CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION (CLINICAL STUDIES)

NDA: 21-136/BL (Dated 2/14/02)

APPLICANT: ChiRhoClin, Inc.

NAME OF DRUG: Synthetic Porcine Secretin.

INDICATION: Diagnosis of pancreatic exocrine —

USER FEE DUE DATE:

DRUG CLASSIFICATION: 1P.

DOCUMENT REVIEWED: Document dated Feburary 14, 2002.

STATISTICAL REVIEWER: Wen-Jen Chen, Ph.D.

KEY WORDS/PHRASES: Clinical studies; NDA review.

BACKGROUND

In this submission, the sponsor proposed a draft labeling package, based on the results from NDA 21-136 and 21-209, for the use of synthetic porcine secretin on the following proposed indications:

1. Diagnosis of pancreatic exocrine —.
2. Facilitation on the identification of the ampulla of vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP); and
3. Diagnosis of gastrinoma.

Due to lack of adequate clinical data submitted by NDA 21-209 to characterize the product as a diagnostic tool in patients with Zollinger-Ellison Syndrome, this reviewer only reviewed NDA 21-236 (review issued on March 7, 2000) in the use of diagnosis of pancreatic exocrine —

However, based on the draft labeling package proposed by the sponsor, this reviewer would like to comment on the issues of the statistical data presented in this submission and recommend what data should and should not be incorporated in the labeling package.

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STATISTICAL REVIEW AND EVALUATION

NDA: 21-136 Date: **March 7, 2000**

APPLICANT: ChiRhoClin, Inc.

NAME OF DRUG: Synthetic Porcine Secretin.

INDICATION: Diagnosis of pancreatic exocrine disease.

USER FEE DUE DATE: March 25, 2000

DRUG CLASSIFICATION: 1S.

DOCUMENT REVIEWED: NDA Volumes 1, 6, 10, 11, 14, and 15; dated May 14, 1999; sponsor's documents dated 10/6/99 and 12/30/99.

MEDICAL REVIEWER: This review has been discussed with medical officer L. Goldkind, MD.

STATISTICAL REVIEWER: Wen-Jen Chen, Ph.D.

STATISTICAL ISSUES: Statistical equivalence based on test of significance.

KEY WORDS/PHRASES: Clinical studies; NDA review; Active control.

1.0 . INTRODUCTION

Synthetic porcine secretin has been proposed as an alternative to the currently approved biological porcine secretin. Biological porcine secretin (bPS) was approved by FDA in 1981 as a diagnostic agent for evaluation of exocrine pancreas function and for diagnosis of chronic pancreatitis, facilitation of collecting desquamated pancreatic duct cells to diagnose cytopatology pancreatic cancer, and for diagnosis of gastrinoma (Zollinger-Ellison syndrome) in terms of stimulation of serum gastric levels.

The sponsor was proposed the following four indications for the use of synthetic porcine secretin (sPS): 1. diagnosis of pancreatic exocrine [redacted] 3. diagnosis of gastrinoma, and 4. facilitation of [redacted] during ERCP procedure. Due to a lack of information provided for indications 3 and 4, the medical division refused to file these two indications. The sponsor

however, filed indication 3 over protest. The submission for this indication has been treated as a priority review with another NDA number (NDA 21-209).

Study# CRC98-1, has been used by the applicant as the primary support for the use of sPS for the diagnosis of pancreatic exocrine disease in patients with a diagnosis of chronic pancreatitis (indication 1). A phase I study, Study# CRC97-1, was submitted as a supportive study using pharmacological data from healthy volunteers to uphold indication 1.

2.0 STUDIES CRC98-1 & CRC97-1

2.1.1 Background Information for Study CRC98-1

Objectives: The objective of this study was to obtain comparative pharmacological and safety data for sPS and bPS as diagnostic agents in patients with a diagnosis of chronic pancreatitis.

Study Design: This study was a randomized, active-controlled, open label (described in protocol), two treatment (bPS and sPS), latin square crossover design from a single center (college of medicine, university of Florida), evaluating sPS and bPS for the assessment of exocrine pancreas function in patients with a diagnosis of chronic pancreatitis. Each patient was to receive both study drugs (bPS and sPS) in randomized sequence. Both bPS and sPS were dispensed in identical appearing syringes to ensure blinding to the patients. Twelve patients were enrolled.

Study Population: The inclusion criteria included the following: 1. males or females of non-childbearing potential, and 2. patients with a diagnosis of chronic pancreatitis documented by a prior secretin stimulation test with bPS and by clinical and laboratory findings consistent with this diagnosis. The main exclusion criteria were: 1. active acute pancreatitis, 2. use of anticholinergic medications within one week of testing, 3. known sensitivity or adverse reaction to secretin, pregnant or nursing female.

Dosing Schedule: A single dose of synthetic porcine secretin at a dose of 0.2 μg/kg and a single dose of biologically derived porcine secretin at a dose of 1 CU/kg were administered at least 24 hours apart for each patient.

Study methods and procedures: Within 7 days prior to administration of the study drug, written informed consent was obtained and prospective patients underwent screening. This included a complete medical history with medication review, and a complete physical examination including vital signs (blood pressure, pulse, temperature, height and weight). In addition, female subjects not medically documented to have had a hysterectomy were given a urine pregnancy test.

Patients meeting all eligibility criteria were enrolled and randomly assigned to a specified sequence of the two treatments, in double-blinded fashion. Each patient received a standard

secretin stimulation test utilizing the exact methodology described in the package labeling for commercial bPS. The study length was 2.5 months, from September 15, 1998 to December 2, 1998. [The sponsor did not provide information on the schedule for patients' follow-up assessments]

Pharmacological variables: The following three pharmacological variables were assessed for equivalence between sPS and bPS: 1. volume of pancreatic juice during specified time periods post secretin dosing, 2. bicarbonate concentration of pancreatic juice during these time periods, and 3. total bicarbonate output for one hour post secretin dosing.

Pharmacological Evaluation: The treatment effect of sPS and bPS on pancreatic juice volume, bicarbonate concentration, and total bicarbonate output were compared using GLM procedure from SAS. Multiple comparison and regression procedures were utilized to compare treatments.

Primary and Secondary Efficacy Variables: The primary diagnostic efficacy variable is the diagnosis of chronic pancreatitis in these patients with a documented diagnosis of chronic pancreatitis. The positive diagnosis of chronic pancreatitis is based on peak bicarbonate concentration < 80 mEq/L. There was no secondary efficacy variable proposed by the sponsor for this study.

Diagnostic Efficacy Variable Evaluation: The diagnostic positive outcomes, between sPS and bPS, for chronic pancreatitis based on peak bicarbonate concentration were compared.

Disposition of Patients: A total of 12 patients completing both treatments were planned. Twelve patients enrolled, completed both treatments, and were fully analyzed.

2.1.2 Background Information for Study CRC97-1

Objectives: The objectives of this study were as follows: 1. to assess the safety and tolerance of 3 sPS doses in normal healthy subjects, 2. to assess the pharmacological effect on pancreatic secretion of 3 sPS doses in these subjects, 3. to define the pharmacological response and variability in normal subjects for sPS and bPS.

Study Design: This was a double-blind, randomized, active controlled, four treatment crossover design, single center study in normal healthy subjects. Subjects were randomly assigned to a specific sequence of administration of the four treatments using a randomization sequence generated at ChirhoClin, Inc.

Study Population: The inclusion criteria included the following: 1. males or females of non-childbearing potential, 2. subjects must have been in good health based on medical history, physical exam and routine laboratory tests, and 3. subjects must have been willing and able to sign written, informed consent. The main exclusion criteria were: 1. ongoing, active acute pancreatitis, 2. history of vagotomy, 3. use medication, within one month of screening, known to

cause pancreatitis, 4. used anticholinergics, within one month of screening, 5. known sensitivity or adverse reaction to secretin, pregnant or nursing female, and 6. use any drug (other than hormone replacement or oral contraceptives) within 72 hours of study entrance.

Selection of doses: The dose level of bPS was the recommended to evaluate the exocrine pancreas (1 CU/kg). The three dose levels of sPS chosen by the sponsor to compare to 1 CU/kg bPS were 0.05 μg/kg, 0.2 μg/kg (equivalent to 1CU/kg), and 0.4 μg/kg (equivalent to 2 CU/kg which is the recommended dose to evaluate suspected gastrinoma).

Duration of treatment: Single doses at 3 different sPS doses and one bPS dose administered on different days.

Disposition of Patients: A total of 12 patients completing all four treatments were planned. Fifteen patients enrolled. Two subjects could not successfully swallow the Dreiling Tube and were withdrawn from the study without having received any drug. One subject completed the first treatment with bPS but did not tolerate the intubation easily and elected to withdraw. This subject did have protocol specified safety follow-up assessments. Twelve subjects completed all four treatments and were fully analyzed.

2.2.1 Sponsor's Statistical Analysis and Results for Study CRC98-1

Demographics and Baseline Characteristics

The sponsor presented summary statistical tables for demography, medical history, and prior medication in Appendix 15.4 of volume 11. No statistical analyses were performed on these data.

There were 4 males and 8 females with a mean age of 56.1 years, a mean height of 166.4 cm, and a mean weight of 73.3 kg. Among these 12 patients, ten were White and two were Black.

All 12 patients had prior secretin stimulation tests with bPS confirming the diagnosis. Many had elevated biochemical markers, imaging studies, or ERCPs. The sponsor concluded that there were no clinically significant abnormalities on physical examination at baseline.

Results for Pharmacological Effect Analysis

The results for the pharmacological effect analysis in the comparisons between 0.2 μg/kg dose of sPS and the 1CU/kg dose of bPS on mean values for pancreatic juice volume and bicarbonate concentration at fifteen minute intervals and for the entire 60 minutes are presented in Table 2.2.1.1 and Table 2.2.1.2, respectively.

Table 2.2.1.1 (Sponsor's) Pancreatic Stimulation Results for 15 Minute Intervals – sPS versus bPS

TREAT		V_B	BC_B	V_15	BC_15	V_30	BC_30	V_45	BC_45	V_60	BC_60
bPS	Mean	35.08	14.83	57.67	42.92	38.17	64.75	28.82	61.08	40.90	56.50
bPS	STD	45.12	15.49	32.59	16.12	30.33	25.53	25.99	31.01	27.22	31.32
bPS	%CV	128.6	104.39	56.52	37.56	79.47	39.44	90.20	50.77	66.56	55.44
sPS	Mean	24.83	19.00	59.33	45.58	34.60	62.17	36.71	62.92	32.29	54.75
sPS	STD	18.72	17.69	35.28	24.84	28.03	30.46	35.90	32.58	34.98	28.26
sPS	%CV	75.39	93.13	59.46	54.50	81.01	48.99	97.80	51.79	108.33	51.62
	Prob	0.3494	0.3978	0.7976	0.5489	0.5624	0.4227	0.1762	0.622	0.3625	0.8044

Source: Sponsor's Table 4 in Volume 11; V_B= baseline volume; BC_B=baseline bicarbonate concentration; BC=bicarbonate concentration (mEq/L); V=volume (mL).

Table 2.2.1.2 (Sponsor's) Pancreatic Stimulation Results for 60 Minute Sample – sPS versus bPS

TREAT		V_1_60	BC_1_60	B_TBC	TBC
bPS	Mean	165.55	55.12	9.59	10.45
bPS	STD	102.67	22.56	9.11	10.38
bPS	%CV	62.01	40.93	94.98	99.35
sPS	Mean	162.93	54.28	10.38	10.85
sPS	STD	122.10	26.58	10.93	11.37
sPS	%CV	74.94	48.96	105.30	104.77
	Prob	0.8848	0.7029	0.4961	0.7099

Source: Sponsor's Table 5 in Volume 11; BC=bicarbonate concentration (mEq/L); V=volume (mL); TBC=total bicarbonate (mEq).

Based on Table 2.2.1.1, the sponsor declared that the mean values for pancreatic juice volume and bicarbonate concentration at each fifteen-minute interval stimulated by the two drugs, sPS and bPS, showed no statistically significant differences. In addition, following Table 2.2.1.2, the sponsor claimed that the mean values for pancreatic juice volume, bicarbonate concentration, and total bicarbonate (adjusted and unadjusted for baseline values) outputs for sPS and bPS for the entire sixty minute sampling period were not statistically different.

In the conclusion for the pharmacological effects, the sponsor asserts that sPS and bPS produced the same pharmacological effects in terms of bicarbonate concentration and pancreatic juice volume, which are statistically equivalent and numerically almost identical in patients with a diagnosis of chronic pancreatitis. [Note: the conclusion of equivalence on the pharmacological effects between sPS and bPS was based on the non-superiority results].

Analysis of Diagnostic Efficacy Results

The sponsor reported that there was 100% agreement in the diagnostic results for the twelve (12) patients between sPS and bPS. Eight of these twelve patients (patient no. 1, 3, 4, 5, 9, 10, 11, &

12) had positive secretin stimulation test results on chronic pancreatitis for both sPS and bPS and four (patient no. 2, 6, 7, & 8) had negative test results on chronic pancreatitis for both sPS and bPS.

In addition, there was 100% agreement between sPS and bPS in characterizing severe chronic pancreatitis. Of the eight patients with positive diagnostic tests, 5 patients (patient no. 1, 3, 9, 11, & 12) had mild to moderate chronic pancreatitis and 3 patients (patient no. 4, 5, & 10) had severe chronic pancreatitis on testing with both sPS and bPS.

Finally, the sponsor concluded that synthetic porcine secretin is a pure, biologically active product that produces essentially identical diagnostic and pharmacological results with biologically derived porcine for diagnosing patients with chronic pancreatitis.

Adverse Events

As for the adverse events, the sponsor declared that both sPS and bPS at the doses tested were safe and well tolerated in this study. Only 2 mild adverse events occurred in 2 different patients. One occurred with sPS and one with bPS. Both were mild, unlikely related to test drug and resloved.

2.2.2 Sponsor's Statistical Analysis and Results for Supportive Study CRC97-1

Demographics and Baseline Characteristics

The sponsor presented summary statistical tables for demography, medical history, and prior medication in Appendix 15.4 and 15.5 of volume 10. No statistical analyses were performed on these data.

The demographic profile of the 13 subjects indicated that there were 4 males and 9 females with a mean age of 28.9 years, a mean height of 101.1 cm, and a mean weight of 67.8 kg. Among these 13 patients, eleven subjects were Caucasian, one Asian, and one Native American.

The sponsor also indicated that medical history showed no current clinically significant medical problems.

Results for Pharmacological Effect Analysis

In the section of overall conclusions, the sponsor indicated that in normal healthy subjects, the 0.2 μg/kg dose of sPS was statistically equivalent to the 1 CU/kg of bPS dose (the recommended dose for evaluating the exocrine pancreas) in terms of pharmacological stimulation of the exocrine pancreas (volume, bicarbonate concentration, and total bicarbonate output). Over the dose range studied for sPS, there was a modest dose response for pancreatic juice volume and total bicarbonate output but similar results for bicarbonate concentration.

The sponsor concluded that synthetic porcine secretin at a dose of 0.2 μg/kg produces an equivalent physiologic response on the pancreas, as does the biologically derived porcine secretin at a dose of 1 CU/kg.

Adverse Events

The sponsor declared that both sPS and bPS at the doses tested were safe and well tolerated at all doses tested. Only 3 mild adverse events observed in the study. These were three episodes of treatment flushing in one subject following the 0.2 and 0.4 μg/kg doses of sPS and the 1 CU/kg dose of bPS which resolved spontaneously and were not associated with any changes in vital signs.

2.3 Reviewer's Analyses and Comments

As indicated in the sponsor's submission, the objective of these two studies was to demonstrate the bio-equivalence for sPS 0.2 μg/kg and bPS 1CU/kg through the pharmacological variables (e.g.: peak bicarbonate concentration, total bicarbonate etc.). However, the applicant used tests of significance rather than the preferred confidence interval approach for evaluating efficacy.

It is noted that the contents of the pharmacological variables are the outcomes stimulated by the two diagnostic agents (sPS and bPS) and not the blood concentrations of these two drugs. Therefore, these pharmacological variables are treated as clinical endpoints and a non-inferiority approach should be applied to assess the efficacy on the pharmacological effects.

As indicated in the applicant's submission, study CRC97-1 was used to support the equivalence for sPS at a dose of 0.2 μg/kg and bPS at a dose of 1CU/kg. In order to assess the attribute differences between pancreatitis patients and healthy volunteers more efficiently, in this reviewer's analyses, data of the two doses from study CRC97-1 are analyzed together with those from the pivotal study CRC98-1.

In order to appraise the sponsor's efficacy claim, this reviewer performs the following three analyses for both studies (CRC98-1 and CRC97-1) on the three pharmacological variables, peak bicarbonate concentration (PEAKBC), total bicarbonate (TBC), and total sixty (60) minute pancreatic juice volume (V_1_60): i.) Confidence interval analysis on the difference of two treatment effects to assess the equivalence between sPS and bPS, ii) Graphic display, and iii.) Probability analysis. Variable PEAKBC in Study CRC98-1 is, as defined by the sponsor, the maximum of 0 to 15, 15 to 30, 30 to 45, and 45 to 60 minute bicarbonate concentrations, while in Study CRC97-1, it is the maximum of 0 to 10, 10 to 20, 20 to 40, and 40 to 60 minute bicarbonate concentrations. Due to the small numbers of patients and lack of pre-specification, these three analyses must be viewed as descriptive in nature.

Since the sample sizes for the sub-groups classified by gender (male and female), age (≤ 65 and > 65), race (Caucasian and Non-Caucasian) are small (2 patients in age > 65 sub-group, 2

patients in Non-Caucasian subgroup, and 4 male patients), no sub-group analysis is performed.

In addition, it is noticed that four patients (patient numbers 2, 6, 7, and 8) in Study CRC98-1 were found recovered from chronicle pancreatitis. Therefore, the statistical analyses on i.) and ii.) for Study CRC98-1 are performed separately for recovered and sick patients on the three variables, PEACKBC, TBC, and V_1_60. Data used in this reviewer's analysis was submitted by the sponsor, dated October 7, 1999.

i.) Confidence interval analysis on the difference of two treatment effects

This reviewer calculated the 95% confidence intervals on the differences of the two treatment effects, sPS and bPS (sPS – bPS), for variables PEACKBC, TBC, and V_1_60, using patients completing both treatments, separately for each of the two studies (CRC98-1 and CRC97-1).

Since four patients (patient numbers 2, 6, 7, and 8) in study CRC98-1 were found to have recovered from chronicle pancreatitis and only one (patient number 7) of them was from the second sequence in the cross over design, the 95% confidence intervals on variables PEACKBC, TBC, and V_1_60 in this study, are calculated only for the eight sick patients.

Due to small sample sizes for both studies (8 and 12 patients for Study CRC98-1 and CRC97-1, respectively), they may not have enough power to detect the carry over effects on the three variables. In addition, data for the two treatments, sPS and bPS, from the supportive study CRC97-1 were not collected by AB/BA cross over design. This reviewer therefore, does not perform the carry over effect test and must assume that there were no carry over effects for both studies. The parameters in the model used to calculate the 95% confidence intervals consist of treatment effect, period effect, and random subject effect.

Table 2.3.1 displays the 95% confidence intervals on the differences (sPS-bPS) of the two treatment effects (sPS and bPS), bPS sample means, and the upper and lower bounds divided by bPS sample means for the three variables, PEACKBC, TBC, and V_1_60, by study.

Table 2.3.1 The 95% confidence intervals on the differences of two treatment effects (sPS – bPS) Pivotal Study CRC98-1 (Eight Sick Patients)

VARIABLES	95% CONF. INT.[#] LWR. BND.[1]	UPR. BND.[2]	BPS SAMPLE MEAN	PERCENTAGE LB/BPS M.[3]	UB/BPS M.[4]
PEAKBC	-11.50	5.03	55.75	-21%	9%
TBC	-3.47	4.14	5.45	-64%	76%
V_1_60	-74.84	57.10	126.88	-59%	45%

Table 2.3.1 The 95% confidence intervals on the differences of two treatment effects (sPS – bPS) (Continued)

Supportive Study CRC97-1 (Twelve Healthy Patients)

VARIABLES	95% CONF. INT.[#] LWR. BND.[1]	UPR. BND.[2]	BPS SAMPLE MEAN	PERCENTAGE LB/BPS M.[3]	UB/BPS M.[4]
PEAKBC	-7.46	1.79	110.92	-6.7%	1.6%
TBC	-4.35	0.57	24.28	-17.9%	2.3%
V_1_60	-33.23	14.5	244.83	-13.6%	5.9%

[#]: Confidence Interval; [1]: Lower Bound; [2]: Upper Bound; [3]: Lower Bound/bPS Sample Mean; [4]: Upper Bound/bPS Sample Mean.

PEAKBC = peak bicarbonate concentration (mEq/L); V=volume (mL); TBC=total bicarbonate (mEq).

For the pivotal study CRC98-1, Table 2.3.1 contains the following results:

- The lower and upper bounds for the mean difference (sPS – bPS) of peak bicarbonate concentration are estimated to be -21% and 9% of the bPS mean, respectively;
- The lower and upper bounds for the mean difference (sPS – bPS) of total bicarbonate are estimated to be -64% and 76% of the bPS mean, respectively;
- The lower and upper bounds for the mean difference (sPS – bPS) of total volume are estimated to be -59% and 45% of the bPS mean, respectively;

For the supportive study CRC97-1, Table 2.3.1 indicates:

- The lower and upper bounds for the mean difference (sPS – bPS) of peak bicarbonate concentration are estimated to be –6.7% and 1.6% of the bPS mean, respectively;
- The lower and upper bounds for the mean difference (sPS – bPS) of total bicarbonate are estimated to be –18% and 2.3% of the bPS mean, respectively;
- The lower and upper bounds for the mean difference (sPS – bPS) of total volume are estimated to be -13.6% and 6.0% of the bPS mean, respectively;

In response to this reviewer's information request with regard to the delta margin for the equivalence analysis, the sponsor indicated that 20% of the bPS mean was selected as the delta margin. However, the sponsor provided neither the rationale for the selection of 20% nor the bPS population means for the above three pharmacological variables. This reviewer therefore, utilizes the percentages of lower and upper bounds divided by the bPS sample mean to estimate the percentages of the lower and upper bounds divided by the bPS population mean. The results from pivotal study CRC98-1 indicate that the equivalence between sPS and bPS is not established since none of the 95% confidence intervals for variables PEAKBC, TBC, and V_1_60 is contained in the interval formed by –20% of bPS sample mean (lower bound) and +20% of bPS sample mean (upper bound).

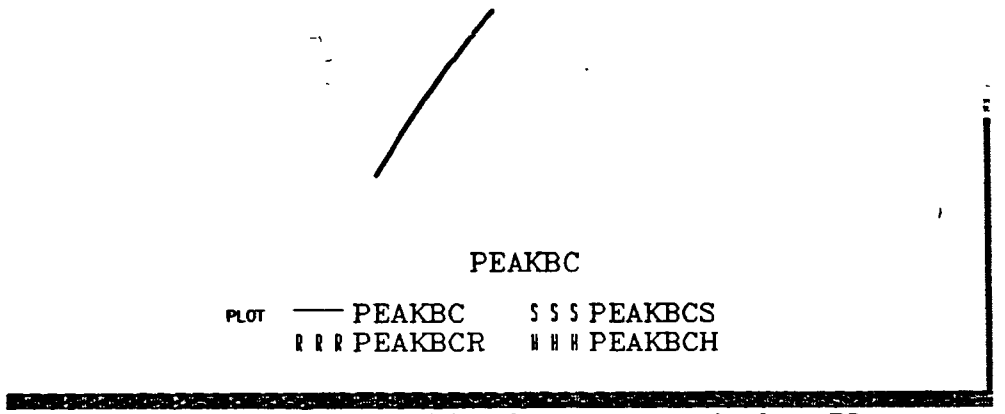
iii) Graphic Display

The following graphs show each patient's sPS data versus bPS data for each of the three

variables, PEACKBC, TBC, and V_1_60, using patients from both studies, CRC98-1 and CRC97-1. The diagrams for the three variables, PEACKBC, TBC, and V_1_60, are given in Fig. 2.3.1, Fig. 2.3.2, and Fig. 2.3.3, respectively. In each plot, symbols 'S', 'R', and 'H' denote data from the sick patients, recovered patients, and healthy volunteers, respectively.

Fig. 2.3.1

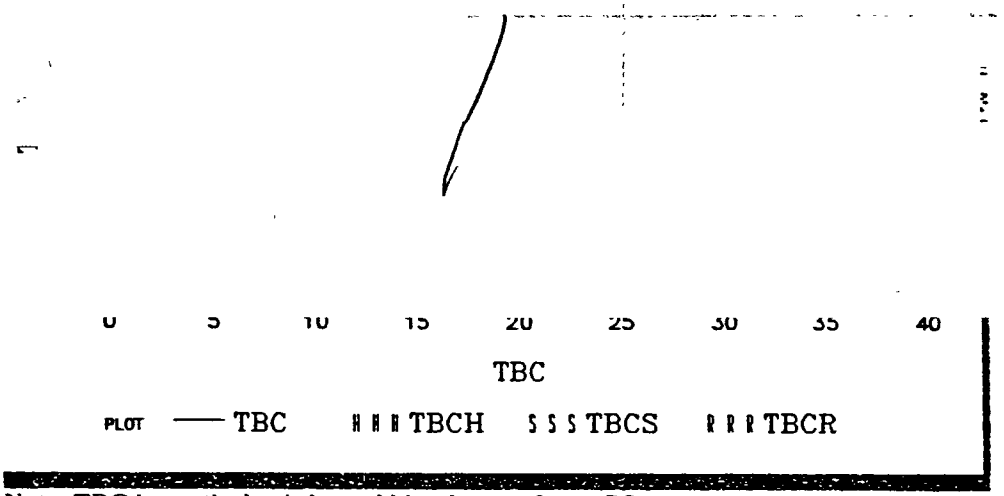
PEAK BICARBONATE DATA PLOT FOR STUDY 97 1 & 98 1



Note: PEAKBC in vertical axis is peak bicarbonate concentration from sPS treatment; PEAKBC in horizontal axis is peak bicarbonate concentration from bPS treatment.

Fig. 2.3.2

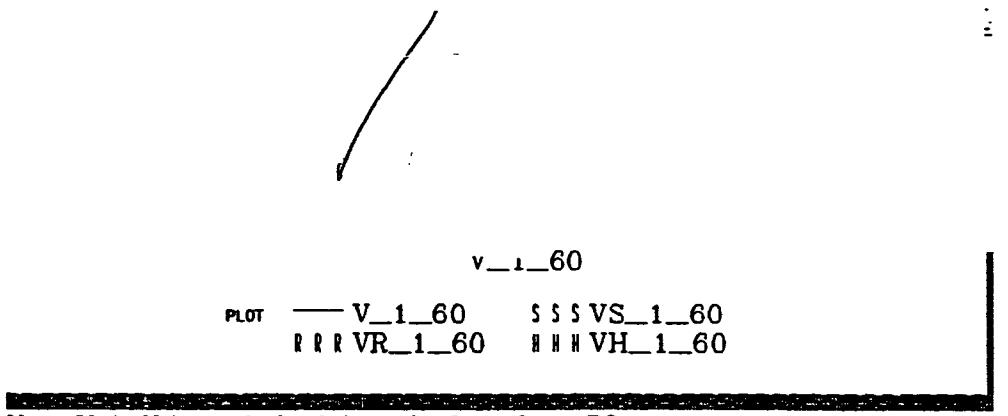
TOTAL BICRABONATE DATA PLOT FOR STUDY 97_1 & 98_1



Note: TBC in vertical axis is total bicarbonate from sPS treatment;
TBC in horizontal axis is total bicarbonate from bPS treatment.

Fig. 2.3.3

TOTAL VOLUME DATA PLOT FOR STUDY 97_1 & 98_1



Note: V_1_60 in vertical axis is total volume from sPS treatment;
V_1_60 in horizontal axis is total volume from bPS treatment.

Figure 2.3.1, 2.3.2, and 2.3.3 indicate the following phenomena:

- The values for the three variables, peak bicarbonate concentration, total bicarbonate, and total volume, from sPS treatment group are in general smaller than those from bPS treatment

group, especially for sick patients;

- The values for the three variables from the sick patients are much smaller than those of healthy volunteers;
- The deviations, between sPS and bPS, of the three variables for the sick patients are relatively greater than those of healthy volunteers.

iii) Probability analysis

In order to assess the robustness of the 100% agreement reported by the applicant for the diagnosis of pancreatitis by the two diagnostic agents, sPS and bPS, for Study CRC-98-1, this reviewer calculated the probability of 100% agreement between sPS and bPS in the diagnosis of pancreatitis using eight sick patients, under the assumption that there exits a certain disagreement probability between these two agents.

For example, if 10% of subjects are expected to differ on the tests, the probability of no disagreement in 8 subjects is 43%. For another example, if the disagreement probability for the two diagnostic agents is 25%, the probability of the 100% agreement in the diagnostic results tested by these two agents on the eight sick patients is 10%. These examples suggest that the observed lack of difference can not rule out a relatively large disagreement rate.

2.4 Comments/Conclusions on treatment effects

- The lower bounds of the 95% confidence intervals on the two mean differences (sPS - bPS) for the three variables, peak bicarbonate concentration, total bicarbonate, and total volume, calculated by the sick patients in pivotal study CRC98-1, are estimated to be –29%, -64%, and –59% of the bPS means, respectively. These results indicate that the sPS means for peak bicarbonate concentration, total bicarbonate, and total volume can be less than those of bPS by up to 21%, 64%, and 59%, respectively.
- Graphic displays suggest:
  i.) Peak bicarbonate concentration, total bicarbonate, and total volume for sPS are smaller than those for bPS, especially for sick patients.
  ii.) The deviations, between sPS and bPS, for the three variables for the sick patients are relatively greater than those of healthy volunteers.
- Under the assumption of 25% disagreement probability for the two diagnostic agents, sPS and bPS, the probability of 100% agreement in the diagnostic results tested by these two agents on the eight sick patients is 10%.
- In conclusion, the results of efficacy analyses from the single pivotal study are not statistically persuasive due to the small sample size and observed differences between the drugs.

[/S/]

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Dr. Flyer [/S/] 3/7/00

Dr. Nevius [/S/] 3/7/00

cc: Archival NDA# 21-136
HFD-180 Div File
HFD-180/Dr. Talarico
HFD-180/Dr. Goldkind
HFD-180/Mr. Strongin
HFD-715/Dr. Nevius
HFD-715/Dr. Welch
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STATISTICAL REVIEW AND EVALUATION

NDA: 21-209 Date: JAN 31 2000

APPLICANT: ChiRhoClin, Inc.

NAME OF DRUG: — (Synthetic Porcine Secretin).

INDICATION: Diagnosis of gastrinoma [redacted].

USER FEE DUE DATE: Feb. 17, 2000

DRUG CLASSIFICATION: 1P.

DOCUMENT REVIEWED: NDA Volumes 1.1, 1.2, and 1.3; dated August 17, 1999.

STATISTICAL REVIEWER: Wen-Jen Chen, Ph.D.

BACKGROUND

NDA 21-209 for — (synthetic porcine secretin) requests an indication for the diagnosis of gastrinoma [redacted]. However, a refusal-to-file letter was sent for this indication on July 22, 1999 because the applicant's submission (CRC 97-2) contained inadequate (see medical reviewer's comments) clinical data to characterize the product as a diagnostic tool in patients with Zollinger-Ellison Syndrome.

The Division of Gastrointestinal and Coagulation Drug Products recommended that the firm submit a complete study report and data from Study CRC 99-8 in support of this indication. The protocol for CRC 98-2 entitled, "A randomized, controlled Crossover Study Evaluating Synthetic Porcine Secretin, Synthetic Human Secretin, and Biologically Derived Porcine Secretin for the Diagnosis of Gastrinoma", was submitted on August 31, 1999. No data has been provided at this time.

CONCLUSION/REMARK

This reviewer can not assess the sponsor's claim that — (synthetic porcine secretin) provides [redacted] for the diagnosis of gastrinoma [redacted], due to the following reasons:

- The original documentation submitted on May 14, 1999 does not contain adequate clinical data related to the use of the product for the diagnosis of gastrinoma.
- No new data from additional studies or data from Study CRC 99-8 with regard to the use of the product for the diagnosis of gastrinoma has been submitted.

/S/

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Flyer /S/ 1/31/00

Dr. Nevius /S/ 1/31/00

cc: Archival NDA# 21-209
HFD-180 Div File
HFD-180/Dr. Talarico
HFD-180/Dr. Goldkind
HFD-180/Mr. Strongin
HFD-715/Dr. Nevius
HFD-715/Dr. Welch
HFD-715/Dr. Flyer
HFD-715/Dr. Chen
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APPEARS THIS WAY
ON ORIGINAL

NDA 21-136
NDA 21-209

This section is Not Applicable

151 - 3.27.02

Alice Kacuba, Regulatory Health Project Manager, HFD-180

STATISTICAL REVIEW AND EVALUATION — NDA
STABILITY STUDY

Medical Division: Gastro-Intestinal and Coagulation Drug Products (HFD-180)
Biometrics Division: Division of Biometrics II (HFD-715)

STATISTICAL KEY WORDS: stability

NDA #: 21-136
SERIAL NUMBER:
DATE RECEIVED BY CENTER: January 22, 2002
DRUG NAME: Synthetic porcine secretin
INDICATION: Diagnosis of pancreatic exocrine
SPONSOR: ChiRhoClin, Inc.
DOCUMENTS REVIEWED: Vol. 1, Dated January 21, 2002
STATISTICAL PRIMARY REVIEWER: Milton C. Fan, Ph.D. (HFD-715)
STATISTICAL SECONDARY REVIEWER: Karl Lin, Ph.D. (HFD-715)
STATISTICAL TEAM LEADER: Thomas Permutt, Ph.D. (HFD-715)
BIOMETRICS DIVISION DIRECTOR: Edward Nevius, Ph.D. (HFD-715)
CHEMICAL REVIEWER: Arthur Shaw, Ph.D. (HFD-180)
PROJECT MANAGER: Alice Kacuba (HFD-180)

A. Background

Per the request for statistical stability review from the review chemist, Arthur Shaw, Ph.D., this reviewer performed the statistical stability studies for LBLPCT (Percent of Label Claim).

The sponsor is requesting a expiration data.

B. Reviewer's Analysis

This reviewer ran the Division E-Review/Stability Web stability program on LBLPCT. As suggested by the review chemist, Dr. Arthur Shaw, the specification limits used were instead of used by the Sponsor. Additional analyses were performed using the sponsor's specification limits

LBLPCT stability data are given in Appendix I. As seen from data, the sponsor did not follow the testing time points, months recommended by FDA. The results from analyses of these data might not be reliable.

The detailed results of analyses are given in Appendix II. Plots are given in Appendix III. As seen from results and plots, Batch 9275 has a very different stability profile from other batches. All data points are above label claim. The intercept for Batch 9275 is larger than those for other batches for Batch 9275 vs. for other batches). The sponsor should provide information to explain the big variation in assay

value among batches.

Separate intercept and common slope was fitted for each batch. Below is a summary of estimated extrapolated expiration dating period based on LBLPCT.

Estimated Expiration Dating Periods Based on Percent of Label Claim

Batch	(month)	(month)
11001		
78104		
92704		
9275		

Based on the specifications of — the estimated dating periods range from — — The minimum of estimated dating periods is — The estimated dating periods for LBLPCT are shorter than those based on specifications — % asked for by sponsor. But, there is no justification for using such wide specification limits.

Furthermore, the sponsor did not follow the testing time points — ... months recommended by FDA. The power for testing for batch by time might be poor. P-value for interaction between batches and time might be misleading. This reviewer also ran the Division E-Review/Stability Web stability program for each individual batch without pooling data. Below are intercept and slope of fitted line for each individual batch.

Intercept and Slope of Fitted Line for Individual Batch

Batch	Intercept Estimated	Slope Estimated
11001		
78104		
92704		
9275		

As seen from Table above, Batch 9275 has a very different stability profile from other batches. Its estimated slope was positive; the estimated slopes for other batches were all negative.

Based on the specification — the estimated dating periods were —

for batch 11001, 78104, 92704, and 9275, respectively. The estimated dating periods obtained without pooling data were significantly shorter than those obtained with pooling data.

This review consists of 3 pages of text and 5 pages of tables.

5 Page(s) Withheld

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Milton Fan
2/13/02 10:45:49 AM
BIOMETRICS

revised, please give comments or signoff

Karl Lin
2/13/02 04:11:58 PM
BIOMETRICS
Concur with review