5%)	1 (3%)	3 (10%)	1.4%	5.5%	75%
Calcium Channel Blockers							
CCB, plain (dihydropyridine, phenylalkylamine, benozothiazepine)	368 (18%)	205 (20%)	7 (23%)	9 (30%)	1.9%	4.9%	57%
CCB plus statin	7 (0.3%)	2 (0.2%)	0	1	-	-	-
Statin, plain and statin + other lipid lowering	1326 (65%)	682 (67%)	26 (84%)	24 (80%)	2.0%	3.5%	44%
Fixed Statin plus CCB	7 (0.3%)	2 (0.2%)	0	1	-	-	-
Fibrates	195 (9%)	92 (9%)	2 (6.5%)	3 (10%)	1.0%	3.3%	69%
Platelet Aggregation Inhibitors	968 (47%)	499 (49%)	20 (64.5%)	24 (80%)	2.1%	4.8%	57%

3 Diabetes medications

Baseline use of diabetes medication is shown in the table below. At the time of this trial, it was generally recommended that metformin should be used in patients whose hyperglycemia could not be controlled with diet alone. A sulfonylurea or thiazolidinedione (rosiglitazone or pioglitazone) was added to patients whose hyperglycemia could not be controlled with metformin. Insulin was used for patients whose hyperglycemia could not be controlled with oral agents.

The proportion of CVD Events by baseline diabetes medication is also shown in the table below. Patients on "diet only" appeared to be the least likely (0.8%) to have a CVD event. Patients on insulin appeared to be the most likely (3.1%). This result is expected when one considers that 'diet only" is used early in the natural history of diabetes and that insulin is required at a late stage of diabetes. Metformin holds an intermediate position (1.7%). Among the other oral agents, CVD events occurred in 1.6% of patients taking pioglitazone 2.5% of patients taking sulfonylureas, and 2.6% of patients taking rosiglitazone. Metformin is generally used before other oral agents and is contraindicated in patients with renal insufficiency. Therefore, it is not surprising that the percentage of patients with CVD events appears lower with metformin than with sulfonylureas or rosiglitazone. The relatively low percentage of CVD events in patients who were taking pioglitazone is noteworthy, although (a) these are not distinct subgroups of patients (patients using two anti-diabetic agents at baseline are counted in the table for each), (b) the pioglitazone-treated patients comprise the smallest of the subgroups (n=244 vs. n=344-1790), and (c) this analysis does not take into account whether there are other underlying baseline differences in cardiovascular risk between subgroups.

Table 3

Diabetes Medication	Subjects on DM-MED at Baseline within the Study Population	Subjects that Experienced a CVD Event by DM-MED	% of subjects experiencing a CVD Event By DM-MED
all	N= 3070	N= 61	2.0%
Insulin	N= 485	N= 15	3.1%
Metformin	N= 1790	N= 31	1.7%
Rosiglitazone	N= 344	N= 9	2.6%
Pioglitazone	N= 244	N= 4	1.6%
Sulfonylurea	N= 1151	N= 29	2.5%
Diet Only	N= 371	N= 3	0.8%

Patients using two medications are counted for each

The following table shows the proportion of CVD events by baseline diabetes medication and percentage event reduction. Patients on Cycloset appeared less likely to have a CVD event if they were taking insulin, metformin, rosiglitazone, or a sulfonylurea. There were too few events in patients on pioglitazone or "diet only" to comment on the possible effect of Cycloset. Although risk reduction seemed greatest for patients on metformin, this type of analysis is not rigorous enough to draw any firm conclusions. On the other hand, it should be noted that metformin was not used in the trials (trials K, L and M) in the original NDA (see sections 6.1 and 7.1). Perhaps this partly explains why reduction in cardiovascular events was not observed in the earlier trials. Other explanations could include differences in patient populations in the earlier trials, and the shorter periods of treatment in the earlier trials.

Table 4 - Diabetes Medications at Baseline and Among Subjects That Experienced a CVD Endpoint with Determination of the Proportion of CVD Events by Baseline Diabetes Medication and Percentage Event Reduction

	Subjects on DM-MED at Baseline within the Study Population		Subjects that Experienced a CVD Event by DM-MED		% of subjects experiencing a CVD Event By DM-MED		Cycloset vs. Placebo % CVD Event Reduction
Diabetes Medication	**Cycloset N = 2054**	**Placebo N = 1016**	**Cycloset N = 31**	**Placebo N = 30**	**Cycloset**	**Placebo**	
Insulin	309 (15%)	176 (17%)	8 (26%)	7 (23%)	2.6%	4.0%	35%
Metformin	1209 (59%)	581 (57%)	13 (42%)	18 (60%)	1.1%	3.1%	65%
Rosiglitazone	233 (11%)	111 (11%)	5 (16%)	4 (13%)	2.1%	3.6%	40%
Pioglitazone	161 (8%)	83 (8%)	3 (10%)	1 (3%)	1.9%	1.2%	-55%
Sulfonylurea	759 (39%)	392 (39%)	16 (52%)	13 (43%)	2.1%	3.3%	36%
Diet Only	257 (13%)	114 (11%)	2 (6.5%)	1 (3%)	0.8%	0.9%	11%

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/s/

Robert Misbin
1/16/2009 09:05:22 AM
MEDICAL OFFICER

Hylton Joffe
1/16/2009 09:39:24 AM
MEDICAL OFFICER
Please see clinical team leader memorandum.

17 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

MEMORANDUM

DATE: October 15, 1999

TO: NDA 20-866

FROM: John K. Jenkins, M.D.
Director, Office of Drug Evaluation II, HFD-102

SUBJECT: Overview of NDA Review Issues

Administrative History

NDA 20-866 for Ergoset[1] (bromocryptine mesylate) was originally submitted by Ergo Science Corporation on August 18, 1997 (received August 22, 1998). The application requested indications for use as either monotherapy or in combination with a sulfonylurea in patients with Type 2 diabetes mellitus. The application was assigned a standard review.

The NDA was presented to a meeting of the Metabolic and Endocrine Drugs Advisory Committee on May 14, 1998. After hearing presentations by the sponsor and the Division and discussing the available data, the Committee voted unanimously against recommending approval of Ergoset for treatment of Type 2 diabetes mellitus. Following the advisory committee meeting, the sponsor requested and was granted a meeting with the Center in July 1998 to present their responses to the advisory committee meeting and vote.

On November 20, 1998, the Division of Metabolic and Endocrine Drug Products issued a Not-Approvable letter to the sponsor for this NDA. The deficiencies listed in the NA letter related to the small treatment effect seen in the phase 3 studies and its questionable clinical significance along with a safety concern regarding the potential for increased cardiac adverse events in patients treated with Ergoset. The safety concern was based on historical events (i.e., the voluntary withdrawal of the postpartum breast engorgement indication by the sponsor of Parlodel[2] due to reports of MI, strokes, and seizures in postpartum women) and the increased number of myocardial infarctions reported in Ergoset-treated patients in the diabetes clinical trials. The NA letter did not suggest any remedy for these deficiencies.

On April 15, 1999, the sponsor submitted a formal appeal of the NA letter to Dr. Lumpkin, the Director of the Office of Review Management. As part of that appeal process, the sponsor was granted a meeting with the Center on May 11, 1999, at which time they were allowed to explain

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1 Ergoset is the tradename proposed by the sponsor. This name has been reviewed and found to be unacceptable by the Labeling and Nomenclature Committee. For convenience Ergoset is used in this document to refer to the Ergo Science Corporation drug product containing bromocryptine mesylate. The sponsor will be informed in the action letter of the need to submit a new proposed tradename.

2 Parlodel is the tradename of a drug product containing bromocryptine mesylate marketed by Novartis. Approved indications for Parlodel include hyperprolactinemia, acromegaly, and Parkinson's Disease.

in detail the basis for their appeal of the NA letter. Following internal review and discussion, Dr. Lumpkin responded to the sponsor's appeal by letter on June 10, 1999. In that letter, Dr. Lumpkin stated his conclusion, which was supported by Drs. Woodcock, Temple, Bilstad, and Jenkins, that the sponsor had demonstrated the efficacy of Ergoset in lowering HbA1c in patients with Type 2 diabetes. Dr. Lumpkin noted that in the sponsor's April 15, 1999, submission there were new data (i.e., Dr. Testa's study using the UK GPRD) that represented a good faith effort on the part of the sponsor to address the cardiac safety concerns raised by the Division in the November 20, 1998, NA letter. Dr Lumpkin reminded the sponsor that the decision to approve a new drug ultimately involved a careful assessment of the benefits and the risks of the drug. Since the sponsor had submitted new data to address the safety concerns noted in the NA letter, Dr. Lumpkin informed the sponsor that their April 15, 1999, submission was considered to be a complete response to the NA letter and that NDA 20-866 would be placed back on the review clock with a user fee goal date of October 15, 1999. Dr. Lumpkin noted that the new data included in the sponsor's appeal would be reviewed by the Division and by CDER epidemiologists in the Office of Postmarketing Drug Risk Assessment.

The remainder of this memorandum represents this reviewer's assessment of the available data to address the safety of Ergoset and the overall benefit versus risk for this drug in the treatment of patients with Type 2 diabetes mellitus. The issue of the efficacy of Ergoset in the phase 3 clinical trials will not be addressed directly as Dr. Lumpkin has already adjudicated this matter. However, the magnitude of the clinical benefit of Ergoset will be factored into the overall risk versus benefit analysis.

Original NDA Safety Database

In the original NDA, a total of 894 volunteers and patients were exposed to Ergoset and a total of 416 patients were exposed to placebo (Note: 217 of the placebo patients subsequently received Ergoset in open-label extension studies and are included in the total of 894 for Ergoset). In the phase 3 clinical trials, 324 patients with Type 2 diabetes mellitus received Ergoset and 329 patients received placebo. The majority of patients were exposed to Ergoset for >20 ≤ 28 weeks; 303 patients received Ergoset for ≥ 6 months and 63 patients received Ergoset for ≥ 12 months. Patients were generally exposed to doses of Ergoset that ranged from 0.8 to 4.8 mg/day. Overall this is a fairly small safety database for a new drug product proposed for chronic use. This is particularly true given the safety concerns that arose regarding the use of Parlodel in postpartum breast engorgement that led the sponsor to withdraw that indication.

Only one death occurred in the clinical trials; an Ergoset-treated patient died of a myocardial infarction during the open-label extension following the monotherapy phase 3 trial. During the phase 3 trials, the incidence of MI in the Ergoset group was 2.4 per 100 patient years (3/124) versus 0.7 per 100 PY (1/137) in the placebo group. When the controlled and uncontrolled portions of all clinical trials were combined, the incidence of MI for Ergoset was 2.15 per 100 PY (8/372) versus 0.59 per 100 PY (1/169) in the placebo group.

The sponsor acknowledged these findings in the original NDA Integrated Safety Summary and

noted that these data for MI could give rise to concern "taking the overall experience with Parlodel into consideration". The sponsor was unable to offer an explanation for the higher incidence rate for MI observed in the Ergoset clinical trials but noted that this finding was not statistically significant. The sponsor attempted to further address this concern by calculating the combined incidence of MI and angina reported as serious adverse events in the Ergoset clinical trials. According to the sponsor's calculations, the combined incidence of MI and angina was 3.4 per 100 PY for Ergoset and 2.4 per 100 PY for placebo. The sponsor concluded that these data further supported a conclusion of no difference between Ergoset and placebo and also noted that the rate of MI for Ergoset was not above the "expected" rate and was similar to the rate observed in the Framingham study. It is important to note that the entry criteria for the Ergoset clinical trials were designed to exclude patients with known cardiovascular disease.

Summary and Analysis of Sponsor's Response to Safety Concerns in the April 15, 1999, Submission

In the response to the NA letter, the sponsor challenged the Division's reference to the events that led the sponsor of Parlodel to withdraw the indication for postpartum breast engorgement. The sponsor contended that the withdrawal of the postpartum breast engorgement indication was not a valid demonstration of an increased cardiovascular risk of bromocryptine (see above for sponsor's somewhat contradictory reference to the Parlodel experience in the original NDA ISS). The sponsor further contended that subsequent published epidemiologic studies by Rothman (Epidemiolgoy 1991) and Herring (Phar World Sci 1995) and the study conducted by Testa using the UK GPRD (see below) showed no increased risk of MI, strokes, or seizures in women who receive bromocryptine for postpartum lactation suppression. While the sponsor is correct in stating that bromocryptine has not been definitively shown to have a causal role in serious cardiovascular adverse events in postpartum women, the epidemiologic studies cited by the sponsor each have serious limitations in methodology and power and cannot be considered as definitive evidence of a lack of a causal association; i.e., failure to show an association in these studies is not proof a the lack of an association. The historical experience with bromocyrptine in postpartum women cannot be ignored when evaluating the safety of bromocryptine for use in patients with diabetes mellitus and is a reasonable "prior" to warrant careful scrutiny of the safety of bromocryptine for the new proposed use. This is particularly true given the small effect seen with Ergoset and the proposed chronic nature of treatment of diabetes.

The sponsor argues that the incidence of MI observed in the Ergoset clinical trials was not significantly different from the placebo rate and was consistent with the expected background rate of MI in patients with Type 2 diabetes. The sponsor is correct in their statement that the incidence of MI seen in the phase 3 Ergoset clinical trials was not statistically significantly different from placebo when analyzed post-hoc. It is important to remember; however, that the phase 3 clinical trials were not prospectively designed and powered to detect a difference in the rate of MI and that the Ergoset clinical trial database was relatively small. Thus, the lack of statistical significance of the observed differences in the incidence of MI is not entirely reassuring and is not in and of itself an adequate basis to discount the observation. It is not unusual that safety findings that are truly causally related to a drug are not statistically different from placebo

when controlled clinical trial databases are analyzed. That said, it is true that the cardiac safety "signal" detected in the Ergoset phase 3 clinical trials was weak (3 MI in the Ergoset group versus 1 MI in the placebo group) and may have occurred due to chance. As noted above, it is appropriate to carefully analyze this "signal" given the history of concerns regarding potential serious cardiovascular adverse events in association with the use of bromocryptine in postpartum women, the small benefit of Ergoset in diabetes, the rather small available safety database for Ergoset, and the chronic nature of treatment of diabetes.

The sponsor's contention that the incidence of MI observed in the Ergoset controlled clinical trials is not different from the expected rate of MI in a population of patients with Type 2 diabetes mellitus is based on the findings from an epidemiologic study conducted by Dr. Testa and published reports. These data are of value in the overall assessment of the cardiac safety of Ergoset; however, it must be kept in mind that each of the epidemiologic studies has methodological flaws that limit their interpretation. It is also not clear that any of the studies cited by the sponsor evaluated the incidence of MI in a patient population identical to that enrolled in the Ergoset phase 3 trials (see below for further comments regarding the Testa study).

The sponsor referenced two epidemiologic studies conducted by Dr. Testa in their April 15, 1999, submission. The first study was an observational study of the incidence of cardiovascular adverse events in a New England insurance claims database (Note: This is not a new study, Dr. Testa presented the results of this study at the May 14, 1998, MEDAC meeting). In this study, the insurance claims records of patients >30 years of age with a prescription for an oral hypoglycemic agent; e.g., Type 2 patients, were screened. A total of 18,847 patients met the study criteria and their records revealed 2,988 hospital claims for ICD-9 code 410. The number of unique patients represented by these claims was 635. Depending on the assumptions used in the calculations, Dr. Testa concluded that the incidence of MI in this cohort of patients with Type 2 diabetes was 2.1 to 4.2 per 100 patient years. Dr. Testa compared this rate to the incidence of MI in the Ergoset clinical trials which depending on the assumptions used she calculated to be 1.6 to 2.4 per 100 patient years. She concluded that the incidence of MI in the Ergoset phase 3 clinical trials was not significantly different from the "background" rate seen in patients with Type 2 diabetes enrolled in the New England insurance database.

Dr. Testa's New England claims database study was reviewed by Dr. Staffa from OPDRA. With regard to the internal validity of the study, Dr Staffa made the following observations: a) Dr. Testa calculated the rate of MI and not a true incidence of MI since there was no screening for prior MI history for the cohort of patients evaluated; b) Dr. Testa estimated the number of MI claims per patient rather than conducting a patient specific analysis of first MI during the study period; and c) Dr. Testa did not employe any control for the severity of diabetes, other drugs used, or history of cardiovascular disease. With regard to the external validity of the study, Dr. Staffa noted that the results from Dr. Testa's study were not generalizable to the population of patients enrolled in the Ergoset controlled trials since the Ergoset trial population was screened to exclude patients with existing cardiac disease. While Dr. Testa's study provides useful information about the "background" rate of MI in the cohort of patients enrolled in the New England insurance database, Dr. Staffa is correct in concluding that the results cannot be directly

compared to the patient population enrolled in the Ergoset controlled trials. Such cross-study comparisons are fraught with hazard and are an unreliable basis for a regulatory decision regarding the safety of a new drug.

The second study conducted by Dr. Testa was a cohort control study in which 5693 bromocryptine-exposed patients and 10,496 non-exposed, matched controls were identified retrospectively using the UK General Practice Research Database (GPRD) of computerized medical records. Approximately 86% of the bromocryptine-exposed cohort was female and the most common indications for the use of bromocryptine were galactorrhea (59%), Parkinson's Disease (15%), and hyperprolactinemia (11%). A total of 92 first MI occurred in bromocryptine-exposed patients; 69 of these MI occurred in patients with Parkinson's disease. The overall relative risk of MI within the exposed group (comparing exposed time to non-exposed time) across all indications was reported as 0.483 (95% CI, 0.27-0.87). The relative risk of MI for the exposed group compared to the non-exposed group across all indications was reported as 0.497 (95% CI, 0.28-0.89). For the subset of 124 patients in the bromocryptine-exposed group that had a history of diabetes the relative risk of MI was reported as 0.26 (95% CI 0.07-0.95). Dr. Testa concluded that this study "rules out with high certainty an overall increased risk of MI due to bromocryptine treatment". During the May 11, 1999, meeting between Ergo Science and the Center, Dr. Testa even suggested that these data show that Ergoset may have a protective effect for MI.

Dr. Staff of OPDRA also reviewed the Testa GPRD study and made the following comments regarding internal validity: a) the study included pre-1991 GPRD data that may be unreliable; b) Dr. Testa's use of the entire available follow-up period as the "exposure" period for the un-exposed group may bias the results in favor of showing no effect of bromocryptine; c) the smoking history data available from such computerized medical records are unreliable; and d) there was no control or examination of the use of other drugs and the impact on MI risk. With regard to external validity, Dr. Staff made the following comments: a) the results of this study are difficult to generalize to patients with Type 2 diabetes since approximately 70% of the bromocryptine-exposed patients were young females with short-term use of bromocryptine; the risk of MI in this group of patients in very different from the risk in patients with Type 2 diabetes; b) the number of patients with diabetes in the population was small; and c) there was no control/evaluation of other therapies received and no information regarding pre-existing cardiovascular disease; i.e., the GPRD study cohort may not be comparable to the Ergoset clinical trials population who were screened to exclude patients with existing cardiac disease. Dr. Staffa's points regarding the limitations of this study are valid, in particular her comments about the "exposure" period chosen by Dr. Testa for the un-exposed group. Dr. Testa did not provide detailed analyses for the comparisons using the shorter "exposure" period for the un-exposed group; however, she did state that the relative risk of MI for all indications using the shorter "exposure" period was 0.86 (95% CI not reported). This RR was substantially different from that calculated by Dr. Testa using the full follow-up period as the "exposure" period (i.e., 0.497) and supports Dr. Staffa's concern that the "exposure" period used by Dr. Testa might bias against a finding. Overall, this study provides information regarding the risk of cardiovascular events in a retrospectively selected cohort of patients treated with bromocryptine; however, I do not agree

with Dr. Testa's conclusion that this study "rules out with high certainty an overall increased risk of MI due to bromocryptine treatment". Such a conclusion is not supported by the data. At most, this study should be interpreted as failing to show an increased risk of MI in the population studied acknowledging the design, and limitations, of the study.

Summary and Analysis of Other Available Data Regarding Safety of Bromocryptine

In an effort to fully evaluate available data for the cardiac safety of bromocryptine, other databases were surveyed for any controlled clinical trial experience not identified by the sponsor that may shed light on this issue. The information that was obtained from this survey is summarized briefly here.

The sponsor recently submitted to the IND for Ergoset the results of a 6-month, double-blind, placebo-controlled study of Ergoset in patients with obesity. The patients in this study did not have diabetes and had a mean age of 42 years. A total of 407 patients were randomized and 213 patients completed the trial. The doses of Ergoset were 2.4 and 4.8 mg/day. There was a high dropout rate in the Ergoset groups in this study due to adverse events. No serious cardiovascular adverse events were reported by the sponsor. There were three adverse events of chest pain in Ergoset-treated patients; however, these appeared to be of non-cardiac origin (see MOR prepared by Dr. Bruce Schneider). Given the different patient population as compared to the patient population in the Ergoset clinical trials in diabetes and the very small size of this study (given the expected rate of MI in this population the study was underpowered to detect any difference in MI rate), it is very difficult to definitively interpret the absence of serious cardiovascular events in this trial. On the other hand, this trial did not produce any worrisome signal of adverse cardiac effects of Ergoset in this population.

One of the major approved clinical uses of Ergoset is the treatment of Parkinson's Disease (PD). Since patients with PD tend to be older with concomitant medical conditions that may predispose them to a high background rate of MI, available controlled clinical trials of bromocryptine in PD were reviewed. The first data source was the original approval of Parlodel for the treatment of PD based on studies conducted in the late 1970's. The original efficacy supplement for Parlodel for PD included two phase 3 controlled clinical trials comparing L-dopa/carbidopa plus bromocryptine to L-dopa/carbidopa alone. There was no placebo in these trials. A total of 458 patients were enrolled into these trials with a 1:1 randomization. The reviews of these studies in the NDA file contained little information about the safety findings from these trials other than the common adverse events. The review did note that three patients died in the clinical trial program, all were in the bromocryptine-treated group. Two patients died from MI and the third patient died from bowel ischemia and obstruction. The review also summarized literature reports of adverse events with bromocyrptine including anecdotal reports of vasospasm. These reports combined with the deaths in the bromocryptine-treated patients led the original reviewer to conclude that there might be evidence of "ergotism" with bromocryptine. The reviewer suggested that bromocryptine should be used with caution in PD patients due to the potential for serious cardiovascular adverse events.

The NDA for ropinirole (tradename Requip), which was approved for the treatment of PD in 1997, included two non-US active control trials comparing bromocryptine to ropinirole. The first study (study 053) was a 3-year trial in patients with early PD. The dose of bromocryptine was titrated to a maximum of 13.3 mg three times daily in this study. The second study (study 043) was a one-year trial in patients with late PD. The dose of bromocryptine was titrated to a maximum of 40 mg three times daily in this study. The medical officer's review of the ISS for this NDA reported the 6-month mortality rates for these two trials. In study 053, the overall mortality in the first six months was 0.6/100 patients (1/168) for ropinirole and 3.4/100 patients (6/167) for bromocryptine (p=0.07 by Fishers exact test). In study 043, the overall mortality during the first six months was 1.4/100 (5/367) for ropinirole and 2.1/100 (4/188) for bromocryptine. Additional follow-up data on these studies were not included in the NDA and the actual causes of the 6-month mortality were not specified in the MOR. It is difficult to reach any definitive conclusion regarding the safety of bromocryptine in this patient population from these data due to the lack of a placebo control and the lack of additional information about the cause of death and the incidence of specific cardiac adverse events. The dose of bromocryptine used in these trials, which is much higher than proposed for Ergoset, must also be kept in mind. It is notable that in both studies the overall 6-month mortality rate was higher for bromocryptine-treated patients compared to ropinirole-treated patients.

The final results of study 053 (three-year data) were recently published (Neurology 1999; 53:364-370). According to that report, a total of 3 ropinirole-treated patients (n=168) died during the study compared to 7 deaths in bromocryptine-treated patients (n=167). It was reported that these deaths were "most commonly due to cardiac failure". In the same report the frequency of serious adverse events was noted as follows: cardiac failure, ropinirole 2.4% versus bromocryptine 3.0%; MI, ropinirole 0.6% versus bromocryptine 2.4%; cerebrovascular disease, ropinirole 2.4% versus bromocryptine 0.6%. It is interesting to note that the increased incidence of mortality in the bromocryptine-treated group observed during the first 6 months of study 053 persisted at the end of the three-year follow-up. It is also interesting that the incidence of MI reported as a serious adverse event was also more common in bromocryptine-treated patients.

The NDA for primepixole (tradename Mirapex) was approved for the treatment of PD in 1997. As part of the development program for primepixole, the sponsor conducted a 9-month, non-US, double-blind, placebo-controlled trial in patients with advanced PD. The study included a bromocryptine active control arm. A report of the study was recently published (Neurology 1997; 49:1060-1065). In the study the bromocryptine dose was titrated to a maximum of 30 mg/day and the overall mean dose of bromocryptine was 22 mg/day. The study enrolled a total of 247 patients and about 80 patients per treatment arm. In the published report there is no reference to any deaths during the study and the only cardiovascular adverse event listed in a table of common adverse events observed during the study was postural hypotension.

The data from the two recently approved drugs for the treatment of PD were discussed with Dr. Greg Burkhart from the Division of Neuropharmacolgoic Drug Products (HFD-120). Dr. Burkhart noted that the Division had questioned the increased death rate in the bromocryptine-treated group when reviewing the ropinirole NDA and had placed this on their list of issues to

follow-up on. Dr. Burkhart has agreed to attempt to obtain more information regarding the studies contained in these NDAs that included bromocryptine active control arms. However, no additional information regarding these studies is expected to be available in advance of the action date for the Ergoset NDA. Since it is unlikely that these studies will provide data adequate to alleviate concerns regarding the potential cardiac adverse effects of bromocryptine in patients with diabetes, the inability to retrieve these data at this time does not warrant delaying action on the Ergoset NDA.

A final relevant study in PD comes from a long-term study of mortality and disability in PD patients in the UK (BMJ 1993: 307:469-472)). In that study 782 patients with early PD were randomized in a 1:1:1 manner to one of three treatments: L-dopa, L-dopa plus selegiline, or bromocryptine. The bromocryptine dose was titrated to a maximum of 30 mg three times daily and the actual mean dose of bromocryptine was 36 mg/day. The published report is a three-year interim analysis of the study. There was a high rate of withdraws of patients in the bromocryptine arm due to adverse events; e.g., nausea, dizziness. The published report does not include any data on mortality and states that "the number of patients who died is still small and longer follow-up will be required". Unfortunately the failure of the study authors to include any mortality data from this study in the published report, despite the fact that mortality was listed as being a co-primary endpoint, precludes any assessment of the long-term safety of bromocryptine in this patient population.

Overall the available data from other controlled clinical trials of bromocryptine in obesity and PD are of limited value in addressing the safety of Ergoset in the treatment of diabetes. The available studies were generally small and did not include a placebo control group. The only studies that produced any "signal" of an adverse effect of bromocryptine, the ropinirole studies, did not include a placebo control and are difficult to interpret.

Summary, Conclusions, and Recommendation

The regulatory decision regarding the appropriate public health action on the Ergoset NDA represents a very complex and difficult weighing of the potential benefits of the drug to patients with Type 2 diabetes mellitus versus the potential risks. Ergoset has been shown to lower HbA1c levels in phase 3 controlled clinical trials compared to placebo as either monotherapy or in combination with a sulfonyhurea. However, the absolute magnitude of the treatment effect of Ergoset in these studies was quite modest and substantially less than that seem with other available therapies for Type 2 diabetes[3]. On the other hand, the safety "signal" identified in the Ergoset clinical trial database is a weak finding (i.e., 3 MI in the Ergoset group versus 1 MI in the placebo group) that could have simply occurred by chance. The "signal" is extremely sensitive to a change of one MI in either the Ergoset group or the placebo group (i.e., had there been one less MI in the Ergoset group and/or one more MI in the placebo group the "signal" would essentially

3 While there is no requirement that a new drug be superior to previously approved therapies for a given indication in order to be approved, the relative benefits of the new drug as compared to other approved therapies does play a role in the regulatory risk versus benefit evaluation, particularly when there are significant questions regarding the safety of the new drug.

disappear). The relatively small size of the Ergoset safety database also makes this "signal" difficult to interpret. A regulatory agency must proceed with great caution in interpreting such a weak "signal" since such signals can and will appear in a safety database purely by chance when a large number of variables are analyzed and tabulated. Such signals must be interpreted in the light of all available data before making a decision regarding the impact of the signal on the regulatory decision. The safety "signal" identified from the Ergoset phase 3 clinical trials in patients with Type 2 diabetes must be interpreted in the context of the serious concerns that have been raised in the past regarding the safety of bromocryptine when used in postpartum women. The "signal" must also be evaluated with regard to the potential adverse effects on the public health if the "signal" is in fact a true representation of an increased risk of MI in patients with Type 2 diabetes treated with Ergoset. If the "signal" is real and Ergoset is approved and widely used to treat Type 2 diabetes, the resulting increase in MI would represent a major public health concern for very little added benefit in the overall management of diabetes. It is important to note that an increased incidence of MI in the diabetic population would be very difficult to detect from postmarketing surveillance data given the high background rate of MI in patients with diabetes[4].

After considering all available data and after considering the views on this issue expressed by the Division and Center leadership (Drs. Woodcock, Lumpkin, Temple, and Bilstad), I have concluded that the concerns regarding the potential adverse cardiac risks of Ergoset outweigh the potential benefits of this treatment in patients with Type 2 diabetes. I believe that the NDA for Ergoset should not be approved until the sponsor has conducted, and submitted to FDA for review, an adequately designed and powered placebo-controlled clinical trial to specifically address the concerns regarding a potential increased risk of serious cardiac adverse events in Ergoset-treated patients with Type 2 diabetes. I recognize that this is a conservative approach; however, I believe that this approach best serves the public health. If Ergoset had been shown to be significantly more effective than it was in the phase 3 clinical trials, then I believe it might have been reasonable to approve the drug with appropriate labeling warnings regarding the potential for increased cardiac adverse events combined with a phase 4 commitment from the sponsor to conduct an adequately designed and powered study to assess this possibility in a timely manner. Given the limited efficacy of Ergoset, I do not believe that such an approach is warranted, nor do I believe that it would be in the public health interest.

A final issue to address is what type of action should be taken on this NDA. Dr. Sobel and the Division have recommended that the action be a Not-Approvable letter to emphasize the seriousness of the concerns regarding the safety of Ergoset. After considering the available options and after discussing this with Drs. Sobel, Woodcock, Lumpkin, Temple, and Bilstad, I have concluded that the action should be an Approvable letter. There are several reasons for this conclusion. First, under the FDAMA the Center has been directed to issue "complete action letters" instead of the current "Approvable and Not-Approvable" letters. This directive, which has not been implemented in CDER to date due to the need to rewrite FDA regulations, has resulted in a marked change in the use of the "Approvable" letter over the past few years and a marked reduction in the use of the "Not-Approvable" letter. I am aware of Center precedents

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4 For the same reason, little reassurance of an absence of an effect of bromocryptine on the incidence of MI in patients with PD can be gained from the long marketing history of Parlodel for this indication.

that support the use of an "Approvable" letter for Ergoset. Second, the sponsor has demonstrated the efficacy of Ergoset and will not be required to conduct any additional studies prior to approval to address this part of the NDA. The fact that efficacy has been established means that this NDA can be approved if the remaining question regarding safety is adequately addressed. Third, while the safety "signal" identified from the phase 3 clinical trials raises significant concerns, especially considering the regulatory history of Parlodel for postpartum breast engorgement, it is entirely possible that the "signal" occurred simply by chance and will not be confirmed by a larger placebo-controlled trial. It seems inappropriate in my judgement to label the Ergoset NDA "Not-Approvable" based on such a "signal"; although I believe that the NDA should not be approved until the repeat safety study has been completed. Finally, I believe that the use of the term "Approvable" for this NDA may provide the sponsor the incentive to conduct the necessary safety study. The conduct of this study is in the public health interest for two major reasons. First, it will more definitively address the important question of the safety of bromocryptine in patients with diabetes and indirectly the safety of bromocryptine in other diseases; e.g., Parkinson's Disease. It is important to remember that bromocryptine is currently approved and marketed in the US for other indications. Thus, the safety concerns raised regarding the Ergoset NDA are not limited to the approval decision regarding this product[5]. Second, Ergoset has been shown to be effective in lowering HbA1c in patients with Type 2 diabetes and some patients in the phase 3 clinical trials had a more favorable response than others. If the safety "signal" for Ergoset is not substantiated by the repeat safety study, then Ergoset can be approved and will offer another option to patients and physicians for the treatment of diabetes, a disease that takes a terrible toll in terms of morbidity and mortality.

Draft Text for Approvable Letter to Address Major Deficiency

The following text should be communicated to the sponsor as the major outstanding deficiency for this NDA in the Approvable letter. Other outstanding deficiencies should also be included in the letter[6].

Based on the data submitted to the NDA, we remain concerned that treatment of patients with Type 2 diabetes with Ergoset may be associated with an increased risk of serious cardiac adverse events. The new data submitted in the April 15, 1999, response to the November 20, 1998, Not-Approvable letter (e.g., the Testa UK GPRD study), do not adequately address this concern. While you have demonstrated the efficacy of Ergoset in patients with Type 2 diabetes (see letter from Dr. Lumpkin dated June 10, 1999), the magnitude of the treatment effect seen in the phase 3 clinical trials was small. Given the small treatment benefit and the outstanding safety concerns, the overall risk versus benefit analysis for Ergoset for the treatment of patients with Type 2 diabetes does not support approval at this time. To address the outstanding safety concerns, we recommend that you conduct a new, placebo-controlled study of the safety of

5 As noted above, Dr. Burkhart from the Divison of Neuropharmacological Drug Products has been made aware of the safety concerns regarding the use of bromocryptine in diabetes and has indicated that his division intends to request data from sponsors to further review the safety of bromocryptine in PD.
6 This text has been shared with Drs. Lumpkin and Temple for their comments and thus may change slightly in the final action letter.

Ergoset in patients with Type 2 diabetes. The new study should be adequately designed and powered to evaluate the potential for a significant increase in the risk of serious cardiac adverse events with Ergoset treatment. We suggest that you consider using a large, "simple" trial design to achieve this objective. You are strongly encouraged to discuss the details of such a study with the Division of Metabolic and Endocrine Drug Products prior to the conduct of the study.

cc:
NDA 20-866
HFD-510 Division File
HFD-102/Jenkins
HFD-510/Weber
HFD-510/Sobel

NDA 20866
Sponsor: ErgoScience
Drug: Bromocriptine

Received: 12/9/97
Reviewed: 4/1/98
Doct: N20866A

MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATION

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MEDICAL REVIEW PROPER

1 GENERAL INFORMATION

1.1 Drug Name and Structure

1.1.1 Generic name

Bromocriptine mesylate

1.1.2 Proposed trade name

Ergoset

1.1.3 Chemical name

[Ergotaman-3',6',18-trione,2-bromo-12'-hydroxy-2'-(1-methyl-ethyl)-5'-(2-methylpropryl)-monomethanesulfonate (salt], 5'alpha)-]

1.2 Scientific Information

1.2.1 Pharmacological Category

Primary activity: Dopamine-D2 receptor agonist.

Secondary activity: sympatholytic.

1.2.2 Proposed Indication(s)

1. Adjunct to diet to improve glycemic control in patients with type 2 diabetes (NIDDM) whose hyperglycemia cannot be satisfactorily managed by diet alone.

2. Given concomitantly with sulfonylureas when diet and Ergoset or sulfonylureas alone do not result in adequate glycemic control.

1.2.3 Dosage Form(s)

Tablets: 0.8, ———————— b(4)

1.2.4 Route(s) of Administration

Oral.

1.3 Regulatory Information

Ergoset (for the proposed anti-diabetic indication) has not been approved in any other countries outside the United States. Thus, no post-marketing surveillance reports are available for this particular drug-indication combination. However, as is well known, bromocriptine itself has been marketed in a great number of countries for more than two decades. The safety profile of the drug is rather well known

and can be conservatively applied to this particular NDA, inasmuch as the average dosing in this NDA (in the 3-5 mg range) is lower than the average given to patients receiving bromocriptine for the previous, i.e., more traditional, indication (mostly Parkinson disease).

2 LISTING OF VOLUMES CONSULTED AND REVIEWED

Human pharmacokinetics: 1.9, 1.10, 1.11, 1.12, 1.13, 1.14, 1.15, 1.16, 1.17, 1.18, 1.19, 1.20, 1.21, 1.22, 1.23, 1.24, 1.25, 1.26, 1.27, 1.28, 1.29, 1.30, 1.31, 1.32.

Clinical data: 1.33, 1.34, 1.35, 1.36, 1.37, 1.38, 1.39, 1.40, 1.41, 1.42, 1.43, 1.44, 1.45, 1.46, 1.47, 1.48, 1.49, 1.50, 1.51, 1.52, 1.53, 1.54, 1.55, 1.56, 1.57, 1.58, 1.59, 1.60, 1.61, 1.62, 1.63, 1.64, 1.65, 1.66, 1.67, 1.68, 1.69, 1.70, 1.71, 1.72, 1.73, 1.74, 1.75, 1.76, 1.77.

Miscellaneous: 1.1, 1.2, 1.7.

3 CHEMISTRY AND MANUFACTURING CONTROLS

See Chemist's review.

4 PRECLINICAL PHARMACOTOXICOLOGY

A number of species (rats, dogs, monkeys,) were administered bromocriptine, sub-chronically or chronically). In all cases, the drug was to be found safe, except in the following cases:

1. Atrophy of testicular germinal epithelium cells with impaired spermiogenesis in rats treated with 400-1400 multiples of the proposed human dose. The rat has a peculiar reproductive physiology with respect to the effects of prolactin inhibition and, in addition, bromocriptine is used to treat infertility in prolactinemic humans. In females of the species, various abnormalities of corpora lutea were observable, all attributable (according to expert) to the fact than in the rat, the corpus luteum is under the control of prolactin.

2. In dogs, sub-chronic administration of bromocriptine, 230 times the average human equivalent used in these studies, some SGPT and BUN elevations were observed, without any histological proof of hepatotoxicity of nephrotoxicity.

Otherwise, see Pharmacologist's review for a more thorough presentation of preclinical findings, particularly in the reproductive as well as the carcinogenetic effects of long term, high-dose administration of bromocriptine to various animal species.

5 CLINICAL BACKGROUND

5.1 Direct Information

5.1.1 Human Pharmacodynamics

Bromocriptine is a Dopamine-D2 receptor agonist, known and used in human therapy for several decades. The various indications currently approved are hyperprolactinemia (resulting in degrees of infertility in both sexes, micro- or macroprolactinomas), acromegaly, and Parkinson's disease.

Some years ago, Cincotta, Moore et al. Introduced a patent request for the timed use of bromocriptine that would hypothetically result in a reduction in obesity and hyperglycemia. Apparently, cells in the suprachiasmatic nuclei are physiologically influenced by photoperiod, circulating hormones, and as yet unspecified seasonal factors. These, in turn, modulate the ventro-medial hypothalamus. These complex interactions (which, biochemically, are dependent on dopaminergic and serotoninergic modulations) result in dual and opposite effects, depending on the season: The animals' fat reserves are increased prior to hibernation; while, in the lenient periods, the fat is shed, to allow the now lean animal to actively pursue food gathering or pursue prey.

The hypothesis has been tested in animals: When bromocriptine (which affects both dopaminergic and serotoninergic cells) was administered at the time of, or immediately after the time of, peak plasma prolactin

concentration found in lean animals of the same species, insulin resistance was reduced in obese animals.

The present NDA asserts that this hypothesis has now been tested in diabetic humans (where insulin resistance and increase in weight create a state roughly comparable to the hibernating animal). Under these circumstances, the Sponsor asserts that bromocriptine should be approved for treatment of diabetic subjects in whom diet alone, or sulfonylurea alone, or diet and sulfonylurea alone do not correct satisfactorily their hyperglycemic levels; either as a monotherapy, or as an adjunctive therapy.

A question to be asked pertains to the chain of causalities in the human. It is stated that a circadian prolactin rhythm can be adequately modified in the diabetic subject, to bring it closer to that seen in the normal individual. We shall see if, indeed, the prolactin levels change during treatment with bromocriptine treatment and, if they do, by how much and when. If the desired change is pres[illegible] would suggest that these changes in [illegible] e the causal agents of the subsequent [illegible]s.

Other question then come to the fore: Through [illegible]echanism(s) are these changes obtained? Is the appetite center affected, directly or indirectly, in any way (in which case, food intake would be reduced)? Or is lipid metabolism accelerated, thus preventing fat deposits in adipocytes (in which case one would expect some change in circulating fatty acid levels and increase of relative lean body mass)? These two mechanisms, however, would have very similar end results, i.e., increase in relative lean body mass and reduction in weight. Thus, it would be very difficult to tease such effects apart, unless one registers carefully food intake in a free and uncontrolled situation, as well as measure O2 consumption and CO2 production before and after timed therapy with bromocriptine, in subjects where the desired clinical effects have been achieved.

In this particular submission, such experimentation may or may not have been performed. In any event, we shall scrutinize carefully the NDA to see if any study might give us some clue as to the particular mechanism(s) of action of the timed treatment, which apparently results in a reduction (a correction) of HbA1c levels in the treated type 2 diabetic.

The additional mechanistic claim is made by the Company that its method can also reduce insulin resistance, hyperinsulinemia or hyperglycemia, or both, in lean as well as obese patients. If this has been verified in studies presented and discussed in this submission, i.e., if timed administration of bromocriptine affects these parameters how is this achieved, by what means and mechanisms? To answer such questions one can extrapolate from the fact that, apparently, bromocriptine treatment reduces ventromedial hypothalamic norepinephrine metabolism, which is elevated in the insulin-resistant state. One can, therefore, postulate that insulin-resistant is somehow caused by increased ventromedial hypothalamic norepinephrine metabolism; and that, conversely, the reduction of norepinephrine metabolism results in normalization or near-normalization of the insulin-resistant state. We know that insulin resistance produces hyperinsulinemia and that its correction is an indication of improvement in insulin receptor sensitivity which, in turn, will tend to correct hyperglycemia.

Practically speaking, the Sponsor advances that bromocriptine, administered early in the morning, would result in the improvement of insulin sensitivity, the reduction of fat stores, and the normalization of hyperglycemia and hyperinsulinemia. Copies of the Company's patents also claim that metoclopramide (or haloperidol, or sulpiride, or pargyline, or estrogen) administration when [illegible] prolactin levels are at their highest (i.e., before [illegible]et of sleep) would also result in the same effects, [illegible] the improvement of insulin sensitivity, the reduction [illegible] fat stores, and the normalization of hyperglycemia and hyperinsulinemia. At present, the Company seems to have forgone, for whatever reasons, the combined use of metoclopramide or other prolactin-inducers and bromocriptine. Apparently, bromocriptine alone is able to affect sufficient dopaminergic increase and serotoninergic decrease to affect the desired metabolic changes. The serotonin mechanism is probably based on the synergism between serotoninergic and adrenergic mechanisms in the ventromedial hypothalamus, to stimulate hepatic glucose production and adipose lipolysis.

Before closing this discussion, two additional comments may be warranted:

1. Initially, the Company thought it possible to determine, in each individual subject and with great precision, the timing and the dose of the bromocriptine needed to redirect the circadian rhythm towards the "lean" state. Later, it was found that this was not possible in certain individuals in whom timing treatment didn't seem to improve HbA1c levels. **The Company then developed and tested prospectively the concept of "non-responders", detected at 8 weeks following initiation of treatment with bromocriptine. "Responders" are those who, at 8 weeks of treatment, have shown a decrease in HbA1c values of 0.3% or more.** This concept of non-responder was then studied, in a prospective fashion, in the various pivotal protocols K, L. & M.

2. At first, the Company had meant to use bromocriptine and metoclopramide in conjunction; the former timed to affect the prolactin levels in early morning, the latter to affect the prolactin levels later in the day. For various reasons (financial exigencies, inability to quickly determine effective yet safe dosing of metoclopramide, etc.), the company has, at least for the present, abandoned the idea of using metoclopramide in combination with bromocriptine. It is probable that future studies may address this question, particularly when dealing with the indication of obesity, given the paucity of really safe and effective drugs in this area.

5.1.2 Human Pharmacokinetics

5.1.2.1. General Overview

The following conclusions pertain to the known and general aspects of bromocriptine pharmacokinetics (a drug that has been in use for more than two decades in the general population) with particular reference to the present formulation:

1. After oral administration, about 60-80% of the dose is absorbed rather rapidly.

2. The drug circulates in the blood, 90% or more of it bound weakly to albumin. Which explains its first pass metabolism of over 90% of the absorbed fraction. Overall, the drug is extensively metabolized.

3.Clearance is mainly through metabolic disposition. The small fraction of unchanged drug and the large bulk of its metabolites are then excreted in the feces, via the bile, with only a small portion of the total absorbed excreted in the urine, probably after being rendered water soluble through conjugation with more polar residues.

Since the timing and kinetics of orally administered bromocriptine are critical for its clinical effectiveness, the availability and kinetics of the drug are crucial to understand. With this in mind, the submitted pharmacokinetics studies have been scrutinized for clinical pertinence.

5.1.2.2. Study DP143

This is a pilot bioavailability study of bromocriptine (0.8 mg)in healthy fasting volunteers.

5.1.2.3. Study EP194

This is a 2-way crossover bio-availability study of bromocriptine (4.8 mg) in healthy fasting male and female volunteers. In this study, the bioavailability of the drug (6 x 0.8mg tablets) was compared to that of an oral bromocriptine mesylate solution, in a single-dose, randomized, open-label fashion, in 19 males and 15 females. Standard meals were served at 4 hrs. after dosing. Timed blood samples were obtained to determine the pharmacokinetic profile of the drug. The respective plasma T1/2 were 3.6 and 3.5 hrs., for the tablet and the solution, respectively. There were slight differences in other parameters, differences that appear to be of little or any consequence from a clinical point of view, given the usual intra- and inter-individual variability in humans. Generally speaking, relative bioavailabilities (of tablets and solution) were similar under fasting conditions.

One final interesting observation: It would appear that females tend to absorb more than males with increased values for AUC, Cmax, and T1/2.

5.1.2.4. Study EP092

This is a 3-way crossover bioequivalency study of bromocriptine (0.8, 1.6, and 4.0 mg) in healthy fasted male and female volunteers. In this single-dose, randomized, open-label study, 19 males and 17 females were given an oral 4.8 mg dose (6 x 0.8 mg tablets) and an oral 4.0 mg dose (1 x 4.0 mg tablet). Again, timed blood samples were obtained before dosing till 36 hrs post-dosing. Meal plans were identical for all three dosing periods and were "fat-loaded--" not exactly a typical meal for a diabetic. The mean plasma T1/2 ranged between 3 to 5 hrs.

Despite the small number of subjects and the probably consequent high variability in results, this Reviewer tentatively concludes that the 0.8 mg and 4.0 mg tablets are probably bioequivalent, but that the 1.6 mg tablet is probably not, when compared to the other doses. This conclusion is not based on the criteria generally utilized by our Biometrics Division; rather, it reflects a clinical sense of comparing these results with the dose-response data obtained in the clinical trials. In addition, this study shows that the intra-individual variability of AUC and Cmax, for example, diminishes and becomes tighter when the tablets are administered with a meal.

5.1.2.5. Study FP519

This is a 4-way crossover bioavailability study comparing various bromocriptine formulations (0.8, 1.6, 4.0 and 4.8 mg.) in fasted and fed male and female volunteers. A single oral dose of 4.0 mg was administered after a supervised fast of 10 hours or more, and after a standard breakfast; a single oral dose of 4.8 mg (6 x 0.8mg) mg was administered after a standard breakfast; and, finally, a single oral dose of 4.8 mg (3 x 1.6 mg) was administered after a standard breakfast. Meals were served 4 hours after dosing.

Our biopharm reviewer concluded that, overall, the relative bioavailabilities of the various bromocriptine tablets were greater in the fed state, as compared to the fasted state. On the other hand, the various bioavailability parameters (AUC, Cmax, t ½) were relatively constant for 0.8, 1.6 and 4.0 mg, in the fed state.

5.1.2.6. Final Conclusion

From a clinical viewpoint, there are two pertinent conclusions:

1. **Our Bioequivalency experts have concluded that the 4.8 mg formulation was not bioequivalent.** I respect their expertise and am aware of the criteria that they have to meet in order to accept bioequivalency. On the other hand, as a clinician, I observe that there is a great inter-individual (and even intra-individual) variability in the data gathered during the above bioequivalency studies. Given this variability, it can be assumed that the 4.8 mg formulation, while being outside the limits set by our Pharmacokineticists, is still useful, because the variability of kinetic and clinical responses negates any untoward or undesirable consequence due to its absorption characteristics. We should also remember that patient compliance and comfort may be affected if they have to swallow, for example, three 1.6 mg tablets instead of a single 4.8 mg tablet. **For all the above reasons reasons, this Reviewer recommends approval of the 4.8 mg tablet.**

2. Generally speaking, the bioavailability of the various formulations are satisfactory, provided that the tablets are taking with a meal. Otherwise, some disturbing variabilities seem to occur, both intra- as well as inter-individual. **It is therefore imperative that the labeling clearly and emphatically proclaim that bromocriptine tablets should <u>always</u> be taken with a meal to ensure safe and predictable absorption and efficacy.**

5.1.3 Human Clinical Experience

As stated earlier, bromocriptine is a Dopamine-D2 receptor agonist, known and used in human therapy for several decades. The various indications currently approved are hyperprolactinemia (resulting in degrees of infertility in both sexes, micro- or macro-prolactinomas), acromegaly, and Parkinson's disease.

This Reviewer remembers that, years ago, and in some exceptional and highly infrequent cases, a few

women, treated with bromocriptine (in the post-partum period) to stop lactation, experienced severe cardiovascular accidents, with some of them dying as a result. The FDA asked that the Company remove this indication from its labeling, which the Company eventually did.

It should be clearly stated that the post-partum population in question was a sensitized and brittle population. Most, if not all, of these women had experienced long and difficult labor, during which much blood was lost, and as a result of which their cardiovascular system became highly destabilized. When bromocriptine was administered to that special highly sensitized population, its real but infrequent hypertensive effect must have provided the extra nudge to result in the known catastrophic accidents which followed. **The very particular population which exceptionally experienced cerebrovascular accidents cannot, by any stretch, be compared to the one that will be treated if this NDA is approved, i.e., an otherwise stable diabetic population.**

6 CLINICAL DATA SOURCES

6.1 IND and NDA Studies

6.1.1 Type of Studies

The NDA contains four different sets of studies: Pivotal, controlled, non-controlled, and other (pharmacokinetic, etc.)

6.1.2 Patient Populations

Two kinds of population were tested: type 2 diabetics and type 2 obese diabetics. Some were treated with bromocriptine alone (the so-called monotherapy trial) and others with bromocriptine + a sulfonylurea, with the understanding that the subjects in the placebo group of these so-called multiple-dose adjunctive therapy trials also received a sulfonylurea.

6.1.3 Human Exposure to Date

Table 1 summarizes the overall patient exposure to bromocriptine with or without other combinatorial therapeutic agents. All studies considered, some 1077 patients were exposed to bromocriptine for various lengths of times, for a total exposure of 320 patient-years, and a mean duration of study for the pivotal or well controlled trials of 26 weeks. There appears to have been an under-representation of women in the studies. African-Americans, Hispanics and Asian-Americans appear to have been adequately represented as an aggregate (since there is no categorical breakdown amongst these three groups).

During bromocriptine monotherapy trials of some 683 patients during phase 3 studies, some 120 subjects received 0.8 mg/d of bromocriptine for about 2 weeks, 118 were on 2.0 mg/d for about 2.5 weeks, 116 were on 2.4 mg/d for about 2.5 weeks, 114 were on 3.2 mg/d for about 2.5 weeks, 107 were on 4.0 mg/d for about 3 weeks, 103 were on 4.9 mg/d for about 17 weeks, 3 were on 4.6 mg/d for about 2.5 weeks, 1 subject was on 6.4 mg/d for 2 weeks, and 1 was on 8.0 mg/d for 2 weeks. Thus, the average exposure was about 3.6 mg/d for about 3 weeks.

In other, multiple-dose adjunctive therapy trials of some 2089 patients treated during phase 3 studies, 367 subjects received 0.8 mg/d of bromocriptine for a about 2.2 weeks, 363 were on 1.6 mg/d for about 2.5 weeks, 359 on 2.4 mg/d for about 3 weeks, 351 on 3.2 mg/d for about 3.2 weeks, 329 on 4.0 mg/d for about 3.5 weeks, 315 on 4.8 mg/d for about 19 weeks, 3 on 5.6 mg/d for about 1.5 weeks, and 2 on 6.4 mg/d for about 1 week. Thus, the average exposure was about 4.4 mg/d for about 26 weeks.

It should also be stated that large populations suffering from a variety of diseases (Parkinson's disease, hyperprolactinemic infertility, micro- and macro-prolactinemas, and acromegaly) have been exposed to the drugs for long average periods of time during the last two decades. A large body of literature (too copious to be submitted in this Review) has been generated to explore all aspects of the safety and effectiveness of the drug. In addition to the FDA, several Western agencies have developped a Pharmacovigilance component which has scrutinized the use of bromocriptine in the affected population.

7 PIVOTAL STUDIES

7.1 First Pivotal Study: Study K

7.1.1 Description of Study

7.1.1.1 Title, Objective, and Rationale

Study K, "A study to evaluate the safety and efficacy of timed medications in the treatment of obese type II diabetics maintained on oral hypoglycemic agents and measured for changes in body composition," was conducted to evaluate the safety and efficacy of bromocriptine (Ergoset) in reducing hyperglycemia in obese type 2 diabetic patients maintained on sulfonylurea oral hypoglycemic agents (sulfonylureas) and who followed an ADA weight-maintaining diet. The rationale for the study was the scientific evidence from pre-clinical and clinical studies of the antihyperglycemic effects of bromocriptine.

7.1.1.2 Experimental Design

Study K, conducted from January 1995 to March 1996, was a randomized, double-blind, multi-center (8 centers), parallel group (two) study comparing the safety and efficacy of 24 weeks treatment with either bromocriptine (targeted dose of 4.8 mg/day) or placebo. The study included NIDDM outpatients who were on stable doses of sulfonylureas for at least 60 days, were obese (body mass index of 26.0 - 40.0 kg/m2 for men, and 28.0 - 40.0 kg/m2 for women), and had glycated hemoglobin A1c (HbA1c) between 7.8 - 12.5%. Eligible patients were placed on an ADA weight-maintaining diet and were randomized to receive bromocriptine (122 patients) or placebo (123 patients). Patients returned for follow-up visits every 4 weeks for 24 weeks. Before the start of treatment and at the 8 and 24 week follow up evaluations, patients spent approximately 12 hours at the study centers after an overnight fast. At these visits patients were fed standard meals (breakfast, lunch, dinner) and had blood samples drawn before each meal and at 1 and 2 hours after the start of each meal for the determination of plasma glucose, insulin, triglycerides, and free-fatty acids.

The goal of treatment was to achieve a target dose of 6 tablets q.d. (placebo or 0.8 mg bromocriptine mesylate/tablet) starting with 1 tablet and increasing the

dose by 1 tablet each week if no intolerance occurred. Each dose of study drug was to be taken at 8 am +/- 30 minutes.

7.1.1.3 Demographics

Patients randomized to receive Ergoset or placebo were similar with respect to their pre-treatment characteristics. Patients were 31 - 73 years of age (mean, 54.4 years), 79% were White, 75% were male, and all were on stable doses of sulfonylureas including 71% on glyburide (Diabeta, Glynase, Micronase).

7.1.1.4 Safety Considerations

Adverse events were recorded at each visit, EKGs and physical examinations were performed before and after treatment, and laboratory safety tests were performed before the start of treatment, after 12 weeks, and at the end of treatment.

7.1.1.5 Efficacy Endpoints

The primary efficacy variable was HbA1c which provided an overall measure of glycemic control. Variables used as supportive measures of glycemic control were fasting and post-prandial (breakfast, lunch, dinner) plasma glucose. Secondary efficacy variables included: fasting and post-prandial (breakfast, lunch, dinner) insulin and triglycerides; fasting plasma lipoproteins (total cholesterol, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol); systolic and diastolic blood pressure; and, body density and body weight.

In addition, normalization of prolactinemia can itself be considered as an efficacy end-point -- albeit a surrogate one -- since this is a direct measurement of the so-called "biochemical" efficacy of bromocriptine. This approach is rational inasmuch as the initial hypothesis to test is, precisely, the timed modulation of circadian prolactin levels. Normalization, however defined, of prolactinemia is a necessary condition for efficacy, but not a sufficient one, since one can postulate that certain "biochemical" normalizations (defined in qualitative as well as quantitative terms) may still not result in clinical efficacy. However, the coexistence of "biochemical" as well as "clinical" efficacies, i.e., reduction of prolactin as well as HbA1c values, is an important element in deciding

whether or not the initial hypothesis, apparently confirmed in certain animal species, is also confirmed in the human species: That a "shift" of circadian prolactin levels from the "fat" to the "lean" profile results in improvements of the diabetic condition.

7.1.1.6 Statistical Approaches

The primary analyses of HbA1c was a repeated measures analysis of variance of the mean changes from baseline over time to week 24. For each efficacy variable, analyses of variance were performed which evaluated the mean change from baseline to week 24 and included the following blocking factors: weight maintained (weight within 2% of baseline weight), diet compliant (consumed +/- 25% of their target calories), and hyperinsulinemia (baseline fasting insulin > 15 mU/mL and post-prandial insulin > 60 mU/mL). Changes from baseline to week 24 in HbA1c also were analyzed to evaluate whether the response to treatment was different "predictive responders" compared to other patients. A predictive responder was defined by the protocol as a patient who achieved a decrease in HbA1c of at least 0.3% at week 8.

Safety and efficacy data were analyzed using an intent-to-treat approach that included all patients randomized to treatment who received at least one dose of study drug and returned for at least one follow up visit/assessment. Excluded from these analyses was the patient who enrolled in the study at two different centers and was treated with bromocriptine at one and with placebo at the other.

In the analyses of safety variables, differences between treatments were compared using a 1-way analysis of variance for continuous variables and using Fisher's exact test for categorical variables. All statistical tests were 2-sided and p-values of < 0.05 defined statistical significance.

7.1.2 Results and Conclusions

7.1.2.1 Patient Comparability

Patients in the two treatment groups were similar for all baseline variables (except for a higher proportion of physically active patients in the bromocriptine group)

including baseline values of all efficacy and safety variables, except for postbreakfast glucose (310 mg/dL bromocriptine; 330 mg/dL placebo).

7.1.2.2 Patient Disposition

A total of 93 (76%) bromocriptine -treated and 106 (86%) placebo-treated patients completed the study. Fourteen (11%) bromocriptine -treated patients and 3 (2%) placebo-treated patients withdrew from the study because of adverse events. The other 29 patients (15 bromocriptine; 14 placebo) withdrew for reasons that were not related to treatment.

7.1.2.3 Efficacy Data

Treatment with bromocriptine, compared to treatment with placebo, resulted in better metabolic control as shown by reductions in HbA1c and fasting and postprandial plasma glucose (p-values < 0.05 for all comparisons). Compared to the placebo group, mean HbA1c in the bromocriptine group was significantly lower by 0.32% at week 12 and by 0.48% at week 24. Specifically, at week 24, HbA1c was decreased by 0.01% in the bromocriptine group and increased by 0.47% in the placebo group. In the analysis of changes to week 24, none of the interactions of treatment with the blocking factors was significant, indicating that the effects of bromocriptine on HbA1c did not depend on whether or not patients were diet compliant, weight-maintained or hyperinsulinemic. At week 24, HbA1c was decreased by 0.39% for so-called bromocriptine-responders and increased by 0.87% for non-responders. The corresponding values in the placebo group were increases of 0.01% and 0.92%, respectively.

Let it be noted that the response of non-responding and placebo-treated subject were essentially the same; i.e., increases of 0.9% in each case. According to the HbA1c criterion, the non-responders are equivalent to non-treated patients. This suggests that the "responder" and "non-responder" populations are two distinct ones; the former is "sensitive" to prolactin modulation, the other simply is not at all sensitive in that respect.

Compared to the placebo group at week 24, mean change in fasting plasma glucose was lower by 26.0 mg/dL in the

bromocriptine group, and postprandial (breakfast, lunch, dinner) plasma glucose was lower by 22.2 - 29.1 mg/dL. In these analyses, none of the interactions of treatment and the blocking factors were significant, indicating that the effects of bromocriptine on plasma glucose did not depend on whether or not patients were diet compliant, weight-maintained or hyperinsulinemic.

The treatment by hyperinsulinemia interaction was significant in the analyses of changes to week 24 in fasting but not for postprandial insulin levels. The difference (bromocriptine - placebo) in the mean changes was -0.7 uU/mL for patients who were not hyperinsulinemic and was -8.0 uU/mL for hyperinsulinemic patients. There were no significant differences between the two treatment groups in the mean changes to week 24 in post-lunch or post-dinner insulin values. The post-breakfast mean changes were significantly greater in the bromocriptine group (2.8 uU/mL vs. -1.0 uU/mL).

The treatment by hyperinsulinemia interaction was significant in the analyses of changes to week 24 in fasting but not for postprandial triglyceride levels. The difference (bromocriptine - placebo) in the mean changes was -6.9 mg/dL for patients who were not hyperinsulinemic and was -190.5 mg/dL for hyperinsulinemic patients. There were no other significant differences between the two treatment groups in the mean changes to week 24 in fasting or postprandial triglyceride values.

In the analysis of the mean changes from baseline to week 24 for total cholesterol, the interaction of hyperinsulinemia with treatment was significant. The difference (bromocriptine- placebo) in the mean changes was -2.4 mg/dL for patients who were not hyperinsulinemic and was 13.6 mg/dL for hyperinsulinemic patients.

This differential response between eu- and hyperinsulinemic patients is interesting, inasmuch as it suggests the following: the improvement of insulinemia occurs only when it is needed and, in all probability, when that happens insulin-receptor sensitivity is improved and the receptor responds better to the endogenous agonist. As a result, the metabolism of fatty acids seems also to change (admittedly, some but not too much - but a little is better than nothing) for the better.

Indeed, treatment with bromocriptine had no significant effects on LDL or HDL cholesterol, or systolic or diastolic blood pressure. Only a trend was apparent. The main conclusion here is that the lipidemic profile didn't worsen though it didn't significantly improve. It improved only marginally.

In the analyses of changes in body weight at week 24, there were significant interactions of treatment and blocking factors. Differences (bromocriptine - placebo) in the mean changes were less than 2 lbs for the levels of the blocking factors except for the following: not weight-maintained patients, 4.0 lb; hyperinsulinemic patients, 4.4 lb; not diet compliant patients 5.4 lb.

With respect to hyperprolactinemic levels, the following results were apparent: At 24 weeks of treatment, the drug group showed a normalization in 76% of treated subjects, as opposed to a normalization seen in only 4% of the treated subjects. The p-value was found to be $p<0.0001$, as determined by Fisher's exact test.

7.1.2.4 Safety Data

Adverse events were reported for 92% bromocriptine-treated patients and for 82% placebo-treated patients ($p=0.036$). The higher rate in the bromocriptine group was mainly due to the higher rates of nausea (29% vs. 3%; $p < 0.0001$), asthenia (18% vs. 7%; $p = 0.006$), rhinitis (11% vs. 4%; $p = 0.054$), and hypoglycemia (8% vs. 1%; $p = 0.005$) in this group. In both treatment groups, approximately 95% of all adverse events were of mild to moderate severity. All hypoglycemic episodes were transient, resolved spontaneously or after food, and did not have any serious sequelae. This indicates that bromocriptine-treatment is effective in treating hyperglycemia (since hypoglycemic episodes were noted in 8% of treated subjects) but the dosing is reasonably well chosen (since most, if not all, of hypoglycemic episodes were of a mild and transient nature).

There were no deaths in either treatment group. Serious adverse events were reported for 4 patients in the bromocriptine group (1 elevated liver function tests, 3 myocardial infarction) and for 3 patients in the placebo group (1 chest pain; 1 cerebrovascular accident; 1 angina

pectoris). All three bromocriptine patients who had myocardial infarction had known cardiovascular risk factors. Fourteen (12%) patients in the bromocriptine group and 3 (2%) in the placebo group withdrew from the study because of AEs. Among bromocriptine-treated patients who withdrew, 7 had gastrointestinal events including 6 with nausea, 2 had asthenia, and 2 had dizziness (which may indicate the occurrence of mild hypoglycemia).

The mean changes from baseline to the last value during treatment for the two treatment groups were significantly different for lymphocytes, BUN, and glucose. The mean changes were smaller for the bromocriptine group. For all laboratory tests (including liver, renal, and thyroid function tests; hematology), the mean changes from baseline in the bromocriptine group were relatively small and not clinically meaningful. There were no significant between treatment group differences in any of the EKG parameters.

The bromocriptine/placebo comparison of any AEs shows a 91.8% and 82.1% frequency rate for, respectively, bromocriptine and placebo. This doesn't show a great additional accretion of untoward events for bromocriptine. As stated before, no deaths could be ascribed to any of the treatment groups. The frequency of serious adverse events were, respectively, 3.3 and 2.4%, while the frequency of severe adverse events were, respectively, 13.1 and 5.7% with a p value of 0.051. Thus, there is a trend in the increase of severe adverse events in the bromocriptine-treated group. When significant pathologies were sought after, the following frequencies were seen for, respectively, bromocriptine and placebo: edema of the face (1.6, 0%), myocardial infarction (2.5, 0%), arrhythmia (1.6, 0.8%), atrial fibrillation (0.8, 0%), thrombophlebitis (0.8, 0%), AV block (0, 0.8%), cerebrovascular accident (0, 0.8%), coronary artery disorder (0, 0.8%), EKG abnormalities (0, 0.8%), right heart failure (0, 0.8%), syncope (0, 0.8%),hepatitis (0.8, 0%), bilirubinemia (0.8, 2.4%), hyperlipemia (1.6, 2.4%), myopathy (0, 0.8%). Perhaps paradoxically, and increase in paresthesias & hyperesthesias was seen (6, bromocriptine; 2%, placebo). Amblyopia was seen more frequently in the bromocriptine group, but no increase was seen due to treatment with respect to cataract, hemorrhage in eye, retinal disorder, or visual abnormalities. Albuminuria did increase (from 0 to

2.5% of subjects). In short, there seems to be a slight tendency for most (but excluding ocular) complications' symptomatology to increase.

As would be expected, hyperglycemia was reduced in frequency from 12.2% (placebo) to 10.7% (bromocriptine), while hypoglycemia was increased from 0.8% (placebo) to 8.2% (bromocriptine); dizziness (presumably due to hypoglycemia) was also increased from 3.3 to 8.2%. It should be noted that the additional therapy (sulfonylureas) must have contributed to the hypoglycemic episodes, though the existence of such subjects in the placebo group allows the statement that any difference between treated and control groups may be safely ascribed to bromocriptine itself. Most hypoglycemic episodes resolved themselves and were, thus, considered to be mild in nature.

Some 11.5% and 2.4% of subjects were forced to discontinue when treated with, respectively, bromocriptine or placebo. Roughly half of the patients treated with bromocriptine discontinued because of nausea. Two thirds of the placebo group that discontinued did so because of hyperglycemia. Thus, some 13% of bromocriptine-treated subjects discontinued because of events directly and immediately ascribable to the drug itself.

7.1.2.5 Sponsor's Conclusions

The Sponsor's conclusions are as follows: "Ergoset (bromocriptine), used as an adjunct to sulfonylureas, in timed 8 am doses at a target dose of 4.8 mg daily:

- Improved glycemic control with significant reductions in the percentage of HbA1c compared with sulfonylureas alone throughout the 6-month period.

- Significantly decreased both fasting and postprandial glucose levels without any clinically meaningful change in insulin levels, indicating facilitation of insulin action at tissue receptor sites.

- Has an excellent safety profile. Most adverse events were of mild or moderate severity and were not cause for treatment withdrawal."

7.1.2.6 Reviewer's Conclusions

This Reviewer agrees with the gist of the Sponsor's conclusions. In addition, he wishes to make the following comments:

1.The per cent response of non-responding and placebo-treated subject, relative to their respective populations, were essentially the same; i.e., increases in HbA1c values of 0.9% in each case. Thus, the non-responders are practically equivalent to non-treated patients. This suggests that the "responder" and "non-responder" populations are two distinct ones; the former is maybe "sensitive" to prolactin modulation, the other simply is not at all sensitive in that respect. Alternate explanations are also possible for this dichotomous situation.

2. Eu- and hyperinsulinemic respond differently to timed bromocriptine. Improvement of insulinemia is absent in the former group while being present in the latter. Thus, it is suggested that prolactin modulation improves the sensitivity of insulin receptors to its endogenous agonist (i.e., insulin) only when it is needed. As a result, the lipid metabolism also improved, albeit marginally.

3. The following mechanism of action is suggested for the timed administration of bromocriptine: Firstly, the circadian prolactin levels are shifted from the "fat" profile to the "lean" one; secondly, this results in an increase in insulin receptor sensitivity (as evidenced by the improvement in hyperinsulinemia among "responders"); and, lastly, endogenous insulin (in part the result of sulfonylurea treatment) is more effective in correcting the metabolic disorders of type 2 diabetes, more importantly hyperglycemia and weight excess.

7.2. Second Pivotal Study: Study L

Description of Study

7.2.1.1 Title, Objective, and Rationale

Study L was intended to "Evaluate the Safety and Efficacy of Timed Medications in the Treatment of Obese Type II Diabetics Maintained on Oral Hypoglycemic Agents," and

was conducted to evaluate the safety and efficacy of bromocriptine in reducing hyperglycemia in obese type II diabetic patients maintained on sulfonylurea oral hypoglycemic agents and who followed an ADA weight-maintaining diet. The rationale for the study was the scientific evidence from pre-clinical and clinical studies of the antihyperglycemic effects of bromocriptine. The design of this study was the same as that of Study K, except body density measurements were not performed here.

7.2.1.2 Experimental Design

Study L, conducted from January 1995 to April 1996, was a randomized, double-blind, multi-center (10 centers), parallel group (two) study comparing the safety and efficacy of 24 weeks treatment with either bromocriptine (targeted dose of 4.8 mg/day) or placebo. The study included NIDDM outpatients who were on stable doses of sulfonylureas for at least 60 days, were obese (body mass index of 26.0 - 40.0 kg/m2 for men, and 28.0 - 40.0 kg/m2 for women), and had glycated hemoglobin A1c (HbA1c) of 7.8 - 12.5%. Eligible patients were placed on an ADA weight-maintaining diet and were randomized to receive bromocriptine (122 patients) or placebo (127 patients). Patients returned for follow-up visits every 4 weeks for 24 weeks. Before the start of treatment and at the 8 and 24 week follow up evaluations, patients spent approximately 12 hours at the study centers after an overnight fast. At these visits patients were fed standard meals (breakfast, lunch, dinner) and had blood samples drawn before each meal and at 1 and 2 hours after the start of each meal for the determination of plasma glucose, insulin, triglycerides, and free-fatty acids.

The goal of treatment was to achieve a target dose of 6 tablets q.d. (placebo or 0.8 mg bromocriptine mesylate/tablet) starting with 1 tablet and increasing the dose by 1 tablet each week if no intolerance occurred. Each dose of study drug was to be taken at 8 am + 30 minutes.

7.2.1.3 Demographics

Patients randomized to receive bromocriptine or placebo were similar with respect to their pre-treatment characteristics. Patients were 30 - 71 years of age (mean, 55.8 years), 69% were White, 70% were male, and all were on stable doses of sulfonylureas including 66% on glyburide (Diabeta, Glynase, Micronase).

7.2.1.4 Safety Considerations

Adverse events were recorded at each visit, EKGs and physical examinations were performed before and after treatment, and laboratory safety tests were performed before and after treatment and after 12 weeks.

7.2.1.5 Efficacy Endpoints

The primary efficacy variable was HbA1c which provided an overall measure of glycemic control. Variables used as supportive measures of glycemic control were fasting and postprandial (breakfast, lunch, dinner) plasma glucose. Secondary efficacy variables included: fasting and postprandial (breakfast, lunch, dinner) insulin, triglycerides, and free fatty acids; fasting plasma lipoproteins (total cholesterol, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol); systolic and diastolic blood pressure; and, body weight.

In addition, normalization of prolactinemia can itself be considered as an efficacy end-point -- albeit a surrogate one -- since this is a direct measurement of the so-called "biochemical" efficacy of bromocriptine. This approach is rational inasmuch as the initial hypothesis to test is, precisely, the timed modulation of circadian prolactin levels. Normalization, however defined, of prolactinemia is a necessary condition for efficacy, but not a sufficient one, since one can postulate that certain "biochemical" normalizations (defined in qualitative as well as quantitative terms) may still not show clinical efficacy. However, the coexistence of "biochemical" as well as "clinical," i.e., reduction of HbA1c values, is an important element in deciding whether or not the initial hypothesis, apparently confirmed in certain animal species, is also confirmed in the human species.

7.2.1.6 Statistical Approaches

The primary analyses of HbA1c was a repeated measures analysis of variance of the mean changes from baseline over time to week 24. For each efficacy variable, analyses of variance were performed which evaluated the mean change from baseline to week 24 and included the following blocking factors: weight maintained (weight within 2% of baseline weight), diet compliant (consumed + 25% of their target

calories), and hyperinsulinemia (baseline fasting insulin > 15 mU/mL and postprandial insulin > 60 mU/mL). Changes from baseline to week 24 in HbA1c also were analyzed to evaluate whether the response to treatment was different for "predictive responders" compared to other patients. A predictive responder was defined by the protocol as a patient who achieved a decrease in HbA1c of at least 0.3% at week 8.

Safety and efficacy data were analyzed using an intent-to-treat approach that included all patients randomized to treatment who received at least one dose of study drug and returned for at least one follow up visit/assessment.

In the analyses of safety variables, differences between treatment were compared using a 1-way analysis of variance for continuous variables and using Fisher's exact test for categorical variables. All statistical tests were 2-sided and p-values of < 0.05 defined statistical significance.

7.2.2 Results and Conclusions

7.2.2.1 Patient Comparability

Patients in the two treatment groups were similar for all baseline variables including baseline values of all efficacy and safety variables.

7.2.2.2 Patient Disposition

A total of 90 (74%) bromocriptine -treated and 109 (86%) placebo-treated patients completed the study. Seventeen (14%) bromocriptine -treated patients and 4 (3%) placebo-treated patients withdrew from the study because of adverse events, and one bromocriptine -treated patient withdrew because of a laboratory test abnormality. The other 28 patients (14 bromocriptine; 14 placebo) withdrew for reasons that were not related to treatment.

7.2.2.3 Efficacy Data

Treatment with bromocriptine compared to treatment with placebo resulted in better metabolic control as shown by reductions in HbA1c and fasting and postprandial plasma glucose (p-values < 0.05 for all comparisons). Compared to

the placebo group, the mean HbA1c in the bromocriptine group was significantly lower by 0.42% at week 12 and by 0.42% at week 24. At week 24, HbA1c was decreased by 0.26% in the bromocriptine group and increased by 0.16% in the placebo group. In the analysis of changes to week 24, none of the interactions of treatment with the blocking factors was significant, indicating that the effects of bromocriptine on HbA1c did not depend on whether or not patients were diet compliant, weight-maintained or hyperinsulinemic. At week 24, HbA1c was decreased by 0.79% for ErgosetTM predictive responders and increased by 0.51% for non-responders. In the placebo group, HbA1c decreased for predictive responders by 0.25% and increased for non-responders by 0.62%.

Compared to the placebo group at week 24, the mean change in fasting plasma glucose was lower by 21.0 mg/dL in the bromocriptine group, and postprandial (breakfast, lunch, dinner) plasma glucose was lower by 23.4 - 27.2 mg/dL. In these analyses, none of the interactions of treatment and the blocking factors was significant, except for the weight-maintained interaction for the post-lunch and post-dinner time points, indicating that the effects of bromocriptine on plasma glucose did not depend on whether or not patients were diet compliant or hyperinsulinemic. At the post-lunch and post-dinner time points, for bromocriptine-treated patients plasma glucose levels were lower by approximately 12 mg/dL for patients who were weight-maintained and by approximately 57 mg/dL for patients who were not weight-maintained.

There were no significant differences between treatment groups or any significant interactions of the blocking factors with treatment in the analyses of changes to week 24 in fasting and postprandial insulin levels.

In the analyses of mean changes in triglycerides from baseline to week 24, the treatment by hyperinsulinemia and treatment by diet maintained interactions were significant for fasting and post-breakfast analyses, treatment was significant in the post-lunch analyses, and there were no significant effects with treatment in the post-dinner analyses. The difference (bromocriptiee - placebo) in the mean changes of the fasting and post-breakfast triglycerides were -135.5 mg/dL and -131.3 mg/dL for patients who were not hyperinsulinemic, -3.1 mg/dL and -35.9 mg/dL for hyperinsulinemic patients, -233.0 mg/dL and 209.2 mg/dL for patients who were not diet compliant, and -54.1 mg/dL and

-70.7 mg/dL for patients who were diet compliant. The difference (bromocriptine - placebo) in the mean change in post-lunch triglycerides was -70.5 mg/dL.

In the analyses of changes in free fatty acids from baseline to week 24, mean post-breakfast and post-lunch values were significantly lower in the bromocriptine group by 0.17 mEq/L and 0.19 mEq/L, respectively. The mean fasting and post-dinner values also were lower in the bromocriptine group (by 0.15 mEq/L and 0.13 mEq/L, respectively), but the differences were not significant.

In the analysis of total and LDL cholesterol, and systolic blood pressure, the interaction of hyperinsulinemia with treatment was significant. The difference (bromocriptine - placebo) in the mean changes in total cholesterol was -18.8 md/dL for patients who were not hyperinsulinemic and was 9.4 mg/dL for hyperinsulinemic patients. The difference (bromocriptine - placebo) in the mean changes in LDL cholesterol was -7.7 md/dL for patients who were not hyperinsulinemic and was 9.7 mg/dL for hyperinsulinemic patients. The difference (bromocriptine - placebo) in the mean changes in systolic blood pressure was 2.5 mmHg for patients who were not hyperinsulinemic and was -12.4 mmHg for hyperinsulinemic patients. Treatment with ErgosetTM had no significant effects on HDL cholesterol or diastolic blood pressure.

In the analysis of body weight, the interaction of weight-maintained with treatment was significant. The difference (bromocriptine - placebo) in the mean changes in weight was 3.7 lbs for patients who were not weight-maintained and was 0.1 lbs for patients who were weight-maintained.

With respect to hyperprolactinemic levels, the following results were apparent: At 24 weeks of treatment, the drug group showed a normalization in 69% of treated subjects, as opposed to a normalization seen in only 4% of the placebo-treated subjects. The p-value was found to be $p<0.0001$, as determined by Fisher's exact test.

7.2.2.4 Safety Data

Adverse events were reported for 83% of patients in each treatment group. The incidence of the following adverse events were significantly higher in the

bromocriptine group: nausea (22% vs. 6%; $p < 0.001$), asthenia (20% vs. 10%; $p = 0.030$), and somnolence (9% vs. 2%; $p = 0.028$). **The incidence of hyperglycemia was significantly lower in the bromocriptine group (1% vs. 6%; $p = 0.036$).** In both treatment groups, approximately 95% of all adverse events were of mild or moderate severity. Since bromocriptine is not directly hypoglycemic, this is further indirect evidence that it may well improve insulin receptor sensitivity.

Hypoglycemia was reported as an adverse event for 11 (9.0%) patients in the bromocriptine group and for 12 (9.5%) patients in the placebo group, though bromocriptine-treated patients incurred 21 hypoglycemic episodes, compared to 13 to those in the placebo group. All hypoglycemic episodes were transient, resolved spontaneously or after food, and did not have any serious sequelae.

There were no deaths in either treatment group. Serious adverse events were reported for two patients in the bromocriptine group (angina pectoris; abnormal liver function tests) and for one patient in the placebo group (myocardial infarction). Seventeen (14%) patients in the bromocriptine group and 4 (3%) in the placebo group withdrew from the study because of adverse events. Among bromocriptine -treated patients who withdrew, 9 had gastrointestinal events including 5 with nausea, 3 with asthenia, and 6 with dizziness.

The mean changes from baseline to the last value during treatment for the two treatment groups were significantly different for lymphocytes, chloride, sodium, glucose, triglycerides, and total cholesterol. For all laboratory tests (including liver, renal, and thyroid function tests; hematology), the mean changes from baseline in the bromocriptine group were relatively small and not clinically meaningful. There were no significant between group differences in any of the EKG parameters.

7.2.2.5 Sponsor's Conclusions

The following are the Sponsors conclusions: " ErgosetTM used as an adjunct to sulfonylureas in timed 8 am doses at a target dose 0.8 mg to 4.8 mg daily:

- Improved glycemic control with significant reductions in the percentage of HbAlc compared with sulfonylureas alone throughout the 6-month period.
- Significantly decreased both fasting and postprandial glucose levels without any change in insulin levels, indicating facilitation of insulin action at tissue receptor sites.
- Consistently decreased both fasting and postprandial triglycerides and free fatty acids.
- Has an excellent safety profile."

7.2.2.6 Reviewer's Conclusions

The Reviewer roughly agrees with the Sponsor's conclusions. In this study, where sulfonylurea treated patients were also treated with either bromocriptine or placebo, several interesting events occurred:

1. Despite a seeming predisposition for hypoglycemic episodes, they were fewer patients suffering hypoglycemia while on bromocriptine than those not treated with it (9.0% vs 9.5% for placebo). When bromocriptine is added to sulfonylureas, there is no evidence that hypoglycemia occurs in a greater number of patients than before; and, if it does, the difference is small.

2. Bromocriptine-treatment seems to possess several advantages in this particular population. Any number of important metabolic parameters (weight gain, hyperglycemia, hypoglycemia, HbAlc values, etc.) are all improved, more or less.

3. In most of the bromocriptine-treated patients, therapeutic effectiveness can be predicted and followed regularly by measuring prolactinemic levels in a given patient and comparing them to baseline values in that same individual. **This is a great advantage over, for example, sulfonylureas, where the practicing physician is not able to assess the continued effectiveness of such therapy.**

7.3 Third Pivotal Study: Study M

7.3.1 Description of Study

7.3.1.1 Title, Objective, and Rationale

The study is meant to "Evaluate the Safety and Efficacy of Timed Medications in the Treatment of Obese Type II Diabetics Maintained on Diet Therapy" was conducted to evaluate the safety and efficacy of bromocriptine in reducing hyperglycemia in obese type II diabetic patients who followed an ADA weight-maintaining diet. The rationale for the study was the scientific evidence from pre-clinical and clinical studies of the antihyperglycemic effects of bromocriptine.

7.3.1.2 Experimental Design

This study, conducted from January 1995 to October 1996, was a randomized, double-blind, multicenter (13 centers), consisting of two parallel group, compared the safety and efficacy of 24 weeks treatment with either bromocriptine (targeted dose of 4.8 mg/day) or placebo. The study included NIDDM outpatients who were obese (body mass index of 26.0 - 40.0 kg/m2 for men, and 28.0 - 40.0 kg/m2 for women), and had glycated hemoglobin A1c (HbA1c) values of 7.5 - 11.0%. Eligible patients were placed on an ADA weight-maintaining diet and were randomized to receive bromocriptine (80 patients) or placebo (79 patients). Patients returned for follow-up visits every 4 weeks for 24 weeks. Before the start of treatment and at the 8 and 24 week follow up evaluations, patients spent approximately 12 hours at the study centers after an overnight fast. At these visits patients were fed standard meals (breakfast, lunch, dinner) and had blood samples drawn before each meal and at 1 and 2 hours after the start of each meal for the determination of plasma glucose, insulin, triglycerides, and free-fatty acids.

The goal of treatment was to achieve a target dose of 6 tablets q.d. (placebo or 0.8 mg bromocriptine mesylate/tablet) starting with 1 tablet and increasing the dose by 1 tablet each week if no intolerance occurred. Each dose of study drug was to be taken at 8 am +/- 30 minutes.

7.3.1.3 Demographics

Patients randomized to receive bromocriptine or placebo were similar with respect to all known important pretreatment characteristics. Patients were 32 - 72 years of age (mean, 54.6 years), 79% were White, and 76% were male.

7.3.1.4 Safety Considerations

Adverse events were recorded at each visit, EKGs and physical examinations were performed before and after treatment, and laboratory safety tests were performed before and after treatment and after 12 weeks.

7.3.1.5 Efficacy Endpoints

The primary efficacy variable was HbA1c which provided an overall measure of glycemic control. Variables used as supportive measures of glycemic control were fasting and postprandial (breakfast, lunch, dinner) plasma glucose. Secondary efficacy variables included: fasting and postprandial (breakfast, lunch, dinner) insulin, triglycerides, and free fatty acids; fasting plasma lipoproteins (total cholesterol, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol); systolic and diastolic blood pressure; and, body weight.

In addition, normalization of prolactinemia can itself be considered as an efficacy end-point -- albeit a surrogate one -- since this is a direct measurement of the so-called "biochemical" efficacy of bromocriptine. This approach is rational inasmuch as the initial hypothesis to test is, precisely, the timed modulation of circadian prolactin levels. Normalization, however defined, of prolactinemia is a necessary condition for efficacy, but not a sufficient one, since one can postulate that certain "biochemical" normalizations (defined in qualitative as well as quantitative terms) may still not show clinical efficacy. However, the coexistence of "biochemical" as well as "clinical," i.e., reduction of HbA1c values, is an important element in deciding whether or not the initial hypothesis, apparently confirmed in certain animal species, is also confirmed in the human species.

7.3.1.6 Statistical Approaches

The primary analyses of HbA1c was a repeated measures analysis of variance of the mean changes from baseline over time to week 24. For each efficacy variable, analyses of variance were performed which evaluated the mean change from baseline to week 24 and included the following blocking factors: weight maintained (weight within 2% of baseline

weight), diet compliant (consumed + 25% of their target calories), and hyperinsulinemia (baseline fasting insulin > 15 mU/mL and postprandial insulin > 60 mU/mL). Changes from baseline to week 24 in HbA1c also were analyzed to evaluate whether the response to treatment was different for "predictive responders" compared to other patients. A predictive responder was defined by the protocol as a patient who achieved a decrease in HbA1c of at least 0.3% at week 8.

Safety and efficacy data were analyzed using an intent-to-treat approach that included all patients randomized to treatment who received at least one dose of study drug and returned for at least one follow up visit/assessment.

In the analyses of safety variables, differences between treatment were compared using a 1-way analysis of variance for continuous variables and using Fisher's exact test for categorical variables. All statistical tests were 2-sided and p-values of < 0.05 defined statistical significance.

7.3.2 Results and Conclusions

7.3.2.1 Patient Comparability

Patients in the two treatment groups were similar for all baseline variables including baseline values of all efficacy and safety variables, except for mean post-breakfast insulin (in bromocriptine-treated patients, 43.9 uU/mL; and in placebo-treated subjects 54.1 uU/mL).

7.3.2.2 Patient Disposition

A total of 60 (75%) bromocriptine-treated and 62 (78%) placebo-treated patients completed the study. Ten (13%) bromocriptine-treated patients and 4 (5%) placebo-treated patients withdrew from the study because of adverse events, and one placebo-treated patient withdrew because of a laboratory test abnormality. The other 22 patients (10 bromocriptine; 12 placebo) withdrew for reasons that were not related to treatment.

7.3.2.3 Efficacy Data

Treatment with bromocriptine compared to treatment with placebo resulted in better metabolic control as shown by reductions in HbA1c and fasting and postprandial plasma

glucose (p-values < 0.05 for all comparisons except for post-dinner glucose, p = 0.068). Compared to placebo group, the mean HbA1c in the bromocriptine group was significantly lower by 0.35% at week 12 and by 0.46% at week 24. At week 24, HbA1c was decreased by 0.09% in the bromocriptine group and increased by 0.36% in the placebo group. In the analysis of changes to week 24, none of the interactions of treatment with the blocking factors was significant, indicating that the effects of bromocriptine on HbA1c did not depend on whether or not patients were diet compliant, weight-maintained or hyperinsulinemic. At week 24, HbA1c was decreased by 0.65% for bromocriptine predictive responders and increased by 0.66% for non-responders. In the placebo group, HbA1c decreased for predictive responders by 0.26% and increased for non-responders by 0.73%.

Compared to the placebo group at week 24, mean fasting plasma glucose was lower by 30.7 mg/dL in the bromocriptine group, and postprandial (breakfast, lunch, dinner) plasma glucose was lower by 27.1 - 47.9 mg/dL. In these analyses, none of the interactions of treatment and the blocking factors was significant, indicating that the effects of bromocriptine on plasma glucose did not depend on whether or not patients were diet compliant, or hyperinsulinemic.

In the analyses of mean changes from baseline to week 24 in insulin, the treatment by hyperinsulinemia interaction was significant for the postprandial assessments. The difference (ErgosetTM - placebo) in the mean post-breakfast, post-lunch, and post-dinner insulin were 4.9 uU/mL, -2.0 uU/mL, and 3.8 uU/mL, respectively for patients who were not hyperinsulinemic. The corresponding changes for hyperinsulinemic patients were -10.7 uU/mL, -21.6 uU/mL, and -15.4 uU/mL.

In the analyses of mean changes from baseline to week 24 in fasting and postprandial triglycerides to week 24, the treatment by weight-maintained interaction was significant for the post-dinner evaluation. There were no other significant effects involving treatment for the fasting or other post-prandial evaluations. The difference (bromocriptine - placebo) in the mean change triglycerides was -42.7 mg/dL for patients who were not weight- maintained and was 10.4 mg/dL for patients who were weight-maintained.

In the analyses of changes in free fatty acids from baseline to week 24, the treatment by hyperinsulinemia

interaction was significant for the post-lunch time period. There were no other significant treatment effects. The difference (bromocriptine - placebo) in the mean change in post-lunch free fatty acids was -0.23 mEq/L for patients who were not hyperinsulinemic and was 0.07 mEq/L for hyperinsulinemic patients.

In the analysis of mean changes from baseline to week 24 in total, LDL, and HDL cholesterol, systolic blood pressure, and body weight there were no significant treatment effects. In the analysis of the mean changes in diastolic blood pressure, the mean changes from baseline to week 24 were significantly lower in the bromocriptine group by 4.2 mmHg.

With respect to hyperprolactinemic levels, the following results were apparent: At 24 weeks of treatment, the drug group showed a normalization in 65% of treated subjects, as opposed to a normalization seen in only 2% of the untreated subjects. The p-value was found to be $p<0.0001$, as determined by Fisher's exact test.

7.3.2.4 Safety Data

Adverse events were reported for 90% of patients in the bromocriptine group and for 80% of patients in the placebo group ($p = 0.080$). In the bromocriptine group there was a significantly higher incidence of nausea (33% vs. 8%; $p < 0.001$) and rhinitis (14% vs. 4%; $p = 0.047$), and a significantly lower incidence of pain (1% vs. 10%; $p = 0.018$). In the ErgosetTM group all adverse events were of mild or moderate severity.

There were no deaths in either treatment group. Serious adverse events were reported for two patients in the placebo group (neoplasm of mouth; peptic ulcer). Ten (13%) patients in the bromocriptine group and 5 (6%) in the placebo group withdrew from the study because of adverse events. Among bromocriptine -treated patients who withdrew, 3 had hyperglycemia, 3 had gastrointestinal events including 2 with nausea, and 2 had rhinitis.

Hypoglycemia was reported as an adverse events for 3 (3.8%) patients in the bromocriptine group and for 1 (1.3%)

patients in the placebo group. All hypoglycemic episodes were transient, resolved spontaneously or after food, and did not have any serious sequelae.

The mean changes from baseline to the last value during treatment for the two treatment groups were significantly different for WBCs, monocytes, alkaline phosphatase, glucose, SGOT, and TSH. For all laboratory tests (including liver, renal, and thyroid function tests; hematology), the mean changes from baseline in the bromocriptine group were relatively small and not clinically meaningful. There were no significant between group differences in any of the EKG parameters.

7.3.2.5 Sponsor's Conclusions

The following are the Sponsor's conclusions. "ErgosetTM monotherapy in timed 8 am doses of 0.8 mg at a target dose of 4.8 mg daily:

- Improved glycemic control with significant consistent reductions in the percentage of HbA1c compared with the untreated placebo group.
- Significantly decreased both fasting and postprandial glucose levels.
- Significantly decreased diastolic blood pressure while maintaining systolic blood pressure.
- Has an excellent safety profile."

7.3.2.6 Reviewer's Conclusions

This Reviewer is basically in agreement with the Sponsor's conclusions. Any additional remarks that are needed have already been made in the two previous pivotal studies' conclusions.

8. NON-PIVOTAL CLINICAL STUDIES

8.1 First Non-Pivotal Study: Study G

8.1.1 Description of Study

8.1.1.1 Title, Objective, and Rationale

Study G, "A Double-blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Timed Medications in the

Treatment of Obese Type II Diabetics" was conducted to evaluate the safety and efficacy of bromocriptine in reducing hyperglycemia in obese type II diabetic patients maintained on diet therapy and/or oral sulfonylurea oral hypoglycemic agents. The rationale for the study was the scientific evidence from pre-clinical and clinical studies of the antihyperglycemic effects of bromocriptine.

8.1.1.2 Experimental Design

Study G, conducted from December 1994 to March, 1996, was a randomized, double-blind, multi-center (2 centers), parallel group (2 groups) study comparing the safety and efficacy of 24 weeks treatment with either bromocriptine (maximum dose 3.2 mg/day) or placebo. The study included NIDDM outpatients who were obese (body mass index of at least 26.0 kg/m2), had glycated hemoglobin A1d (HbA1c) of at least 7.5%, and had an average of 8 + 2 hours sleep per night. At Week -2 (Week 0 = start of treatment), patients were randomly assigned to either a weight-maintaining ADA isocaloric diet or an ADA hypocaloric diet. Following a 2-week "run-in" period in which patients received single-blind placebo, patients in each diet group were randomly assigned to treatment with bromocriptine or placebo. Patients returned for follow-up visits every 4 weeks for 24 weeks. Before the start of treatment and at the 4, 12, and 24 week follow up evaluations, patients spent approximately 12 hours at the study centers after an overnight fast. At these visits patients were fed standard meals (breakfast, lunch, dinner) and had blood samples drawn before each meal and at 1 and 2 hours after the start of each meal for the determination of plasma glucose, prolactin, insulin, and thyroid hormones.

The initial dose of study drug was 1 tablet of 0.8 mg bromocriptine or 1 tablet placebo. After one week the dose was increased by 1 tablet if no intolerance occurred. At week 4 and at week 12, the dose of study drug for each patient could be increased/decreased by either 1 or two tablets depending on the value of the patient's prolactin measurements. In addition, the patient's prolactin values determined the time each morning patients took their assigned study medication. Patients took 1-3 tablets at 5:00 - 8:30 am and 0-1 tablets at 8:30 am or 10:30 am. Each dose of study drug was to be taken within 15 minutes of the scheduled time of dosing.

8.1.1.3 Demographics

Patients randomized to receive bromocriptine or placebo were similar with respect to their pre-treatment characteristics. The mean age of patients was 55.3 years, and the majority of them were male (85%) and were Caucasian (95%).

8.1.1.4 Safety Considerations

Adverse events were recorded at each visit, EKGs and physical examinations were performed before and after treatment, and laboratory safety tests were performed before and after treatment and after 12 weeks.

8.1.1.5 Efficacy Endpoints

The primary efficacy variable was HbA1c which provided an overall measure of glycemic control. Variables used as supportive measures of glycemic control were fasting glucose and the glucose AUC, i.e., the area under the glucose-vs-time curve. Secondary efficacy variables included fasting insulin, fasting serum lipoproteins (total cholesterol; high density lipoprotein cholesterol, HDL-C; low density lipoprotein cholesterol, LDL-C), systolic and diastolic blood pressure; and body weight and body density.

8.1.1.6 Statistical Approaches

For each efficacy variable, analyses of variance were performed to evaluate differences between treatment groups in changes from baseline to endpoint (last post baseline value) for all patients, patients on isocaloric and hypocaloric diets, patients using sulfonylureas, and for patients who were weight-maintained (defined as being within 1% of their baseline weight).

In the analyses of safety variables, differences between treatment were compared using a 1-way analysis of variance for continuous variables and using Fisher's exact test for categorical variables. All statistical tests were 2-sided and p-values of < 0.05 defined statistical significance.

Safety and efficacy data were analyzed using an intent-to-treat approach that included all patients randomized to

treatment who received at least one dose of study drug and returned for at least one follow up visit/assessment.

8.1.2 Results and Conclusions

8.1.2.1 Patient Comparability

Patients in the two treatment groups were similar with respect to all baseline variables (age, height, weight, race, sex, duration of NIDDM, use of sulfonylureas).

8.1.2.2 Patient Disposition

A total of 42 (88%) bromocriptine-treated and 47 (92%) placebo-treated patients completed the study. Two (4%) bromocriptine -treated patients and 1 (2%) placebo-treated patient withdrew from the study because of adverse events, one patient in each treatment group withdrew because of an intercurrent illness, and the other 5 patients (3 bromocriptine; 2 placebo) withdrew for reasons that were not related to treatment (i.e., protocol violations were noted).

8.1.2.3 Efficacy Data

Treatment with bromocriptine compared to treatment with placebo resulted in better metabolic control as shown by reductions in HbA1c for patients who were weight-maintained and patients using sulfonylureas. At endpoint, mean HbA1c values were significantly decreased by 0.5% in the bromocriptine group and increased by 0.4% in the placebo group for weight-maintained patients. Also, those values were significantly decreased by 0.1% in the bromocriptine group and increased by 0.5% in the placebo group for patients using sulfonylureas. For all patients, mean HbA1c values were decreased by 0.1% in the bromocriptine group and increased by 0.3% in the placebo group (p=0.10).

For weight-maintained patients, mean fasting glucose values at endpoint were decreased by 6.6 md/dL in the bromocriptine group and increased by 26.9 mg/dL in the placebo group (p=0.02), and the mean change from baseline in glucose AUC at endpoint was significantly lower in the bromocriptine group by 516 mg/dL.hr. There were no significant differences between the to treatment groups in the analyses for mean changes in actual values of glucose AUC for any of the other groups of patients (all patients,

patients on isocaloric or hypocaloric diets, weight-maintained patients, patients using sulfonylureas).

There were no significant differences between the two treatment groups in the mean changes from baseline to endpoint in fasting insulin, total cholesterol, HDL-C, LDL-C, triglycerides, diastolic blood pressure, or body weight. The difference between the two treatment groups in the mean change in systolic blood pressure from baseline to endpoint approached statistical significance (p=0.06) for all patients, patients on hypocaloric diet, and weight-maintained patients, and was significantly lower for the bromocriptine groups for patients using sulfonylureas. The mean changes in the bromocriptine group were from -6.2 to -7.7 mm Hg, compared to -1.8 to 0.9 mm Hg in the placebo group.

The mean change in body density was significantly different for the two treatment groups for patients on isocaloric diet, weight-maintained patients, and patients using sulfonylureas. In the bromocriptine group, the mean changes were 0.002 to 0.003 g/cc compared to -0.001 to 0.001 g/cc in the placebo group.

8.1.2.4 Safety Data

Adverse events were reported for the majority of patients in both treatment groups. Adverse events that occurred in 10% or more of patients in the bromocriptine group were headache (20.8% vs. 17.6% placebo), hypoglycemia/hypoglycemic reaction (16.7% vs. 3.9% placebo), asthenia (12.5% vs. 2.0%, placebo), cold (12.5% vs. 9.8% placebo), accidental injury (12.5% vs. 5.9% placebo), abdominal pain (10.4% vs. 5.9% placebo), diarrhea (10.4% vs. 3.9% placebo), and dizziness (10.4% vs. 7.8% placebo). All but eight adverse events (6 bromocriptine; 2 placebo) were of mild or moderate severity.

Hypoglycemia was reported as an adverse event for 8 (16.7%) patients in the bromocriptine group and 7 (13.7%) patients in the placebo group. bromocriptine-treated patients had 14 hypoglycemic episodes compared to 15 episodes among-placebo-treated patients. All hypoglycemic episodes were treansient, resolved spontaneously or after food ingestion, did not result in any serious sequelae, and

were rated as mild except for one episode in the placebo group which was rated as being of moderate severity.

There were no deaths in either treatment group. Serious adverse events were reported for one patient in the bromocriptine group (neoplasm of mouth; peptic ulcer). Ten (13%) patients in the bromocriptine group and 5 (6%) in the placebo group withdrew from the study because of adverse events. Among bromocriptine-treated patients who withdrew, 3 had hyperglycemia, 3 had gastrointestinal events including 2 with nausea, and 2 had rhinitis.

The mean changes from baseline to the last value during treatment for the two treatment groups were significantly different for WBCs, monocytes, alkaline phosphatase, glucose, SGOT, and TSH. But the proportions of patients with clinically significant laboratory values at endpoint for any test (liver and renal function, hematology, etc.) were similar for patients in the two treatment groups. For all laboratory tests (including liver, renal, and thyroid function tests; hematology), the mean changes from baseline in the bromocriptine group were relatively small and not clinically meaningful. There were no significant between group differences in any of the EKG parameters.

8.1.2.5 Sponsor's Conclusions

The following are the Sponsor's conclusions: "bromocriptine monotherapy in timed doses of 0.8 mg to 3.2 mg daily:

- Improved glycemic control with significant consistent reductions in the percentage of HbA1c compared with the untreated placebo group in patients who maintained their body weight and in patients on sulfonylureas.

- Improved both fasting and postprandial glucose levels in patients who maintained their body weight.

- Significantly decreased systolic blood pressure without changing diastolic blood pressure.

- Significantly increased body density with the exception of patients assigned to a hypocaloric diet where weight reduction in the placebo group confounded the results.

Has an excellent safety profile."

8.1.2.6 Reviewers Conclusions

This Reviewer basically agrees with the Sponsor's conclusions.

8.2 Second Non-Pivotal Study: Study H

8.2.1 Description of Study

8.2.1.1 Title, Objective and Rationale

Study H, "An Open-Label, Single Blind Study to Evaluate the Efficacy of Various Dosing Ranges of Timed Medications in the Treatment of Type II Diabetics" was a dose-ranging study to establish a safe and effective dose of bromocriptine in reducing hyperglycemia in obese type 2 diabetics maintained on sulfonylureas. The rationale for the study was the scientific evidence from preclinical and clinical studies of the glycemia-correcting effects of bromocriptine.

8.2.1.2 Experimental Design

Trial H, conducted from July 1994 till December 1994, was a randomized, open-label, single center, parallel group (seven) study to establish a safe and effective dose of bromocriptine. The study included NIDDM outpatients who were obese (with a body mass index of 26.0 to 35.0 kg/m2 for men and 28.0 to 37.0 kg/m2 for women), had HbAlc values between 6.8-9.2%, and were receiving concurrent treatment with sulfonylureas.

At week 0 (start of treatment), patients were randomly assigned to maximum doses of 1.6, 3.2, 4.8, 7.2, 9.6 and 15 mg bromocriptine, or placebo). All patients received an initial dose of 0.8 mg bromocriptine for 2 days, after which they had the dose increased by 0.8 mg every 2 days until they reached the maximum assigned dose - which dose was maintained for the remainder of the 35-day study period. Patients were to take their individually assigned dose of study medication at 8:00 a.m. +/- 30 minutes. Patients returned for follow-up visits after 3 and 5 weeks. Before the start of treatment and at their final visit, patients

were fed standard meals (breakfast, lunch, dinner) and had blood samples drawn before and after each meal and every 1-3 hrs over the 24-hr period for the determination of plasma glucose, insulin, prolactin, cortisol and thyroid hormones. Subjects were excluded from the study if, before the start of treatment, they had abnormal thyroid hormone levels or if prolactin levels were equal or smaller than 5.5 ng/mL for males and equal or smaller than 7.0 ng/mL for females.

8.2.1.3 Demographics

Patients randomized to receive 1.6 (9 patients), 3.2 (9), 4.8 (8), 7.2 (9), 9.6 (11), or 15.2 mg (4) bromocriptine, or placebo (9) were similar with respect to their pretreatment characteristics. The mean age of patients was 51.2 yrs, the majority male (56%), and Hispanic (51%), with 47% of Caucasians.

8.2.1.4 Safety Considerations

Adverse events were recorded at each visit, EKGs and physical examinations were performed before and after treatment, and laboratory tests were done also before and after treatment.

8.2.1.5 Efficacy Endpoints

The primary efficacy variable was serum fructosamine which provided an overall measure of glycemic control. Secondary efficacy variables were body weight, HbAlc, fasting glucose, glucose AUC, oral glucose tolerance test, systolic and diastolic blood pressure, and fasting triglycerides, total cholesterol, LDL-cholesterol and HDL-cholesterol.

8.2.1.6 Statistical Approaches

For each efficacy parameter, analyses of variances were performed to evaluate differences among treatment groups in changes from baseline to endpoint. In the analyses of safety variables, differences between treatment were compared suing a one-way analysis of variance for continuous variables and using Fisher's exact test for categorical values. All statistical tests were two-sided and p-values of smaller or equal to 0.05 defined as statistically significant. Safety and efficacy data were

analyzed using an intent-to-treat approach that included all patients randomized to treatment who received at least one dose of study drug and returned for at least one follow-up visit or assessment.

8.2.2 Results and conclusions

8.2.2.1 Patient Compatibility

Patients in the seven treatment groups were similar with respect to all baseline variables (age, race, sex, height, weight).

8.2.2.2 Patient Disposition

Some forty (or about 80%) out of the 50 bromocriptine-treated patients and 8 (89%) out of the 9 placebo-treated patients completed the study. Ten (10) patients who treated with bromocriptine withdrew from the study, because of adverse events, and one patient in the placebo group was lost to follow-up.

8.2.2.3 Efficacy Data

The mean change, from baseline to endpoint, in fructosamine were significantly different across treatment groups. The mean values were decreased in all treatment groups. The mean changes were significantly greater in the 7.2 mg group (equal to -71.2 mg/dL) and 15.2 mg group (equal to -99.5 mg/dL), as compared to the placebo group (where the decrease was -23.1 mg/dL). The mean changes from baseline to endpoint were not significantly different across treatment groups for body weight, HbA1c, fasting glucose, glucose AUC, OGTT AUC, insulin, systolic or diastolic blood pressure, triglycerides, total-cholesterol, LDL-cholesterol, and HDL-cholesterol. The mean fasting glucose values at endpoint were decreased from baseline in all bromocriptine-treated groups of patients by 5.2 mg/dL compared to an increase of 7.6 mg/dL in the placebo group.

Because of the small sample size in all the treatment groups, the study could not be expected to effectively discriminate between the effects of the doses of bromocriptine used. Even though the mean changes from baseline were significant only for fructosamine, the study

did suggest greater efficacy at the highest used doses of bromocriptine used.

To investigate a possible dose-response relationship in this small study, the Company determined the proportion of the fructosamine, HbA1c, fasting glucose, weight, systolic blood pressure, and triglycerides variables for which a 5% decrease was observed, from week 0 to 4. The analysis apparently showed that a higher proportion of efficacy measurements were tending towards a clinically meaningful change as the dose increased from 4.8 to 7.2 mg.

8.2.2.4 Safety Data

Adverse events reported for the majority of patients in all treatment groups (56% in the placebo-treated group' and, respectively, 67% in the 1.6 mg group; 78% in the 3.2 mg group; and 100% in the three remaining groups, i.e., the 7.2, 9.6,a and 15.2 mg groups). The incidence of adverse events of the digestive system was significantly different across treatment groups (respectively, 11%, 22%, 44%, 38%, 89%, 73%, and 50%, by increasing dosing from placebo to 15.2 mg bromocriptine). For all other body systems there were no significant differences in the adverse events' frequencies acroo all treatment groups.

Hypoglycemia was reported as an adverse event in four (4) patients (one each in3.2, 7.2 nd 9.6 mg bromocriptine). Bromocriptine-treated patients had 14 hypoglycemic episodes compared to 15bepisodes among the placebo-treated subjects. All such episodes were transient, of as mild-to-moderate nature and resolved spontaneously upon food intake. None were followed by any serious sequel.

There were no deaths in any of the treatment groups. The only serious adverse event that was reported (gastroenteritis) was seen in a subject to whom 7.2 mg bromocriptine was being administered. Some ten (10) bromocriptine-treated patients (2 in the 1.6 mg; 3 in the 3.2; 1 in the 4.8; 1 in the 7,2; and 3 in the 9.6 mg groups) had treatment discontinued because of an adverse event. All of these patients (except one in the 1.6 mg and another in the 9.6 mg groups) had gastrointestinal problems.

There were no clinically meaningful changes in any of the laboratory tests which could be attributed to bromocriptine-treatment.

8.2.2.5 Sponsor's Conclusions

The Sponsor states that " a mid range dose of 4.8 mg bromocriptine appears to be the logical safe and affective dose for use in the phase 3 pivotal trials."

8.2.2.6 Reviewer's Conclusions

The various doses that were tested allowed the sponsor to reach the conclusion that the timed administration of bromocriptine:

1. Permitted to determine, albeit not conclusively and with a with a certain degree of uncertainty, the safe and effective dose for the NDA phase 3 pivotal studies;

2. Was able to decrease the fructosamine levels (from baseline) at all doses and particularly at 7.2 mg/day (which reduced fructosamine from baseline by 71.2 mg/dL) and at 15.2 mg/day (with a decrease of 99.5 mg/dL);

3. Caused the HbA1c levels to decrease by 0.7% but only for the 7.2 mg/day dose;

4. Resulted in a reduction of mean fasting glucose levels of between 5.2 and 40.1 mg/dL;

5. Allowed the observation of the same pattern of response with the other studied efficacy parameters;

6. Did not result in a perfect dose-response proportionality in the various efficacy parameters that were studied (weight, systolic and diastolic pressures, blood lipid changes etc., probably due to the small sample population size. To address this issue, a composite score was created reflecting improvement in the major variables, i.e., fructosamine, fasting glucose, etc., in order to be able to decide which dose or doses would be optimal to use during phase 3 pivotal studies. After such an analysis, doses of 4.8 and 7.2 mg/day were selected as the ones more suitable to be further tested in larger and more conclusive trials.

8.3 Third Non-Pivotal Study: Study A

Study A is entitled "A Double-blind Placebo-

controlled Study to Evaluate the Safety and Efficacy of Timed Bromocriptine in the Treatment of Obese Type II Diabetics." This was a 16-week four center trial with a randomized, parallel-group design. The primary objective was to demonstrate a clinically significant difference in the fasting plasma glucose levels, oral glucose tolerance test, and glycated hemoglobin in patients treated with bromocriptine and placebo.

A total of 49 patients (25 on drug and 24 on placebo) were entered and 48 patients completed the study. This study tried to determine the effect on hyperglycemia of a low, 1.6 mg, bromocriptine dose, administered to obese, type 2 diabetic subjects maintained on diet therapy or treated with sulfonylureas, but without the benefit of a hypocaloric diet.

No patients died during the period of study. After weighing the database generated by this trial, no tangible modification could be brought to the general safety profile of the drug, as seen in previous, pivotal or non-pivotal placebo-controlled studies. The numbers were too small to gain any solid quantitative insight in the efficacy of the drug.

8.4 Fourth Non-Pivotal Study: Study D

The study is entitled "A Pilot Study to Evaluate the Effect of Single Doses of Bromocriptine on Serum Prolactin Concentrations in Obese Volunteers."

This study was conducted to evaluate the decrease in serum prolactin concentrations in obese volunteers after administration of one of four different doses (0.8, 1.6, 2.4 and 3.2 mg) of bromocriptine manufactured by Geneva Pharmaceuticals, Inc., and a 2.5 mg tablet of same, manufactured by Sandoz Pharmaceuticals Corp. The study measured 24-hour prolactinemia profiles before and after drug administration. Fifteen obese volunteers were admitted in the study. In both men and women, a single bromocriptine dose at 8 a.m. suppressed the elevated daytime (14:00 hours) prolactin levels and blunted the night time (4:00 hours) prolactin level increases.

No patients died during the period of study. After weighing the database generated by this trial, no tangible modification could be brought to the general safety profile

of the drug, as seen in previous, pivotal or non-pivotal placebo-controlled studies.

8.5 Fifth Non-Pivotal Study: Study E

The study is entitled "A Study to Evaluate the Effect of Multiple Doses of Bromocriptine and Metoclopramide on Serum Prolactin Concentrations in Obese Volunteers.

On the basis of the information generated from the previous study, this particular one was conducted in obese volunteers to evaluate a possible synergistic effect between bromocriptine and metoclopramide with respect to their individual prolactin-reducing activities. Subjects were administered 1.6 mg of bromocriptine and one of four different doses (1, 2, 3, and 4mg) of metoclopramide. Some 25 obese volunteers were administered bromocriptine ((1.6 mg per day), to which was added varying doses of metoclopramide. Bromocriptine again suppressed daytime (14:00 hours) and blunted nighttime (4:00 hours) blood prolactin levels, both in men and women. The treatment results of the added metoclopramide were not included in this submission.

No patients died during the period of study. After weighing the database generated by this trial, no tangible modification could be brought to the general safety profile of the drug, as seen in previous, pivotal or non-pivotal placebo-controlled studies.

8.6 Sixth Non-Pivotal Study: Study J

The study is entitled "A Study to Evaluate the Insulin Sensitivity of Obese Hyperinsulinemic Subjects Utilizing a Novel Timed Medication Treatment."

The study, using obese, non-diabetic, hyperinsulinemic women, sought to generate information regarding the metabolic responses in such women, following bromocriptine administration. Some 13 patients were studied during an 8-week treatment period, during which they were administered from 0.8 to 4.8 mg of bromocriptine per day. Serum prolactin concentrations were significantly reduced ($p<0.001$) while a significant ($p<0.05$) decrease also

occurred in their 24 hour plasma glucose. Insulinemia was not affected. Body density increased ($p<0.05$) from 0.981 to 0.982 kg/L.

No patients died during the period of study. After weighing the database generated by this trial, no tangible modification could be brought to the general safety profile of the drug, as seen in previous, pivotal or non-pivotal placebo-controlled studies.

8.7 Seventh Non-Pivotal Study: Study B

The study is entitled "An Open-label Study to evaluate the Safety and Efficacy of Timed Medications in the Treatment of Obese type II Diabetics." The primary objective was to demonstrate significant difference in the fasting plasma glucose levels, oral glucose tolerance test, and glycated hemoglobin in patients treated with bromocriptine, bromocriptine + metoclopramide, or metoclopramide alone.

This study also tried to evaluate the potential for synergistic effects between bromocriptine and metoclopramide, with respect to correcting hyperglycemia in obese, type 2 diabetic patients, who were randomized to receive either bromocriptine, or metoclopramide, or a combination of the two, but without the benefit of either a hypocaloric diet or sulfonylurea treatment. Metoclopramide was given at a dosage of 5 mg per day, while bromocriptine dosing ranged from 0.8 to 4.8 mg per day.

No patient died in this study which is, however, interesting from the point of view of the changes in the safety profile when metoclopramide (at the indicated dosa) is used in diabetics, either alone, or in conjunctioin with bromocriptine. Indeed, 21 of 22 patients (95%) in the bromocriptine+metoclopramide group, as compared to only 1 patient (50%) on bromocriptine alone had adverse events. In addition 3 patients (100%) in the metoclopramide alone group also presented adverse events. Despite the small number of subjects studied, the conclusion of this study (from a safety viewpoint) is apparent: at the least, careful studies ought to determine the safe threshold of metoclopramide dosing, before any systematic attempt at estimating its efficacy can be performed. Another very interesting observation is as follows: All metoclopramide-treated patients, but only half of those on bromocriptine+ metoclopramide experienced hypoglycemia. Clearly,

hypoglycemia will be the major safety issue if and when metoclopramide is studied in the future.

8.8 Eight Non-Pivotal Study: Study C

The study is entitled "An Open-label, placebo-controlled Study to Evaluate the Safety and Efficacy of Timed Medications in the Treatment of Type II Diabetes."

This very small study (5 patients in all!) tried to evaluate, in obese patients, the effects of bromocriptine +metoclopromide on body weight, body fat, glycemia and insulinemia, using up to 3.2 mg of bromocriptine per day. No conclusion could, obviously, be derived from such a small study where, however, nothing untoward occurred.

8.9 Other Non-Pivotal Studies

8.9.2 Common features of these studies

These were all uncontrolled, open-label extension studies, that generated additional safety data over a period of 24 additional weeks of treatment, using a maximum of 4.8 mg of bromocriptine per day. Each patient was started on 0.8 mg per day of bromocriptine and later titrated upward to obtain a satisfactory pharmacodynamic response. A further extension of 24 weeks was performed for studies KX, LX and MX, but the data of these additional extensions have not yet been analyzed, except to say that deaths, serious adverse events, and discontinuation of treatment were reported in the present submission. Thus, and as far the safety analysis of the proposed treatment is concerned, we have had three study extensions of some 48 weeks.

In all groups, bromocriptine was administered at 8 a.m. to induce a dopamine surge in early morning. Patients with normal diurnal prolactin levels were excluded from participation in all of the following studies.

8.9.1 Study GX

This was an open-label extension of non-pivotal study G, evaluating 53 patients during a total of 24 weeks, for the purpose of generating additional safety data, also

comparing the effects of an isocaloric vs. An hypocaloric diet.

No patients died during the period of study. After weighing the database generated by this trial, no tangible modification could be brought to the general safety profile of the drug, as seen in previous, pivotal or non-pivotal placebo-controlled studies.

8.9.2 Study KX

This was an open-label extension of pivotal study K, evaluating 131 patients during a total of 24 weeks, for the purpose of generating additional safety data. The subjects were maintained on sulfonylurea treatment and measured for changes in body composition.

No patients died during the period of study. After weighing the database generated by this trial, no tangible modification could be brought to the general safety profile of the drug, as seen in previous, pivotal or non-pivotal placebo-controlled studies.

8.9.3 Study LX

This study, an open-label extension of study L, evaluated the safety of bromocriptine, using 131 obese type 2 diabetics maintained on sulfonylurea treatment.

No patients died during the period of study. After weighing the database generated by this trial, no tangible modification could be brought to the general safety profile of the drug, as seen in previous, pivotal or non-pivotal placebo-controlled studies.

8.9.4 Study MX

This study was an open-label follow up of study M, the evaluate further the safety and efficacy of bromocriptine in the treatment of obese, type 2 diabetic patients. Some 85 patients were treated with bromocriptine over a 24 week period.

Patient 1338259, a 67 yr-old Caucasian man who had been diabetic since the age of 47, suffered a severe myocardial infarction on 12/24/95 (day 45 of study) and died the same

day. This event was not considered related to the study medication. Otherwise, and after weighing the database generated by this trial, no tangible modification could be brought to the general safety profile of the drug, as seen in previous, pivotal or non-pivotal placebo-controlled studies.

9 OVERVIEW OF EFFICACY

9.1 Effects on prolactinemia

9.1.1 In obese type 2 diabetics

In the three pivotal (K,L,M) studies, treatment with timed (8 a.m.) bromocriptine (from 0.8 to mg per day for a period of 24-weeks. In study M, patients were maintained on an American Diabetes Association (ADA) weight-maintaining diet alone (monotherapy). In the other two studies, patients were also treatment with sulfonylureas. In all cases the subjects who had an abnormal prolactinemic profile at baseline showed the following percentages of improvement: In study K, prolactin profiles were normalized in 4.0% of the cases in the placebo group, as opposed to 76.1% of the cases in bromocriptine-treated patients; the respective figures for study L were 3.7 and 68.6%; and, in study M 1.6 and 63.8%. It can thus be seen that, quite consistently, about 2/3 of bromocriptine patients see a statistically significant normalization of their blood prolactin profiles at 24 weeks.

In study G, patients in each group (bromocriptine or placebo) were randomly assigned to either an isocaloric diet, or a hypocaloric diet. All patients had an abnormal prolactin profile at baseline. Prolactin AUC levels were reduced from 144.6 to 72.1 ng/mL.hr in the bromocriptine group, a statistically significant decrease ($p<0.0001$). In the placebo group, the corresponding values were 143.3 and 144.7 ng/mL.hr., respectively.

9.1.2 In obese subjects

In study D, bromocriptine administration (0.8 to 3.2 mg) decreased serum prolactin levels throughout the 24-hour period starting at 10 a.m. Early afternoon increases were greatly reduced. with all doses, while early morning (4 a.m.) increases were blunted, again with all doses. Similar

results were seen in study E which studied a group 25 obese volunteers (13 men and 12 women).

9.2. Effects on glycemia

9.2.1. Fasting glucose

In phase 2 study H, mean fasting glucose levels were statistically not different from one another at baseline. At the end of the study, mean fasting blood glucose levels had decreased from between 5.2 to 40.1 mg/dL in all bromocriptine-treated groups while increasing slightly (+7.6 mg/dL) in the placebo group.

The three pivotal studies (study M, bromocriptine monotherapy; and studies K & L, bromocriptine added adjunctively to sulfonylureas), essentially confirmed the results observed in the previously cited study, i.e., the timed administration of bromocriptine (at 8 a.m., +/- 30 minutes) resulted in a statistically significant reduction (p values between 0.001 and 0.004 in studies K & M, and 0.002 in study L) of fasting blood glucose values.

9.2.2 Postprandial glucose

In study M (bromocriptine monotherapy), the timed administration of bromocriptine (at 8 a.m., +/- 30 minutes) decreased postprandial glucose in the treated groups by 20.3 mg/dL, compared with an increase of 17.3 mg/dL in the placebo group. The between-group difference was highly significant. Similar changes were shown to exist during the other studies (studies K & L, bromocriptine added adjunctively to sulfonylureas). Such differences that were found were also statistically highly significant.

All other studies (G, H, etc.) essentially reproduced the same results as the ones described immediately above, i.e., timed bromocriptine treatment resulted in a statistically significant improvement of the postprandial fasting glucose levels.

9.3 Effects on insulinemia

Fasting and postprandial insulin levels were determined in the three pivotal studies mentioned in the preceding paragraph. There were no significant differences in fasting

or in postprandial blood insulin levels between treatment and placebo groups, except in study L, where postprandial insulin levels were increased by 3.6 uU/mL in the bromocriptine treated patients (who were also on sulfonylurea) and slightly decreased by 1.6 uU/mL in the placebo group - the difference being statistically significant. Since study K was very similar to study L, and since no such difference was seen in said study K, this discrepancy is hard if not impossible to understand or explain, except by invoking chance errors. Overall, however, the net impression is that timed bromocriptine therapy does not seem to measurably and directly affect insulinemia.

Also (and as seen previously), the analysis of changes of efficacy variables (e.g., HbA1c) at endpoint shows that the effects of bromocriptine on these variables did not depend on whether or not patients were diet compliant, weight-maintained or hyperinsulinemic. On the other hand, the treatment by hyperinsulinemia interaction was significant in the analyses of changes to week 24 in fasting but not for postprandial insulin levels. In one pivotal trial, the difference (bromocriptine - placebo) in the mean changes was -0.7 uU/mL for patients who were not hyperinsulinemic and was -8.0 uU/mL for hyperinsulinemic patients.

Upon reflection, several tentative conclusions may be reached between these seemingly contradictory data sets:

1. The effects of bromocriptine on blood insulin levels cannot be explained in a simplistic fashion, as the Company claims in its patents, for example.

2. On average, neither fasting nor postprandial hyperinsulinemia are significantly normalized during timed treatment with bromocriptine.

3. However, when individual patients are hyperinsulinemic pre-treatment, their fasting (but not postprandial) blood insulin values decrease significantly during bromocriptine treatment without, seemingly, affecting the mean insulinemic levels of the group.

4. In parallel to that decrease, glucose and lipid metabolisms gradually normalize.

5. In other words, and more precisely, glucose and lipid metabolisms are affected differentially, depending on

whether the treated subject is normo-insulinemic or hyperinsulinemic. This differential response between is interesting, inasmuch as it suggests the following: a slight yet apparently physiologically significant improvement of fasting insulinemia occurs, but only when it is needed; when that happens, insulin-receptor sensitivity is improved and the receptor responds better to the endogenous agonist insulin.

6. The possibility is also raised that bromocriptine affects glucose metabolism through other means than improvement of insulin-receptor sensitivity.

9.4. Effects on fructosamine levels

Baseline fructosamine levels were essentially the same in study H, while they significantly decreased in all dose groups (from 1.6 to 15.2 mg/day) with the largest mean decreases in the 7.2 mg group (-71.2 mg/dL) and the 15.2 mg group (-99.5 md/dL). In fact, some dose-effect relationship could be discerned but couldn't be ascertained, given the relatively small populations treated in each group. Similar conclusions were reached in all pivotal studies.

9.5 Effects on glycated hemoglobin levels

In study H, mean HbA1c levels decreased from baseline to endpoint in all dose groups (including placebo!), with the greatest decrease (-0.7 %) seen in the 7.2 mg group. Again, populations were too small to gain anything more than a general insight on the intensity of the pharmacodynamic effects of the drug. One should note that this study didn't last long enough for the full effect of the drug to be appreciated with this particular end-point. Under the circumstances, therefore, the 0.7% reduction from baseline in the most responsive group was no more than an encouraging sign to perform better and, hopefully, more conclusive trials.

In study K, mean HbA1c levels decreased from baseline to endpoint by 0.07% in the bromocriptine group and increased by 0.43% in the placebo group. Thus, the final end-point delta value is a 0.50% improvement of the treated group, as compared to the placebo group. Comparing bromocriptine-responders to all placebo patients, mean HbA1c levels decreased from baseline to endpoint by 0.45% in the

bromocriptine group and increased by 0.46% in the placebo group. Thus, the final end-point delta is a 0.91% improvement of the "bromocriptine-responder" group (grouping only those individuals with at least a 0.30% reduction in their HbAlc values at week 8 of treatment, representing 58% of the those treated with bromocriptine), as compared to the entire placebo group.

In this study, the HbAlc improvement in this "bromocriptine-responder" group, which counts 55 patients, from its own baseline to the endpoint value is -0.47%. Of these, 13 showed some level of "worsening" of their HbAlc values from their own baseline to week 24 (or end-point) HbAlc values; thus, some 24% of those qualified as responders at week 8 were actually doing less well than baseline at week 24.

Of course, these numbers should be compared to what happens in "placebo-responders" and "placebo-non-responders" in order to fairly assess the drug's effect on HbAlc values. In the 37 "placebo-responders," i.e., 30% of the placebo group as a whole, the mean change in HbAlc value, from their own baseline to end-point, is +0.02%. As a result when one compares the "bromocriptine-responders," i.e., 48% of the total bromocriptine-treated patients, the end-point comparison between that group and the "placebo-responder" group represents, for the former, an overall improvement of HbAlc values at end-point of 0.49%. This is the same as when all bromocriptine-patients are compared to all placebo patients (0.50% versus 0.49%).

In the opinion of this reviewer, the "bromocriptine-responders" vs. "all placebos" analysis tends to overstate the drug's efficacy; on the other hand, the "bromocriptine-responders" vs. "placebo-responders" analysis tends to understate the drug's efficacy. This is so, mainly because the post-8 week treated and placebo groups are, for various reasons, not comparable; and, the "bromocriptine-responders" vs. "all placebos" analysis is a prospective (not retrospective one). Thus, it is fair and prudent to take a middle course, as it were.

Similar results and conclusions can be reached though the analysis of the data in the other pivotal or non-pivotal controlled trials.

9.6 Critical discussion of the drug's efficacy

Putting the conclusions reached in the two highlighted paragraphs in the preceding section, one arrives naturally to the following conclusion: **The labeling should state that all "bromocriptine-non responders" should cease treatment at the end of 8 weeks; and also that patient-response should be monitored at week 24 with an HbA1c measurement, to compare it to baseline values and decide whether the patient appears to be responsive to treatment. As a rule of thumb, those patients who show no visible improvement at week 24, from baseline HbA1c levels, or have shown a worsening of that measurement over that span of time - such patients should be deemed as none-responding sufficiently to bromocriptine to treatment to justify continuation of said treatment.**

In other words, this Reviewer feels that the benefit-vs.-risk ratio is favorable only in patients who show an improvement in their HbA1c values at week 8 equal to or greater than 0.30%, provided that their HbA1c value is no worse than baseline (i.e., prior to treatment) at week 24.

In conclusion, it can be stated that the peculiar nature of the study protocol, with the concept of "responders" and "non-responders" folded in, makes it quasi-impossible to ascribe a real numerical value of HbA1c values in "bromocriptine-responders." Under the circumstances, this Reviewer has proceeded with the hypothesis that one approach overemphasizes the drug's efficacy in the so-called "bromocriptine-responders" (therefore the real improvement in HbA1c values at week 24, when "bromocriptine-responders" are compared to "all placebos" is overemphasized - and therefore is less than about -1.0%); on the other hand, the so-called "responder-to-responder" analysis underestimates the drug's real efficacy (which is therefore greater than -0.5 to -0.6%). These two inequalities create a middle ground to allow us to state **that the "real" efficacy of bromocriptine at week 24 (when the so-called "non-responders have been eliminated since week 8) is probably around -0.7 to -0.8% for the remaining patients. It would be further increased if, at week 24, therapy was discontinued in a second batch of "non-responders.".**

The above considerations are based on the pooled results from studies K, L, and M; in which the delta of

HbA1c values are given, at week 24, either on the "Resp-vs-Resp" analysis (bromocriptine-responders versus placebo-responders), or in the "Resp-vs-All" analysis (where bromocriptine-responders versus all-placebo patients)

Study	"Resp-vs-Resp	Resp-vs-All
K	-0.5%	-0.9%
L	-0.6%	-1.0%
M	-0.45%	-1.05%

One can see that the "center of gravity" of the data set is -0.75% (i.e., and in all probability, somewhere between -0.7% and -0.8%, as stated above).

The following comments are also germane to the further satisfactory analysis of the rather complex situation created by the so-called "responder-analysis," with the additional suggestion that the approach suggested above by this Reviewer is, probably, rather conservative:

1. At week 8, those who had an HbA1c value change of less than -0.3% represented, respectively, 87% among those treated with bromocriptine and 85% among those treated with placebo. It is as if bromocriptine is no better, and therefore no different, than placebo in the group that doesn't "respond" to bromocriptine (as defined arbitrarily) at week 8. Thus, the "bromocriptine-unresponsive" population is not "sensitive" to the drug. It behaves as if bromocriptine didn't have any effect in that group, at least in semi-quantitative terms around the arbitrary cutoff point. One can wonder why this is so. Perhaps, the "timing" and "dosing" windows are not, in these individuals, the ones that should have been used. Perhaps, in these individuals the dopaminergic cells are totally "insentitive" to the hypoglycemia-modulating effect of bromocriptine. Regardless of the mechanism, these individuals seem to act as if they were administered placebo instead of bromocriptine. The conclusion of such an observation is that the larger population may well be bimodal with respect to its response to bromocriptine, at least as far as its effects on HbA1c values are considered: The majority (some 2/3) of the treated subjects respond but the rest, a minority, appears to be practically insensitive to the drug.

2. When rough correlation studies are attempted between prolactin response (PR) to therapy (PR being defined as week 24 fasting prolactin levels of 7 ng/mL for women and 5.5 ng/mL for men)and) and glycemic response (GR) to therapy (GR being defined using the arbitrary cut-off point of 0.3% HbAlc at week 8), the following data have been generated by the Company, in response to a specific query from this Reviewer:

> In the placebo group, 7.7% of subjects were PR+/GR+; 10.6% were PR+/GR-; 35.2% were PR-/GR+; and 46.5% were PR-/GR-; **Thus, it can be seen that, in this group not treated with bromocriptine, the percentage of "clinical responders" (as arbitrarily defined) is gradually and smoothly decreasing when two "clinical predictors" are taken into account. The majority of "non-responders" were to be found when both predictors were negative.**
>
> Likewise, in the bromocriptine group, 11.1% of subjects were PR-/GR-; 16.2% were PR+/GR-; 25.5% were PR-/GR+; and 47.2% were PR+/GR+; **Thus, it can be seen that, in this group treated with bromocriptine, the percentage of "clinical responders" (as arbitrarily defined) is gradually and smoothly increasing when two "clinical predictors" are taken into account. The majority of "responders" were to be found when both predictors were positive.**

3. The above observation is consistent with the hypothesis that prolactin sentivity to bromocriptine is a marker for the existence of a modulation of dopaminergic cells by bromocriptine; that this activation results in an improvement in insulin receptor sensitivity which, in turn, improves the glucose and (somewhat less) lipid metabolisms in the treated (and "responsive") diabetic.

All the pertinent facts contained in this NDA are consistent with the above hypothesis which, then, provides a theoretical mechanistic underpinning to this NDA, supporting the basis, so to speak, of its efficacy.

Further, this Reviewer suggests to the Company to perform a similar correlative analysis as the one described above, using the same GR test (at 8 weeks, but with a set of different "cut-off points); and, if available, a slightly

different PR test (measured at 8 weeks or earlier). The purpose of the exercise would be to find out if the value of prolactin response for predicting glycemic response can be increased; if found, this information could be included in the labeling of the product, to permit an enhanced probability of detecting, at wekk 8, bromocriptine-responders.

A final comment concerns changes in weight during the various pivotal clinical trials. In study L (where patients maintained on sulfonylureas are additionally treated, either with bromocriptine or with placebo), there is, at endpoint, a small yet significant weight gain of 1.80 lbs in the bromocriptine group, compared to the placebo group. In study M, the same observation can be made with respect to average weight gains or losses, from baseline to endpoint, whether on bromocriptine or not. Thus, there is no significant change in average weight in these studies. It can therefore be stated that **bromocriptine treatment, while not being able to reduce weight during monotherapy, seems able to maintain weight during monotherapy and mitigate the weight gain due to sulfonylurea treatment during adjunctive therapy.**

10 OVERVIEW OF SAFETY

10.1 Significant events or leads

10.1.1 Exposure and deaths during drug use

In controlled studies, no patient died in the bromocriptine or the placebo groups. In all of the remaining studies, one patient died in the bromocriptine groups versus no deaths in the placebo group. That death could not be attributed to an untoward effect of bromocriptine.

Table 1 summarizes the overall patient exposure to bromocriptine with or without other combinatorial therapeutic agents. All studies considered, some 1077 patients were exposed to bromocriptine for various lengths of times, for a total exposure of 320 patient-years, and a

mean duration of study for the pivotal or well controlled trials of 26 weeks. There appears to have been an under-representation of women in the studies. African-Americans, Hispanics and Asian-Americans appear to have been adequately represented as an aggregate (since there is no categorical breakdown amongst these three groups).

With respect to the so-called multiple-dose adjunctive therapy (treatment with bromocriptine together with another form of diabetic therapy), some 2089 patients were treated during phase 3 studies, some 367 subjects received 0.8 mg/d of bromocriptine for a about 2.2 weeks, 363 were on 1.6 mg/d for about 2.5 weeks, 359 on 2.4 mg/d for about 3 weeks, 351 on 3.2 mg/d for about 3.2 weeks, 329 on 4.0 mg/d for about 3.5 weeks, 315 on 4.8 mg/d for about 19 weeks, 3 on 5.6 mg/d for about 1.5 weeks, and 2 on 6.4 mg/d for about 1 week. Thus, the average exposure was about 4.4 mg/d for about 26 weeks.

With respect to bromocriptine monotherapy, some 683 patients were treated during phase 3 studies, some 120 subjects received 0.8 mg/d of bromocriptine for about 2 weeks, 118 were on 2.0 mg/d for about 2.5 weeks, 116 were on 2.4 mg/d for about 2.5 weeks, 114 were on 3.2 mg/d for about 2.5 weeks, 107 were on 4.0 mg/d for about 3 weeks, 103 were on 4.9 mg/d for about 17 weeks, 3 were on 4.6 mg/d for about 2.5 weeks, 1 subject was on 6.4 mg/d for 2 weeks, and 1 was on 8.0 mg/d for 2 weeks. Thus, the average exposure was about 3.6 mg/d for about 3 weeks.

10.1.2 Severe to serious drug effects

Table 2 provides a rather comprehensive picture of the incidence of adverse events when they were seen during the pivotal trials with a frequency equal or greater than 5%. Tables 3 and 4 give quantitative appreciation of the frequency and nature of those adverse events that could be termed to have been serious to severe.

In phase 3 controlled studies, serious adverse events occurred in 0.7% of those treated with bromocriptine and 1.4% in the placebo groups. In phase 2 controlled studies, serious adverse events occurred in 0.2% of those treated with bromocriptine and 0.2% in the placebo groups.

Moderate to severe events, encountered during study K of this drug (a fairly representative study for all

pivotal and non-pivotal studies), comprise the following relatively rare events for which there seems to be a slight (but not significant) increased frequency in the bromocriptine-treated group as compared to the placebo group: allergic reactions (edema of the face, peripheral edema), amblyoplia, anorexia, cardiovascular events (angina pectoris, arrhythmia, atrial fibrillation, dyspnea, hypertension, migraine, myocardial infarction), flatulence, flu syndrome, headache, infections (abcess, bronchitis), pain (abdominal, back, chest, pelvic), and vomiting.

On the other hand, the following rare events were observed in the placebo group and not in the bromocriptine-treated group: anxiety, AV block, cerebrovascular accident, coronary artery disease, EKG abnormalities, fungal infection, increased urinary frequency, neuropathy, skin rash, retinal disease, right heart failure, tendinitis, urinary tract infection, vaginitis,

Finally, the following rare events were observed more frequently in the placebo group as compared to the bromocriptine-treated group: arthralgia, bilirubinemia, dyspepsia, esophagitis, infections (pharyngitis,),

Some 11.5% of bromocriptine-treated patients discontinued from treatment due to adverse events, as compared to 2.44% in the placebo-treated group. Assuming that those subjects who experience moderate-to-severe reactions are those more likely to decide to withdraw from a study, it would seem that (like any drug) bromocriptine toxicity is not trivial. Nevertheless, the experienced adverse events are rarely, if ever, of great severity. The individual cases of withdrawal from bromocriptine-therapy due to a severe condition are as follows: liver abcess (1 case), myocardial infarction,(2 cases), out of a total of 14 withdrawals.

10.2 Other drug-related safety issues

10.2.1 Most common adverse events

These include: Abdominal pain, accidental injury, asthenia (about 20% for drug vs. about for 9.5% placebo), cold, constipation, diarrhea, dizziness (16% vs 8%), dyspepsia, flu syndrome, headache, hyperglycemia, hypoglycemia, infection, nausea (22% vs. 6%, rhinitis (11% vs 5.5%), and sinusitis (see also Table 3) :

10.2.2 Gender & race analysis

Analytical breakdown, according to race or sex, didn't yield any significant difference between males and females, or between Caucasians and non-Caucasians, except for the following: There seemed to be a greater propensity in non-Caucasians to experience dizziness, somnolence and paresthesia; also a greater number of women had headaches, flu syndrome, abdominal pains with nausea, vomiting, and other ancillary digestive symptoms. Men, on the other hand, experienced a slightly increased incidence of dizziness.

10.2.3 Hypoglycemic effects of bromocriptine

By calculating the difference between the frequency of hypoglycemic episodes between placebo and bromocriptine (in the monotherapy study M), one can estimate, in the 2.4-4.8 mg/d range of bromocriptine treatment, the contribution to hypoglycemia of bromocriptine alone, which is 1.3%-1.2%, i.e. 0.1%.

When one scrutinizes the bi-therapy studies K & L, one notices that the frequency of hypoglycemic episodes is 5.2% in the placebo group (which contains subjects treated with a sulfonylurea), but only 2.9% for bromocriptine in the 2.4-4.8 mg/d dose range. The difference between these two values is -2.3%; i.e., **the addition of bromocriptine to sulfonylureas reduces the frequency of hypoglycemia by some 2.3%**. When the time of first occurrence of hypoglycemia is recorded, it is apparent that few additional events are recorded during the first month of monotherapy (4 events for bromocriptine versus 1 event in the placebo group), whereas (during that same laps of time) a relatively great number of first events are recorded in the placebo group (i.e., 13 in those who receive sulfonylurea alone), as well as the bromocriptine +sulfonylurea group (i.e., 24 cases) of bi-therapy.

The overall tentative conclusion of such calculations is inescapable and yet surprising: **Bromocriptine therapy, used as an adjunctive add-on to another therapy, seems to protect a fraction of that population from hypoglycemia**, while contributing very little, if at all, as monotherapy, to hypoglycemic frequency. No ready explanation comes to this Reviewer's mind to explain these observations.

10.2.2 Laboratory tests & vital signs

10.2.2.1 Routine laboratory results

Table 5 lists the mean changes in laboratory values resulting from drug therapy, as compared with placebo therapy. One can see that few tests are affected significantly during bromocriptine treatment. Those that are elicit changes deemed to be of little clinical consequence; except when one considers the potential for liver toxicity.

In study K, one patient (131267) out of 110 had a significant and high increase in its LFTs: SGPT values (31 at baseline to 923 U/L at endpoint) and SGOT values (24 at baseline to 856 U/L at endpoint) were elevated.

In study L, one patient (1326558) had a high increase in LFT values; however, a complete analysis of the situation revealed that the patient (a 51 yr-old Hispanic woman) had elevated liver enzyme values 3 days after the initial start of treatment with low dose bromocriptine. This raises the possibility that such enzyme levels were perhaps high even before treatment with bromocriptine. Histo-pathology of biopsed specimens revealed the strong possibility of an underlying autoimmune hepatic process, particularly since, post-treatment, liver enzymes values first came down, but later soared above baseline values. In the same study, patient 1326554 also showed elevated SGOT and SGPT values during treatment (compared to baseline); however, the elevated values had subsided at endpoint despite continued treatment with bromocriptine.

Taking into account all 3 pivotal studies, the average change from baseline to endpoint, for SGOT levels, was -0.14 for bromocriptine-treated patients and +0.41 in the placebo group. The equivalent numbers for SGPT were, respectively, +0.38 and -0.07. On average, therefore, there is no difference, in liver function explored by these two tests, bromocriptine treatment and placebo. Nevertheless, a minority of patiuents may have liver-sensitivity to bromocriptine.

Overall, the following conclusions can be reached when all changes in the pivotal studies are carefully scrutinized:

1. Hemoglobin: One bromocriptine patient (132528) had a clinically significant decrease in Hb (17 at baseline to 14.3 g/dL at endpoint; however, the same thing occurred in a placebo subject (133754).

2. Total Bilirubin: 0.68% of patients on bromocriptine showed at least one abnormal value, versus 1.3% for placebo.

3. BUN: 1.0% of patients on bromocriptine had BUN abnormalities, versus 0.65% for placebo.

4. LFTs: For both SGPT and SGOT, bromocriptine patients showed 0.68% abnormalities, versus 0.33% for placebo.

5. All the other laboratory tests show no signs of untoward response to therapy with bromocriptine.

In conclusion, the only slightly meaningful untoward effect of bromocriptine with respect to laboratory results and their safety consequences, concern a "slight touch" of liver effect which may become worrisome in certain highly sensitive patients.

10.2.2.2 Electrocardiograms

Taking into account all the pivotal studies, the following changes were observed: The patients who received bromocriptine and those on placebo had comparable mean changes from baseline in PR, QRS, and QT intervals; a statistically significant change from baseline occurred in the PR and QRS intervals. From baseline to endpoint, in bromocriptine-treated patients and in the placebo group, respectively: The QT interval was reduced by 3.4 and 7.7 msec. These changes were not thought to be of clinical significance. It should be noted here that one patient who received bromocriptine in open-label study MX died of a myocardial infarction, though the clinical investigator and the Company thought this event to be unrelated to study medication. Also (see Table 4), myocardial infarction was experienced by 7 out of 894 patients (0.8%) on bromocriptine and in 1 out 416 patients (0.2%) on placebo.

10.2.2.3 Vital signs

The heart rate was reduced on average by 0.1 bpm, from baseline to endpoint, in the bromocriptine-treated patients, while it increased by 2.2 bpm in the placebo group.

11 LABELING REVIEW

11.1 Drug description

Acceptable, but see Chemist's Review and Conclusions.

11.2 Clinical pharmacology

I don't agree with the straightfoward statement that "Bromocriptine... ameliorat[es] hyperinsulinemia." See my discussion in section 9.3, pp. 51-53 of this Review. However, I'll defer to our pharmacologists to settle this point.

Also, the sentence "ERGOSET treatment improves serum lipids," should be replaced by "ERGOSET treatment improves some, but not all, serum lipid levels. The clinical significance of such reductions are not readily apparent."

11.3 Indications and usage

The last sentence should be modified as follows: "If, after a similar trial period, a patient has not achieved this decrease, it is recommended that bromocriptine be replaced by other treatment modalities."

At the end of this section, the following new paragraph should be added: "About 24% of patients who had achieved such a decrease in hemoglobin A1c after 8 weeks of treatment, showed some level of worsening of their Hemoglobin A1c values after 24 weeks of treatment. If this occurs in individual patients, it is again recommended that bromocriptine be replaced by other treatment modalities."

See discussion under section 9.5, p.54 of this Review.

11.4 Contraindications

To the list of contraindications add: "female diabetics from the onset of pregnancy to several days post-partum."

11.5 Warnings

Acceptable

11.6 Precautions

11.6.1 General

Acceptable.

11.6.2 Information for patients

Acceptable.

11.6.3 Laboratory tests

Acceptable.

11.6.4 Drug interactions

Acceptable.

11.6.5 Carcinogenesis, mutagenesis, fertility

Acceptable but too verbose.

11.6.6 Pregnancy

Acceptable.

11.7 Adverse reactions

Acceptable.

11.10 Dosage and administration

The following statements should be (modified as indicated and) **bolded**:

"Administration time should always be 8 AM +/- 30 minutes."

"Given its absorption characteristics, ERGOSET (bromocriptine mesylate) must be taken with food."

Table 1: Patient Exposure in the Completed Studies

Study	Number of Patients					
	Ergoset	Ergo + Met	Metoclo-pramide	Placebo	Total Ergo (Ergo ± Met)	Overall Total
Double-Blind, Placebo-Controlled Clinical Studies						
Adjunctive Therapy Studies						
K	122	—	—	123	122	245
L	122	—	—	127	122	249
G	48	—	—	51	48	99
Subtotal	292	—	—	301	292	593
Monotherapy Study						
M	80	—	—	79	80	159
Subtotal	372	—	—	380	372	752
Uncontrolled Clinical Studies						
Adjunctive Therapy Studies						
KX	131 (71)[a]	—	—	—	131 (71)[a]	131 (71)[a]
LX	131 (73)[a]	—	—	—	131 (73)[a]	131 (73)[a]
GX	53 (28)[a]	—	—	—	53 (28)[a]	53 (28)[a]
Subtotal	316 (172)[a]	—	—	—	316 (172)[a]	316 (172)[a]
Monotherapy Study						
MX	85 (45)[a]	—	—	—	85 (45)[a]	85 (45)[a]
Subtotal	400 (217)[a]	—	—	—	400 (217)[a]	400 (217)[a]
Controlled and Uncontrolled Studies Combined						
Subtotal	585[b] (217)[c]	—	—	380	585 (217)[c]	965 (217)[c]
Other Clinical Studies						
A	25	—	—	24	25	49
B	2	22	3	—	24	27
C	—	2	—	3	2	5
Subtotal	27	24	3	27	51	81
Clinical Pharmacology Studies						
Bioavailability/Bioequivalence Studies						
DP143	8	—	—	—	8	8
EP194	36[d]	—	—	—	36	36
EP002	50[d]	—	—	—	50	50
FP519	54[d]	—	—	—	54	54
Dose-Range Study						
H	50	—	—	9	50	59
Effects on Specific Parameters						
D	15	—	—	—	15	15
E	—	25	—	—	25	25
J	16	—	—	—	16	16
Subtotal	229	25	—	9	254	263
Overall Total	846[b]	49	3	416	894[c]	1096[c]

Ergo=Ergoset. Met=Metoclopramide.

[a] The number of patients who previously received placebo in the double-blind, placebo-controlled studies.

[b] The 183 patients who received Ergoset in both the double-blind, placebo-controlled studies and the uncontrolled studies are counted only once in this total.

[c] The 217 patients who received placebo in the controlled and Ergoset in the uncontrolled studies are only counted once in the overall total (846+49+3+416-217=1096).

[d] All patients were pretreated with metoclopramide.

Data source: Individual Study Reports

Table 2 : Incidence of Adverse Events in ≥5% of Ergoset Patients in Either Study K, L, or M

Body System Adverse Event	Number (%) of Patients					
	Adjunctive Therapy Studies K and L		Monotherapy Study M		Total Studies K, L, and M	
	Ergoset (N=244)	Placebo (N=250)	Ergoset (N=80)	Placebo (N=79)	Ergoset (N=324)	Placebo (N=329)
Body as a Whole						
Asthenia	46 (18.9)	20 (8.0)	10 (12.5)	5 (6.3)	56 (17.3)	25 (7.6)[c]
Headache	41 (16.8)	40 (16.0)	10 (12.5)	7 (8.9)	51 (15.7)	47 (14.3)
Flu syndrome	23 (9.4)	19 (7.6)	6 (7.5)	6 (7.6)	29 (9.0)	25 (7.6)
Cold	20 (8.2)	20 (8.0)	5 (6.3)	7 (8.9)	25 (7.7)	27 (8.2)
Infection	17 (7.0)	32 (12.8)	5 (6.3)	4 (5.1)	22 (6.8)	36 (10.9)
Injury accidental	17 (7.0)	18 (7.2)	2 (2.5)	1 (1.3)	19 (5.9)	19 (5.8)
Pain abdominal	12 (4.9)	8 (3.2)	3 (3.8)	3 (3.8)	15 (4.6)	11 (3.3)
Pain	9 (3.7)	16 (6.4)	1 (1.3)	8 (10.1)	10 (3.1)	24 (7.3)[a]
Digestive System						
Nausea	62 (25.4)	12 (4.8)	26 (32.5)	6 (7.6)	88 (27.2)	18 (5.5)[c]
Constipation	24 (9.8)	11 (4.4)	9 (11.3)	3 (3.8)	33 (10.2)	14 (4.3)[c]
Diarrhea	18 (7.4)	20 (8.0)	7 (8.8)	4 (5.1)	25 (7.7)	24 (7.3)
Vomit	13 (5.3)	8 (3.2)	5 (6.3)	1 (1.3)	18 (5.6)	9 (2.7)
Dyspepsia	10 (4.1)	16 (6.4)	6 (7.5)	2 (2.5)	16 (4.9)	18 (5.5)
Anorexia	6 (2.5)	2 (0.8)	4 (5.0)	1 (1.3)	10 (3.1)	3 (0.9)
Metabolic & Nutritional Disorders						
Hyperglycemia	14 (5.7)	23 (9.2)	10 (12.5)	9 (11.4)	24 (7.4)	32 (9.7)
Hypoglycemia	21 (8.6)	13 (5.2)	2 (2.5)	1 (1.3)	23 (7.1)	14 (4.3)
Nervous System						
Dizziness	29 (11.9)	14 (5.6)	10 (12.5)	6 (7.6)	39 (12.0)	20 (6.1)[b]
Somnolence	16 (6.6)	5 (2.0)	3 (3.8)	0 (0.0)	19 (5.9)	5 (1.5)[b]
Paresthesia	10 (4.1)	13 (5.2)	4 (5.0)	4 (5.1)	14 (4.3)	17 (5.2)
Respiratory System						
Rhinitis	26 (10.7)	12 (4.8)	11 (13.8)	3 (3.8)	37 (11.4)	15 (4.6)[b]
Sinusitis	18 (7.4)	16 (6.4)	8 (10.0)	2 (2.5)	26 (8.0)	18 (5.5)
Skin & Appendages						
Rash	10 (4.1)	13 (5.2)	2 (2.5)	3 (3.8)	12 (3.7)	16 (4.9)
Special Senses						
Amblyopia	13 (5.3)	6 (2.4)	6 (7.5)	1 (1.3)	19 (5.9)	7 (2.1)[a]

P-values calculated by Fisher's exact test (two-tail)

[a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$

Data source: Appendices C.1.1; C.1.2; C.1.3 (Vol. 2)

Table 3 : Incidence of Adverse Events Occurring in ≥5% of Ergoset Patients in Either Study K, L, or M by Severity: Monotherapy Study M

Body System / Adverse Event	Number of Patients by Severity							
	Ergoset (N=80)				Placebo (N=79)			
	Total[b]	Mild	Mod[a]	Sev[a]	Total[b]	Mild	Mod[a]	Sev[a]
Body as a Whole								
Asthenia	10	9	1	-	5	5	-	-
Headache	10	6	4	-	7	6	1	-
Flu syndrome	6	2	4	-	6	4	2	-
Cold	5	5	-	-	7	5	2	-
Infection	5	5	-	-	4	2	2	-
Pain abdominal	3	3	-	-	3	2	1	-
Injury accidental	2	1	1	-	1	1	-	-
Pain	1	1	-	-	8	6	2	-
Digestive System								
Nausea	26	18	8	-	6	5	1	-
Constipation	9	8	1	-	3	2	1	-
Diarrhea	7	4	3	-	4	3	1	-
Dyspepsia	6	4	2	-	2	1	1	-
Vomit	5	3	2	-	1	1	-	-
Anorexia	4	4	-	-	1	1	-	-
Metabolic & Nutritional Disorders								
Hyperglycemia	10	8	2	-	9	8	1	-
Hypoglycemia	3	2	1	-	1	1	-	-
Nervous System								
Dizziness	10	8	2	-	6	6	-	-
Paresthesia	4	4	-	-	4	4	-	-
Somnolence	3	3	-	-	-	-	-	-
Respiratory System								
Rhinitis	11	9	2	-	3	2	1	-
Sinusitis	8	7	1	-	2	2	-	-
Skin & Appendages								
Rash	2	1	1	-	3	3	-	-
Special Senses								
Amblyopia	6	6	-	-	1	1	-	-

[a] Mod = moderate; Sev = severe
[b] Total = number of patients with the adverse event
Data source: Appendix C.4.2 (Vol. 2)

Table 4 : Serious Adverse Events in All Studies in NDA Combined

COSTART Code	Number (%) of Patients	
	Ergoset (N=894)	Placebo (N=416)
Infarction myocardial	7 (0.8)	1 (0.2)
Carcinoma	2 (0.2)	0 (0.0)
Cholecystitis	2 (0.2)	0 (0.0)
Coronary artery disorder	2 (0.2)	0 (0.0)
Liver function abnormal	2 (0.2)	0 (0.0)
Angina pectoris	1 (0.1)	1 (0.2)
Cerebrovascular accident	0 (0.0)	1 (0.2)
Cholelithiasis	1 (0.1)	0 (0.0)
Flutter atrial	1 (0.1)	0 (0.0)
Heart failure right	1 (0.1)	0 (0.0)
Lymphoma-like reaction	1 (0.1)	0 (0.0)
Nausea	1 (0.1)	0 (0.0)
Neoplasm	0 (0.0)	1 (0.2)
Neoplasm mouth	0 (0.0)	1 (0.2)
Pain chest	1 (0.1)	1 (0.2)
Peptic ulcer	0 (0.0)	1 (0.2)

Data source: Appendix C.14 (Vol. 2)

Table 5[illegible]: Mean Changes from Baseline to Endpoint in Laboratory Values for Studies K, L, and M Combined

Test	Ergoset				Placebo			
	N	Baseline Value	Endpoint Value	Mean Change	N	Baseline Value	Endpoint Value	Mean Change
Hematology								
Hemoglobin (g/dL)	279	14.7	14.8	0.1	300	14.8	14.9	0.1[c]
Hematocrit (%)	280	43.4	43.7	0.3	300	43.5	43.7	0.2[c]
Red Blood Cells (10^{12} cells/L)	280	4.9	4.9	0.03	299	4.9	4.9	0.03[c]
White Blood Cells (cells/µL)	279	6700	6700	-0.028	300	6700	6846	0.196 b
Basophils	241	54.5	56.1	0.6	264	54.8	57.4	2.5
Eosinophils	269	200.8	203.8	3.0	293	202.1	207.9	5.8[c]
Neutrophils	271	3949.7	3975.2	25.5	298	3903.4	3981.4	78.0
Lymphocytes	271	2035.5	1988.8	-46.8	298	2013.8	2107.0	93.3 c
Monocytes	271	478.2	453.4	-24.8	298	472.4	481.4	9.0[c]
Platelets (10^3/µL)	274	234.3	221.9	-12.4	297	231.9	225.1	-6.8[c]
Biochemistry								
Albumin (g/dL)	293	4.4	4.4	-0.01	308	4.4	4.3	-0.02[c]
Alkaline Phosphatase (U/L)	293	86.6	87.1	0.5	308	87.0	89.5	2.5
Total Bilirubin (mg/dL)	292	0.7	0.7	0.004	308	0.7	0.7	-0.02
BUN (mg/dL)	293	15.9	16.4	0.5	308	15.5	16.5	1.0
Calcium (mg/dL)	293	9.1	9.2	0.04	308	9.1	9.2	0.02[c]
Chloride (mmol/L)	293	102.3	102.8	0.6	308	102.5	102.7	0.2[c]
Creatinine (mg/dL)	293	0.8	0.8	-0.01	308	0.8	0.8	-0.01
Glucose (mg/dL)	293	218.3	223.4	5.1	308	218.4	246.5	27.1 c
LDH (U/L)	293	149.2	146.8	0.6	308	146.3	142.9	-3.4
Phosphorous (mg/dL)	293	3.5	3.6	0.1	308	3.5	3.6	0.2
Potassium (mmol/L)	293	4.4	4.3	-0.1	308	4.4	4.3	-0.1c
Protein, Total (g/dL)	293	7.2	7.2	-0.04	308	7.2	7.2	-0.06[c]
SGOT/AST (U/L)	292	22.3	25.0	2.8	307	22.0	21.5	-0.5
SGPT/ALT (U/L)	292	30.2	33.7	3.5	307	30.0	29.9	-0.1
Sodium (mmol/L)	293	138.4	138.3	-0.1	308	138.5	137.8	-0.8
Uric Acid (mg/dL)	293	5.4	5.3	-0.1	308	5.3	5.2	-0.2[c]

Data source: Appendix: E.1 – E.32.2 (Vol. 3).

Table 56 (continued)

Test	Ergoset				Placebo			
	N	Baseline Value	Endpoint Value	Mean Change	N	Baseline Value	Endpoint Value	Mean Change
Serum Lipids								
Triglycerides (mg/dL)	293	239.5	235.8	-3.8	308	235.1	277.2	42.1
Cholesterol (mg/dL)	293	215.4	~~294.2~~ 213.9	~~78.8~~ -1.55	308	210.2	215.4	5.2
HDL (mg/dL)	286	34.3	34.3	0.004	300	33.9	33.3	-0.5[a]
LDL (mg/dL)	286	137.0	136.6	-0.4	300	132.3	131.5	-0.8
Thyroid Hormones								
Total T_4 (µg/dL)	293	8.2	8.2	-0.1	308	8.3	8.2	-0.1
Free T_4 (ng/dL)	293	1.0	1.1	0.1	308	1.0	1.1	0.1[b]
T_3 (ng/dL)	293	142.5	142.3	-0.2	308	144.9	144.3	-0.6
TSH (µU/mL)	293	2.2	2.5	0.3	308	2.3	2.4	0.1

[a] P-value ≤0.05.
[b] P-value ≤0.01.
[c] P-value ≤0.001.
Data source: Appendix: E.1 – E.32.2 (Vol. 3).

7.3.1 *Clinically Significant Changes in Laboratory Test Values*

Laboratory test results in the phase III studies were evaluated for clinically significant changes, which are presented in the following table.