CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-256

Medical Review(s)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	**21-256**
Date Submitted:	**December 15, 2003**
Sponsor:	***ChiRho*Clin, Inc.** **Burtonsville, MD**
Drug name:	**Synthetic Human Secretin**
Route of Administration:	**Intravenous**
Pharmacological Category:	**Hormone**
Proposed Indication:	**Aid in the Diagnosis of Exocrine Pancreatic Dysfunction and Gastrinoma and Identification of the Ampulla of Vater During ERCP**
Material Submitted:	**Safety Update**
Reviewer:	**Gail I. Moreschi, MD, MPH, FACP** **Medical Officer**

I. Introduction

Synthetic Human Secretin (sHS) produces specific physiologic responses which include stimulation of pancreatic secretions and pancreatic bicarbonate output, and increases in gastrin levels. These physiologic responses to sHS may be used to assist in the diagnosis of exocrine pancreatic dysfunction and gastrinoma, and identification of the ampulla of Vater during ERCP.

The original NDA for sHS was received by the Agency June 14, 2001. The Sponsor, ChiRhoClin, Inc. received an approvable letter from the Office Director dated December 12, 2001, which delineated Chemistry, Manufacturing, and Controls issues that needed to be addressed before the application could be approved. The Sponsor resubmitted this NDA on October 10, 2003 addressing the deficiencies outlined in the approvable letter.

II. Updated Safety Review

The Sponsor was requested to submit all the safety information available regarding sHS since the original application. In the additional 140 patients enrolled in clinical trials, there was one moderate adverse event (AE) which was a post-ERCP pancreatitis considered unlikely related to the drug. This patient required hospitalization. No new studies were initiated in Autism. In the diagnostic clinical studies the total number of human subjects that received a dose of sHS was 641. NOTE: Tables 1 through 4 are listed in Appendix 1, at the end of the current document. The total number of patients who received 0.2 mcg/kg was 543. The total number of patients who received 0.4 mcg/kg was 98. The total number of patients by studies is displayed in Table 1 in the Appendix. Table 2 lists all the adverse events with the secretin preparations. Table 3 lists probable and definite adverse events. In Table 4 the severity of adverse events is given.

For the diagnostic indication two severe adverse events were reported. They included one case of nausea and one of stomach pain that were almost definitely related to sHS. Both AEs resolved or improved with no treatment. This information should be included in the label.

There were no dropouts or premature study discontinuation in the entire clinical program. Also, there were no deaths for sHS in the clinical program. There were no significant changes or findings related to safety since the original NDA submission. There have been no clinical studies using sHS outside the United States. This drug has not been marketed in any territory. There is no approved or pending foreign labeling for this drug.

III. Recommendations

The Pharmacology/Toxicology reviewers and the Biopharmaceutics reviewers have no changes to the original NDA.

There are no significant safety issues and therefore this clinical reviewer recommends that Synthetic Human Secretin be approved pending:

1. The Sponsor adequately responds to all the CMC issues.
2. The Sponsor reaches a satisfactory agreement with the Division regarding revisions to the Label. These multidisciplinary labeling changes are addressed separately.

APPENDIX

NDA 21-256
SAFETY UPDATE

TABLE 1
DIAGNOSTIC STUDIES

STUDY	TOTAL	Additional Pts. Since Dec. 3, 2001 Submission	0.2 mcg/kg	0.4 mcg/kg
CRC98-2	12	---	12	---
CRC98-4	532	140	453	79
CRC98-4 Amendment	24	---	24	---
FL00-1	9	9	9	---
CRC00-2	1	1	---	1
CRC99-8	6	---	---	6
CRC99-9	6	---	6	---
CRC99-10*	12	---	---	12
CRC2000-1**	39	---	39	---
TOTAL	**641**	**150**	**543**	**98**

*PK study in normals
**Secretin function test in normals

NDA 21-256
SAFETY UPDATE

TABLE 2
ALL ADVERSE EVENTS
STUDIES 98-2, 98-4, 98-4 Amendment, 99-8, 99-9, 99-10, 2000-1, 2000-2 and FL00-1

Event	Diagnostic		
	sHS N = 641 Incidence	sPS* N = 27 Incidence	bPS* N = 15 Incidence
Abdominal pain	3	0	0
Anxiety	1	0	0
Burning in stomach or abdomen	1	3	1
Clammy skin	1	0	0
Decreased O_2 saturation	1	0	0
Diarrhea (loose stools)	1	0	0
Early removal of Dreiling tube	3	0	0
Faintness	1	0	0
Flushing	4	0	1
Headache	0	1	0
Hypotension	1	3	0
Increased heart rate	2	0	0
Infiltrated IV	1	0	0
Lightheaded	0	3	0
Mild Pancreatitis	1	0	0
Nausea	11	1	1
Numbness	0	1	0
Oral secretions, increased	1	0	0
Pallor	0	1	0
Pancreatitis Post-ERCP	1	0	0
Panic attack (before sHS administration)	1	0	0
Sedation	1	0	0
Slow heart rate (57)	1	0	0
Sweating	0	3	0
Sweating feet	0	1	0
Sweating hands	0	1	0
Thready Pulse	0	1	0
Tingling (extremities)	1	1	0
Unresponsiveness	1	0	0
Upset stomach	2	0	0
Vomiting	3	0	0
Warm sensation in abdomen	1	0	1
Warm sensation in face	1	0	1
TOTAL AEs	**46**	**20**	**5**

* - Studies in which sHS is also a treatment arm.

Depicted are the number of AEs per treatment, irrespective of causality.

Table 3
PROBABLE AND DEFINITE ADVERSE EVENTS
STUDIES 98-2, 98-4, 98-4 Amendment, 99-8, 99-9, 99-10, 2000-1, 2000-2 and FL00-1

Event	Diagnostic		
	sHS N = 641 Patients	sPS* N = 27 Patients	bPS* N = 15 Patients
Abdominal pain	1		
Burning in stomach or abdomen	1	3	1
Diarrhea (loose stools)	1		
Faintness	1		
Flushing	4		1
Increased heart rate	1		
Nausea	6		1
Sweating feet		1	
Sweating hands		1	
Tingling in legs	1		
Upset stomach	2		
Warm sensation in abdomen	1		1
Warm sensation in face	1		1
TOTAL # OF PATIENTS WITH PROBABLE & DEFINITE AEs	20	5	5

* - Studies in which sHS is also a treatment arm.

Table 4
SEVERITY OF ADVERSE EVENTS
STUDIES 98-2, 98-4, 98-4 Amendment, 99-8, 99-9, 99-10, 2000-1, 2000-2 and FL00-1

Adverse Events	Diagnostic		
	sHS N = 46 Event	sPS* N = 20 Event	bPS* N = 5 Event
Mild	32 (69.5%)	12 (60%)	4 (80%)
Moderate	9 (19.6%)	8 (40%)	1 (20%)
Severe	3 (6.5%)	0	0
Unknown	2 (4.3%)	0	0

* - Studies in which sHS is also a treatment arm.

Depicted are the number of AEs, not the number of patients.

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/s/

Gail Moreschi
3/9/04 02:50:13 PM
MEDICAL OFFICER

Hugo Gallo Torres
3/9/04 04:38:20 PM
MEDICAL OFFICER
The MTL agrees with the Approval recommendation, provided that the CMC and Labeling revision issues are adequately resolved.,

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW
ADDENDUM

NDA: 21-256

DATE SUBMITTED: March 16, 2000

REFUSED TO FILE: May 11, 2000

DATE RESUBMITTED: June 15, 2001

GENERIC NAME: SYNTHETIC HUMAN SECRETIN (sHS)

PROPOSED TRADE NAME: —

SPONSOR: ChiRhoClin Inc.

PHARMACOLOGICAL CATEGORY: Polypeptide Secretagogue

INDICATIONS FILED: 1) Diagnosis of Pancreatic Exocrine Disease
2) Diagnosis of Gastrinoma
3) Facilitation of
Papilla during ERCP

MEDICAL OFFICER: Marcelo A. Barreiro, MD, MSc

I – **Clinical Issues**.

ChiRhoClin Inc., the sponsor of sHS, submitted an NDA requesting approval for the following indications:

1) Diagnosis of Pancreatic Exocrine —
2) Diagnosis of Gastrinoma
3) Facilitation of papilla during Endoscopic Retrograde Cholangio Pancreatography (ERCP)

Indications # 1 and 2 are approved for biological pancreatic secretin (bPS), and considered approvable for synthetic porcine secretin (sPS).

This reviewer considered that although the number of patients studied was small and did not allow for formal statistical analysis, there was enough information accumulated to **grant approval of the first two indications,** pending resolution of manufacturing problems and appropriate labeling.

The third indication was supposed to be supported by a randomized, double blind, placebo controlled study. The research protocol had, in this reviewer's opinion, significant flaws that invalidated the results. One of the reasons for this, was that the dose of sHS administered was the same as that given for the 60 minute testing of exocrine pancreatic function. This dose appears to be much higher than necessary to visualize the opening of the pancreatic duct in the duodenal mucosa. The interval between attempts at cannulation between the injection of drug or placebo being only five minutes, resulted in a carry over effect, unblinding the study. Additionally, drugs commonly administered during the performance of ERCP to induce sedation, inhibit gastrointestinal motility or to reverse the effect of these drugs, had not been listed in the CRFs. This omission represent a protocol violation, although admittedly, of unknown clinical significance. Another larger group of patients had been part of an open-label, uncontrolled study. There was evidence of a pharmacological effect of sHS, although the role of the drug in facilitating cannulation of the pancreatic duct(s) couldn't be established because of the lack of controls. In addition, the facilitation — indication does depend upon the dexterity of the endoscopist. This reviewer considered **sHP approvable for the third indication** and suggested the performance of another clinical trial, with a protocol developed by the sponsor, the Agency and outside experts.

In all these studies, for the three requested indications, sHS had demonstrated a satisfactory safety profile.

All these facts were discussed with Drs. Houn, Korvick and Gallo-Torres. Two relevant points came to the fore:

1) The drug was not tested in the intended-use population. The drug was tested in patients with previously diagnosed chronic pancreatitis or gastrinoma, and all it did was confirm the diagnosis. We do not have information on how sHS will perform in patients with symptoms suggesting the disease but without a clinical diagnosis.

2) In all the studies performed for the three requested indications, the drug showed the expected physiological effect, stimulating exocrine pancreatic function and an increase in the production of gastrin by the gastrinoma tumors. These are the responses anticipated from secretin, for which there are known mechanisms of action. These responses can, in turn, be used for diagnostic purposes.

In view of these additional points, namely:

- That sHP is an orphan drug to be used in a limited number of patients per year.
- That it doesn't lend itself to the performance of clinical trials with large number of patients
- That the studies do not allow for formal statistical analysis
- That sHS has demonstrated the expected physiological effects

This reviewer has modified the recommendations for regulatory action **to grant approval of sHS for the stimulation of pancreatic function as an aid of diagnosis in the following clinical settings:**

1) The diagnosis of exocrine pancreatic

2) The diagnosis of gastrinoma

3) The identification of the ampula of Vater and the accesory papilla during ERCP.

Final approval of this drug is contingent on the resolution of manufacturing problems and appropriate labeling

II - **Financial disclosures**. Certification/Disclosure Form of Financial Disclosure by Clinical Investigators complying with 21 CFR 314.50 (k) (3) have been submitted for all investigators. After reviewing this information, I testify that the financial arrangements did not bias the results of the clinical trials.

[1] Telephone conversation of 28 November, 2001. MEMORANDUM to H Gallo-Torres, MD, PhD.

Marcelo A. Barreiro, MD, MSc

NDA 21-256
cc: Florence Houn, MD/HFD-103
Victor Raczkowski, MD/HFD-180
Joyce Korvick, MD, MPH/HFD-180
Hugo Gallo-Torres, MD, PhD/HFD-180
M. A. Barreiro, MD, MSc/HFD-180
Melodi McNeil/HFD-181

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/s/

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MEDICAL OFFICER

Hugo Gallo Torres
12/12/01 03:18:10 PM
MEDICAL OFFICER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL TEAM LEADER'S SECONDARY REVIEW

NDA:	21-256
Date Submitted: Refused to File: Date Resubmitted:	March 16, 2000 May 11, 2000 June 15, 2001
Sponsor:	ChiRhoClin
Drug Substance: (Generic Name)	Synthetic Human Secretin **(sHS)**
Proposed Trade Name:	—
Pharmacological Category:	Polypeptide secretagogue. Used as an agent that incites or promotes secretion.
Proposed Indications:	1. "For diagnosis use in pancreatic exocrine dysfunction" 2. "Diagnosis of gastrinoma" 3. "Facilitation of papilla during ERCP"
Dosage Form and Route of Administration:	Lyophilized Sterile Powder for Injection: • Bolus (1 minute) intravenous (I.V.) Administration • 0.2 μg/Kg B_{wt} for indications 1. and 3. • 0.4 μg/Kg B_{wt} for indication 2.
Material Reviewed:	• MOR of NDA 21-256 (Dr. M. Barreiro; November 27, 2001) including Statistics (Dr. Wen-Jen Chen) and Biopharm (Dr. Sandip K. Roy) • MORs of synthetic porcine secretion **(sPS)**, NDAs 21-136 and 21-209 by Drs. L. Goldkind (March 17, 2000 and June 16, 2000) and S. Kress (November 28, 2000), respectively. • MORs of biologic porcine secretin **(bPS);** NDA 18-290 by Drs. A. Schulman (June 12, 1979) and T.Q. Garvey III (February 24, 1981).
Reviewer	Hugo E. Gallo-Torres, M.D., Ph.D. Medical Team Leader, (G.I. Drugs) HFD-180

NDA 21-256

Medical Team Leader Secondary Review
TABLE OF CONTENTS

		Page
I.	**Background Introduction**	**3**
II.	**Summary of Regulatory History**	**3**
III.	**Pharmacokinetic Profile**	**6**
	Study CRC 99-10	**6**
	Results of PK Evaluations	**7**
	Results of PD Evaluations	**8**
	"Other Issues"	**9**
IV.	**Summary Review of Efficacy**	**9**
	A. Parameters of Evaluation	**9**
	1. Diagnosis of Pancreatic Exocrine Dysfunction	**10**
	2. Diagnosis of gastrinoma	**10**
	3. Facilitation of pancreatic duct cannulation of the minor papilla during ERCP in patients with pancreas divisum	**11**
	B. Basis for Recommendations for Regulatory Action	**12**
	1. Diagnosis of Pancreatic Exocrine Dysfunction	**12**
	2. Diagnosis of gastrinoma	**17**
	3. Facilitation of pancreatic duct cannulation of the minor papilla during ERCP in patients with pancreas divisum	**18**
V.	**Summary Review of Safety**	**21**
VI.	**MTL's Recommendations for Regulatory Action**	**22**
VII.	**Labeling**	**23**
	Pediatric Use	**23**

I. BACKGROUND/INTRODUCTION

SECRETIN is a naturally occurring, 27-amino acid peptide hormone, normally formed by the epithelial cells of the duodenum. The secretion of secretin is stimulated by gastric hydrochloric acid.[1] The principal action of secretin[2] is to stimulate the pancreas to produce water (volume) and bicarbonate (measured as **peak** bicarbonate concentration and **total bicarbonate** concentration). Pancreatic juice contains many groups of enzymes,[3] but none of these has been standardized to the point of being useful as a diagnostic test. However, spilling into blood of some of these enzymes (e.g. amylase, lipase) is used in the clinic to aid in the diagnosis of acute pancreatitis.

Following purification of biologically derived secretin from a porcine extract, in 1970s, by the Karolinska Instituet in Stockholm, this product was transferred to Kabi Diagnostic in 1977. **Secretin-Kabi** (NDA 18-290) was approved by the US FDA in 1981. In 1989, **Ferring** assumed production and marketing of this product. Ferring has informed the FDA that it has ceased production of secretin as of June 1999. The rights were sold to **Repligen Labs** [redacted] Because there was no secretin available for diagnostic testing in the USA, the sponsor of NDA 21-256 **(sHS)** was granted permission to make **sPS** (IND 54-196) available to patients via a **treatment IND**. This was done after clinical appraisal demonstrating that the secretin stimulation test is a **medical necessity.**[4] No other source of secretin, biologically or synthetically produced is presently available in the USA. There is anecdotal information that for "off label" uses, such as treatment of autism [redacted] patients obtain secretin from non-USA sources such as Canada.

In summary, although within the last 5 years clinical use of secretin in **autism** has been proposed, the proven pharmacological use of this hormone is as a **diagnostic test** for a) pancreatic exocrine function and b) gastrinoma [redacted]. The third indication the sponsor of NDA 21-256 is seeking ("3. [redacted]) is a **new** indication for **sHS** and **sPS** (under NDA 21-136).

II. SUMMARY OF REGULATORY HISTORY (Table 1)

There have been and continue to be a number of constraints and limitations for the use of secretin as a diagnostic tool. Points raised by Dr. T. Garvey's review of bPS (NDA 18-290) in

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[1] HCl stimulates the secretion of secretin, which in turn stimulates the release of bicarbonate from the pancreas into the duodenum via the pancreatic duct(s).

[2] Secretin counters the effects of gastrin (e.g. by lowering LES pressure). It accounts for the inhibitory effect of high pH on gastric motility.

[3] **Endopeptidases** and **carboxypeptidases** in pancreatic juice are secreted as **proenzymes** from the pancrease acinar cells under the influence of secretin and CCK-PZ. Activation of the proenzymes occurs by the action of **enteropeptidase** (enterokinase), secreted by the duodenal epithelial cells. Enteropeptidase activates **trypsinogen** by cleaving off 6 amino acids, and the activated **trypsin** in turn activates more trypsinogen. Trypsin also activates the proenzymes of the endopeptidases **chymotrypsin** and **elastase**, and the proenzymes of the exopeptidases **carboxypeptidase A and B**. Pancreatic juice also contains endonucleases.

[4] October 27, 2000 memorandum from MTL to HFD-180 Division Director, IND 54,196 Synthetic Porcine Secretin.

1981 remain valid twenty years later. These include incomplete characterization of the diagnostic test and stability of the drug product. In addition, the sponsor of NDAs 21-256, 21-136 and 21-209 (ChiRhoClin) has not been able to assemble these submissions adequately, although, in the final analysis, the **clinical information** provided seems enough to recommend **approval** of the test for two of the three sought indications: a) diagnosis of pancreatic exocrine dysfunction and b) diagnosis of gastrinoma. However, there continue to be **outstanding chemistry issues** that preclude regulatory actions on these submissions.

TABLE 1
Synthetic Human Secretin (sHS) and sHS-related Secretins

Highlights of Regulatory History

DATE	EVENT
1962 et al.	• Purification of porcine intestinal mucosal extract, leading to the sequencing of the 27 amino acid peptide, secretin. • Aspartamine and serine in **bPS** in positions **15** and **16** are replaced with glutamine and glycine in **sHS** • Studies in animals have suggested, but not proven, the presence of secretin in extra-intestinal sites.
1970s	The Karolinska Instituet in Stockholm produced the most highly purified form of secretin
1977	Manufacture of product transferred to Kabi Diagnostica
April 24, 1978 December 12, 1978 June 1, 1979	AC discussion of Secretin-Kabi (NDA 18-290)
June 12, 1979	MOR of NDA 18-290 **(bPS)** by A. Schulman
February 24, 1981	Supplemental MOR of NDA 18-290 by Dr. T.Q. Garvey III
May 29, 1981	SBA of NDA 18-290
1981	Secretin-Kabi approved by US FDA
1989	**Ferring** assumes production and marketing of **bPS** (NDA 18-290)
November 18, 1998	Pre-NDA meeting minutes with sponsor (ChiRhoClin)
June 1999	**Ferring** ceases production of **bPS** (NDA 18-290)
May 14, 1999	Submission of NDA 21-136 **(sPS**, ChiRhoClin) **Indications Filed:** 1. "For diagnostic use in pancreatic exocrine function" 2. [redacted] **Indications not Filed:** 1. Diagnosis of gastrinoma 2. [redacted]

August 19, 1999 September 14. 1999 October 16, 1999	Filing of NDA 21-209 (ChiRhoClin) Minutes of Meeting with the sponsor Filing over protest of NDA 21-209 [indication: "diagnosis of [redacted] (gastrinoma)]
February 11, 2000	MOR of NDA 21-209 by Dr. L. Goldkind Recommends: 1. Not to approve ("approvable") sPS for the diagnosis of gastrinoma
March 16, 2000	NDA 21-256 for sHS submitted
March 17, 2000	MOR of NDA 21-136 by Dr. L. Goldkind. Includes review of amendments dated 10/17/99, 11/9/99, 12/30/99 and 1/28/2000. Recommendations (page 58) 1. Approval of sPS for the diagnosis of pancreatic exocrine dysfunction. This recommendation is based on results of studies **97-1** and **98-1**, supported by published medical literature. 2, [redacted] 3, Labeling revisions, including incorporation of certain Tables (pages 58 through 70)
May 11, 2000	NDA 21-256: Refuse to file letter because application was not sufficiently complete to merit review, citing a lack of adequate clinical data.
May 16, 2000	NDA 21-209: "Approvable" letter on diagnosis of gastrinoma indication.
June 16, 2000	MOR of NDA 21-209 by Dr. L. Goldkind (NDA filed over protest August 19, 2000), including amendments of dated 2/3/2000, 2/18/2000, 3/8/2000, 3/16,2000, 3/31/2000 and 4/14/2000. Recommends: 1. Approvability of sPS for the diagnosis of gastrinoma. 2. Submission by sponsor, before approval, of identification and CRFs and primary source documents on subjects #5 and 6 (studies CRC 99-8 and CRC 97-2)
November 27, 2000	MOR of NDA 21-209 by Dr. S. Kress, on May 26, 2000 sponsor's reply to approvable letter of May 16, 2000 Recommends: 1. Secretin be approvable for the diagnosis of gastrinoma [redacted] 2. Calls attention to the fact that approvability remains subject to resolution of the outstanding chemistry manufacturing and control deficiencies in NDA 21-136.
June 15, 2001	NDA 21-256 resubmitted, containing our May 11, 2000 refuse-to-file letter

It is worth noting that of the 3 indications requested by the sponsor in NDA 21-256 for **sHS**, two are at least approvable for **sPS** (NDAs 21-136 and 21-209). For this synthetic form of secretin, diagnosis of pancreatic exocrine dysfunction should be approved per Dr. Goldkind's recommendation of March 17, 2000. The other (diagnosis of gastrinoma) is approvable based on the November 27, 2000 review of NDA 21-209 by Dr. Kress. Both are approved indications for the marketed but no longer available **bPS** (NDA 18-290). The facilitation [redacted] indication was never brought up for **bPS**, has apparently been dropped for **sPS** and constitutes a brand new indication for **sHS**.

The items highlighted in Table 1 are essential to the understanding of the approach used by the G.I. Team to demonstrate that efficacy (and safety) for the ChiRhoClin synthetic secretins (both of porcine and human origin) has been proven. This applies particularly to the chronic pancreatitis and gastrinoma indications. As summarized below, the data for sHS in NDA 21-256 **stand by itself**: the expected PK profile and PD effects are shown in the small number of patients studied. And small number of observations **is** among the existing constraints. **First,** these are **orphan indications**. **Second,** the number of patients with exocrine pancreatic dysfunction or gastrinoma that merit secretin stimulation test (SST) is rather small. **Third,** nasoduodenal intubation is an unpleasant procedure that patients might be willing to endure once, but very few would voluntarily subject themselves to repeated intubations and the concomitant inconveniences including overnight fast, no medications before the test and day missed of work for some of them. When these constraints, addressed in the MOR of NDA 21-256 by Dr. M. Barreiro are taken into account, it becomes evident that the results from experiments where a double crossover has been used - so that the patients were tested with the two synthetic preparations - are very meaningful. The data are **even more meaningful** when a **triple crossover approach** was used. This is stated because this approach means that each patient was not only tested with each of the two synthetic preparations of the hormone, but also with the biologically form of secretin. Actually, since the latter is **the only approved secretin,** it can be considered the **"gold standard"** although, admittedly, this comparator was not consistently used, most likely due to lack of availability.

Therefore, the characterization of the SST for the indications requested in NDA 21-256 cannot be done in the usual way when assessing diagnostic tests. Specifically, the MTL proposes that issues regarding specificity, sensitivity, positive predictive value and negative predictive value of the proposed **bioassay** cannot be assessed in the usual statistical fashion, simply because the number of cells per indication does not lend itself to formal statistics. Instead, in addition to descriptive statistics of the data attempting to show that the sHS data stand by itself for each indication, the most important approach is **(graphic)** comparison of the PK and PD effects of sHS to those of sPS and when available, to those of bPS.

III. PHARMACOKINETIC PROFILE OF sHS (Table 2)

Study Report **CRC99-10** [Reviewed by Dr. Sandip K. Roy, July 27, 2000]

> *"A Single Center Study Evaluating the Pharmacokinetic Profile of Single Intravenous Dose of Synthetic Porcine and Synthetic Human Secretin" Protocol No. CRC 99-10*

- The objectives of this trial were:

1. To characterize the PK profile of one dose of sHS and one dose of sPS (both ChiRhoClin single I.V. products) at doses of 0.4 μg/Kg B_{wt}, in normal subjects.

2. To evaluate the effect of sHS and sPS on serum gastrin concentrations in normal subjects.

3. To evaluate the safety and tolerance of these products in normal subjects.

- Single I.V. doses of sHS (0.4 μg/Kg) and sPS (0.4 μg/Kg) over 60 seconds were administered one week apart. Other methodological approaches[5] were adequate.

Results of PK Evaluations with sHS (Fig. 1)

After I.V. bolus administration, plasma concentration of synthetic human secretin rapidly declined to baseline secretin concentrations within 60 to 90 min. in most of subjects. The mean AUC observed, which represented sampling to 120 min was nearly 79% of the estimated AUC_{α}. The α-half-life of sHS is 3.26 ± 0.28 minutes. The β-half-life was calculated as 45 min. The clearance synthetic human secretin is 580.9 ± 51.3 mL/min and the volume of distribution is 2.7 liter.

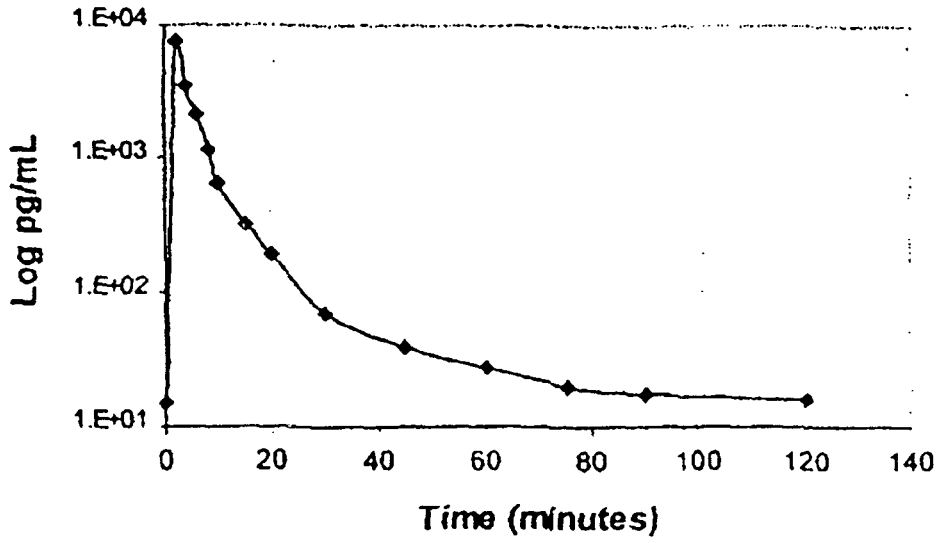

Fig. 1 - Study CRC99-10: Mean Human Secretin Plasma Concentrations

- As shown in the June 27, 2000 review by Dr. Roy, the PK profile for sPS was very similar to that depicted in Fig. 1 for sHS.

- The comparative PK information is summarized in **Table 2**.

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[5] Sampling time for PK and PD parameters were adequate. A radioimmunoassay method was used which employs rabbit antisera, XAD-2 resin for rapid extraction of secretin from plasma, ^{125}I labeled secretin, .

The precision and accuracy were not tested for this assay. The following data were provided based on repeated assay of human plasma sample containing endogenous secretin.

Limit of quantitation:
Intra-assay coefficient of variation: <18%
Inter-assay coefficient of variation: 18%

TABLE 2

Study CRC99-10: Comparative PK profile

PARAMETERS	sHS	sPS
Clearance (ml/min)	580.9 ± 51.3	487.2 ± 136.3
V_d (ml)	2715 ± 2.3	1938.2 ± 579.2
α-$T_{1/2}$ (min)	3.26 ± 0.28	2.74 ± 0.32
β-$T_{1/2}$ (min)	45.0	27.4

Results of PD Evaluations (Fig. 2)

Although the comments provided are for results with sHS, they also apply to sPS (Fig. on page 6 of Dr. Roy's review, not reproduced here).

- **sHS and sPS** had minimal effects on **serum gastrin concentrations** in normal volunteers. These results are as expected.
- For serum gastrin concentrations, the maximum increase from baseline in an individual was 32 pg/ml (63 to 95 pg/ml at 4 min) for sHS and 24 pg/ml (34 to 58 pg/ml at 2 min) for sPS.
- A **threshold increase of 110 pg/ml** is used as the diagnostic paradigm for gastrinoma
- Serum gastrin concentrations returned to near baseline by 15 min in most subjects and by 30 min in all.
- The above results are as expected in normal subjects.
- There were no clinical AEs reported for sHS.

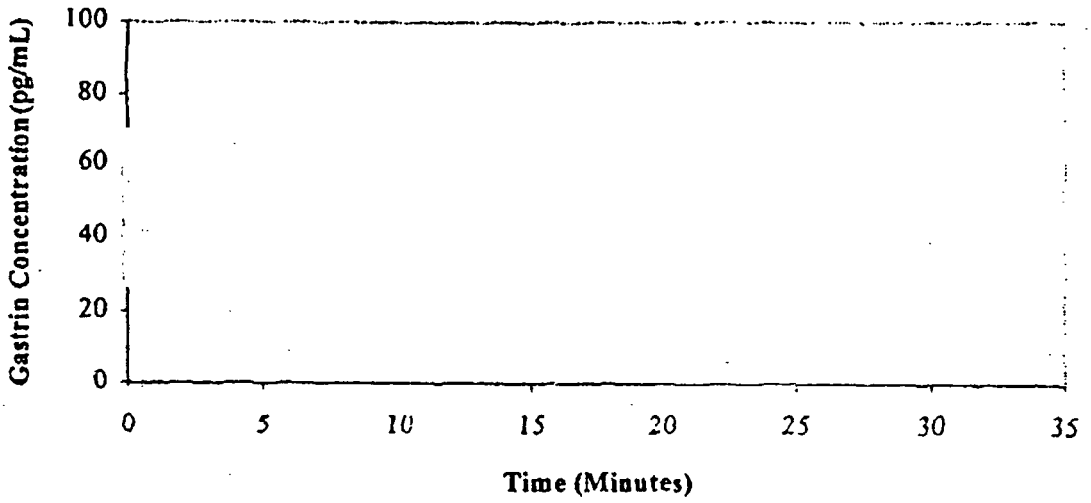

Fig. 2. - Study CRC99-10: PD Data for Synthetic Human Secretin Gastrin Concentrations in Plasma

Other "Issues"

- Fasting plasma concentrations of secretin were elevated and half-life disappearances were prolonged in patients with chronic renal failure. Half-life was approximately doubled from a mean of 2.39 min to 5.95 min in chronic renal failure. The MTL believes that no dose adjustment is necessary in renally impaired patients because a) sHS is safe and b) doubling the half-life of sHS in these patients may - if anything - increase the possibility of eliciting a positive test response. **This is not an issue.**

- L-Cysteine HCl is included in the product [redacted] The sponsor submitted results of a study, which showed negligible loss of synthetic human secretin during the 60-min interval storage in syringes.

  Although the L-Cysteine matter is brought up for completion, this is not an issue because the amount of this essential amino acid injected with sHS is <2 mg, far lower than the 20 mg being injected with sPS (**not an issue either**).

IV. SUMMARY REVIEW OF EFFICACY

A. Parameters of Evaluation

For the SST, the parameters of evaluation are PD results following I.V. injection of the hormone. Changes in signs and symptoms of disease are not evaluated.

1. Diagnosis of Pancreatic Exocrine Dysfunction

A single dose of sHS (0.2 μg/Kg B_{wt}) is administered in a 1-min bolus intravenous injection. The parameters of evaluation include measurements of a) volume; b) bicarbonate concentration (<80 mEq/L in each 15-min aliquot is indicative of pancreatic dysfunction) and c) total bicarbonate output (mEq/L) for the 60-min sample.

2. Diagnosis of gastrinoma

A single dose of sHS (0.4 μg/Kg B_{wt}) is administered in a 1-min bolus I.V. injection. Serum gastrin concentration (RIA) is measured at 0, 1, 2, 5, 10, 15 and 30 min post-secretin injection. Positive diagnosis of gastrinoma is based on >110 pg/ml increase over basal levels in serum gastrin concentration post sHS injection. Interpretation of results ought to be individualized.

The Zollinger-Ellison syndrome is characterized by gastric hypersecretion (manifested as severe dyspeptic symptoms and diarrhea), fulmunating atypical peptic ulceration (duodenal and gastric ulcers and GERD) and pancreatic islet cell hyperplasia. When the SST is done for the first time in a patient in whom Z-E is suspected, the serum gastrin concentrations are interpreted as follows: **normal**, up to 125 pg/ml; **gray zone**, over 125, up to 500 pg/ml [in this instance, gastric acid secretion tests are helpful since in the Z-E patient, maximal acid output (MAO) is >15 mEq/h]; serum gastrin concentrations >500 pg/ml are diagnostic of Z-E. But to catch naive Z-E patients is extremely hard because these patients are quickly referred to specialized centers around the country where they undergo gastric acid secretion tests and are enrolled in antisecretory drug testing. The >110 pg/ml increase over basal level in serum gastrin concentration rule is - clinically - not very useful in a patient in whom the baseline serum gastrin concentrations are already very high because in such patients, the suspicion of Z-E has already been confirmed. However, in practice, the accepted paradigm for diagnosis of gastrinoma after the SST is an increase in serum gastrin concentration of >110 pg/ml within 5 min. of the over 1 min I.V. bolus injection (in this case at the dose of 0.4 μg/Kg) and this is the parameter of evaluation used in the sHS diagnosis of gastrinoma trials.

An illustration of the results of the secretin provocative test in Z-E patients is given in **Fig. 33**, taken from Dr. Gallo-Torres original review of NDA 19-810 (omeprazole). As seen in this Figure, in patients with gastrinoma, secretin usually produces a rapid increase in serum gastrin concentration. Rapid intravenous infusion of secretin, 2 units/Kg, leads to an increase over basal of more than 100 pg/ml in more than 90% of gastrinoma patients. The size of the response is related to the basal gastrin level, but as already aluded, the test is most useful in patients with gastrin concentrations less than 1000 pg/ml. Peak responses occur between 2 and 10 min. after injection and may disappear by 30 min. False positives are rare but have been reported in occasional patients with atrophic gastritis and after vagotomy. Therefore a positive test alone should not be used to diagnose gastrinoma without also measurement of gastric acid secretion. Use of impure secretin preparations, such as Boots, can cause false positives if the radioimmunoassay used to measure gastrin also measures cholecystokinin that contaminates such preparations. In the case illustrated in Fig. 33 the test for gastrinoma is **positive** because the increment in serum gastrin concentration over baseline was >200 pg/ml, which is higher than the conventional >110 pg/ml increase over baseline accepted paradigm for diagnosis of gastrinoma.

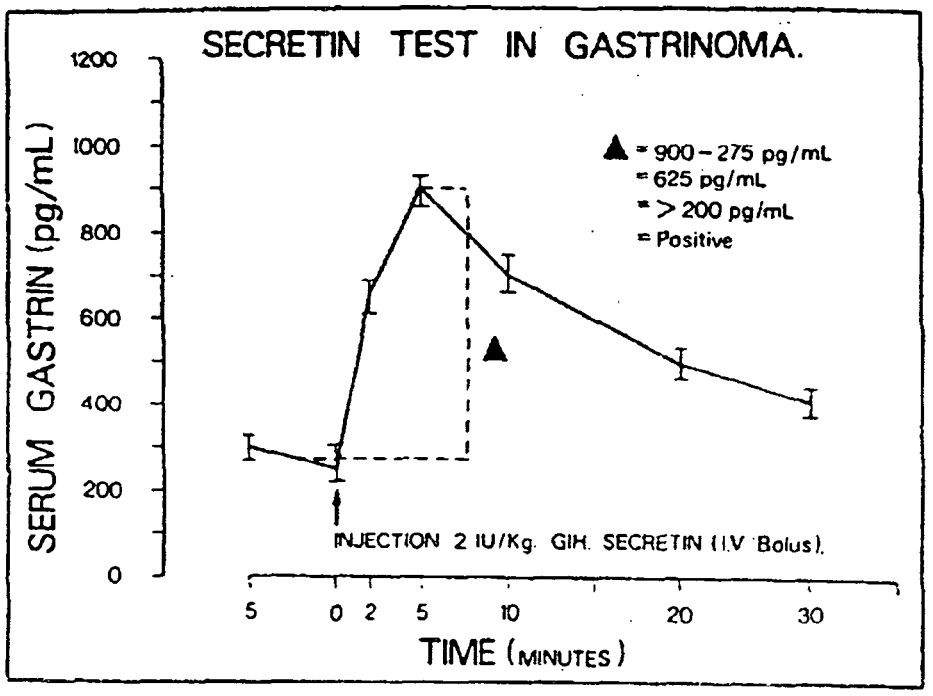

Fig. 33 *Results of a typical positive secretin (bolus) test in a patient with gastrinoma.*
▲ = Increment post secretin
Bars = Standard deviation of within assay variation.

3. Facilitation of pancreatic duct cannulation of the minor papilla during ERCP in patients with pancreas divisum

ERCP means **E**ndoscopic; **R**etrograde [contrast dye is injected into the pancreatic ducts against the natural flow of biliary and pancreatic secretion]; **C**holangio [fluroscopy and radiography of the biliary tree are done]; and **P**ancreatography [fluoroscopy and radiography of the pancreatic ductal system are obtained]. The procedure is done in many patients including those in whom the diagnosis of conditions such as chronic pancreatitis, pancreatic carcinoma, or gastrinoma **is suspected**. ERCP is also done in patients with pancreas divisum (bifid or divided pancreas). In some instances during ERCP, identification of the pancreatic duct in the ancillary papilla is very difficult if not impossible without SST. The patient is given sHS (0.2 μg/Kg B_{wt}). The cannulation is expected to be facilitated because the opening of this orifice becomes easy to identify by the visible outpour (often times a squirting) of pancreatic juice for several minutes. This is enough for the endoscopist to reset the instrument and with a better angle approach accomplish successful cannulation of either papilla. The endpoint of efficacy is the proportion of patients in whom the SST helped localize the pancreatic duct opening resulting in successful ERCP cannulation. Obviously, this endpoint does not only depend on the pharmacological effect of the injected secretin, but also on the dexterity of the endoscopist.

It is important to mention that administration of secretin to facilitate cannulation during ERCP has been common practice for the last 20 years. The sponsor first requested this indication for **sPS** (NDA 21-136). Their submission included a letter[6] from [redacted] and one of the leading authorities in ERCP. After review of these materials by Dr. L. Goldkind and conversations between ChiRhoClin and FDA, it was agreed that to obtain approval and labeling of sHS for this indication, a formal trial to specifically answer this question was needed. This was to be a randomized, double-blind, placebo-controlled study in 10 patients in whom successful cannulation of the accessory pancreatic duct would be accomplished.

B. Basis for and Recommendations for Regulatory Action

NOTE: In this section, only highlights of results are given. Details of study design and execution are found in the corresponding sections of Dr. M. Barreiro's review of NDA 21-156 (November 27, 2001).

1. Diagnosis of Pancreatic Exocrine Dysfunction

In support of this indication, the sponsor submitted results of studies **CRC 98-2** [randomized, crossover comparison of sHS to sPS in 12 patients with proven diagnosis of chronic pancreatitis (CP) by a previous SST] and **CRC 99-9** (randomized, crossover comparison of sHS to sPS and bPS in patients with a diagnosis of CP).

In study 98-2 (Tables 2 and 3 of the MOR), both sHS and sPS produced mean values for pancreatic juice volume and bicarbonate concentration at each 15 min. sampling period and for

---

[6] Excerpt of August 10, 1999 letter from [redacted]
RE: Use of secretin during ERCP

Dear Dr. Fein:

You asked me to provide some more documentation about the use of intravenous injections of secretin preparations during ERCP examinations.

For at least 20 years I have used secretin routinely in selected cases (perhaps 5% of all cases) for several indications. The commonest initially was for the collection of pure pancreatic juice secretions after cannulating the pancreatic duct, for biochemical analyses. Nowadays we do not do that very often, but it is still useful to very specific cases. The second indication [redacted] This remains useful, although often we replace that examination (or compliment it) with [redacted]

Our biggest current usage is to help identify the orifice of the pancreatic duct when this is not obvious endoscopically. Almost always this occurs in patients with the congenital anomaly of pancreas divisum, which occurs in 5-8% of the population, at least in western countries. Attached you will find a series of color photographs, illustrating this phenomenon. Image 6 shows the catheter in the main papilla of Vater (actually in the bile duct). Frame I shows the area of the accessory papilla, the papilla itself is not visible. Frames 2, 3, and 4 show the open accessory papilla 2, 3, and 4 minutes after an intravenous injection of secretin (50 units). This injection allowed us to place a catheter deep into the accessory orifice for the diagnosis and therapy.

I do not believe that anyone has done a very specific scientific study demonstrating the value of secretin in this context, however, it is in routine use in many centers. I enclose some comments about its use from standard textbooks, including my own.

the entire 60-min. The MOR concluded that, despite variability of results within patients and in between patients, both synthetic secretin products produced similar results during the SST, thus meeting the efficacy criteria of concordance between sHS and sPS. The drug was well tolerated by all 12 patients.

In study 99-9 (Tables 4 and 5 of the MOR) all six participant patients tested positive for CP (HCO_3 concentration <80 mEq/L in each aliquot) after stimulation with sHS, sPS and bPS in a crossover fashion. The MOR concludes that, in essence, sHS, sPS and bPS produce a similar pharmacological effect and are well tolerated.

- Based on the results of studies 98-2 and 99-9, Dr. Barreiro supports the approval of sHS as a diagnostic tool in the evaluation of pancreatic exocrine dysfunction.

- **The MTL agrees with this recommendation.**

    1) The data on sHS **stand on its own**. In both 98-2 (Fig. 3) and 99-9 (Fig. 4) the bicarbonate concentration values following SST, although higher than at the 0 time baseline are all lower than 70 mEq/L which in turn is lower than the conventional 80 mEq/L denoting pancreatic exocrine dysfunction. Similarly, the pancreatic secretion volume (<80 ml in all instances) was low both in study 98-2 (Fig. 5) and 99-9 (Fig. 6).

    2) For bicarbonate concentration and pancreatic secretion volume, the effects of sHS are nearly identical to those seen with sPS (Fig. 3 and 5) and not too dissimilar to those seen with bPS (Fig. 4 and 6), although, as expected, the variations in pancreatic secretion volume are greater than those in bicarbonate concentration.

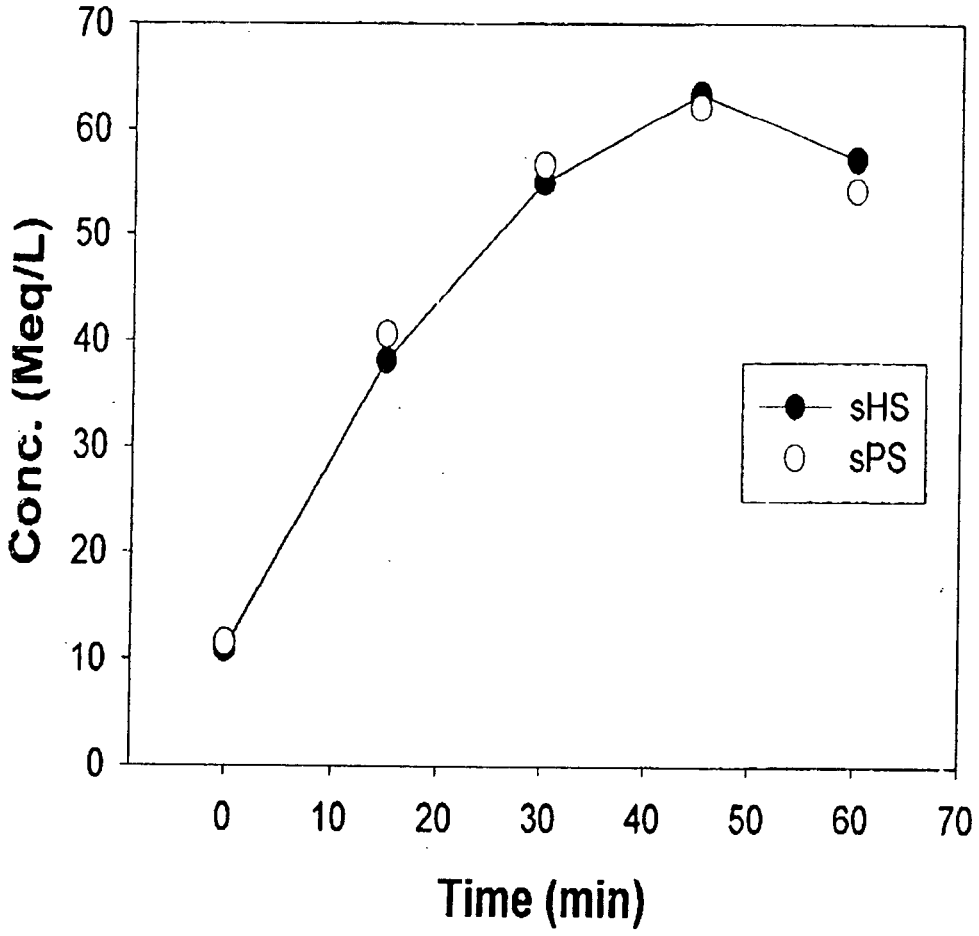

Fig. 3. - Study 98-2: Bicarbonate Concentration
(Depicted are mean values)

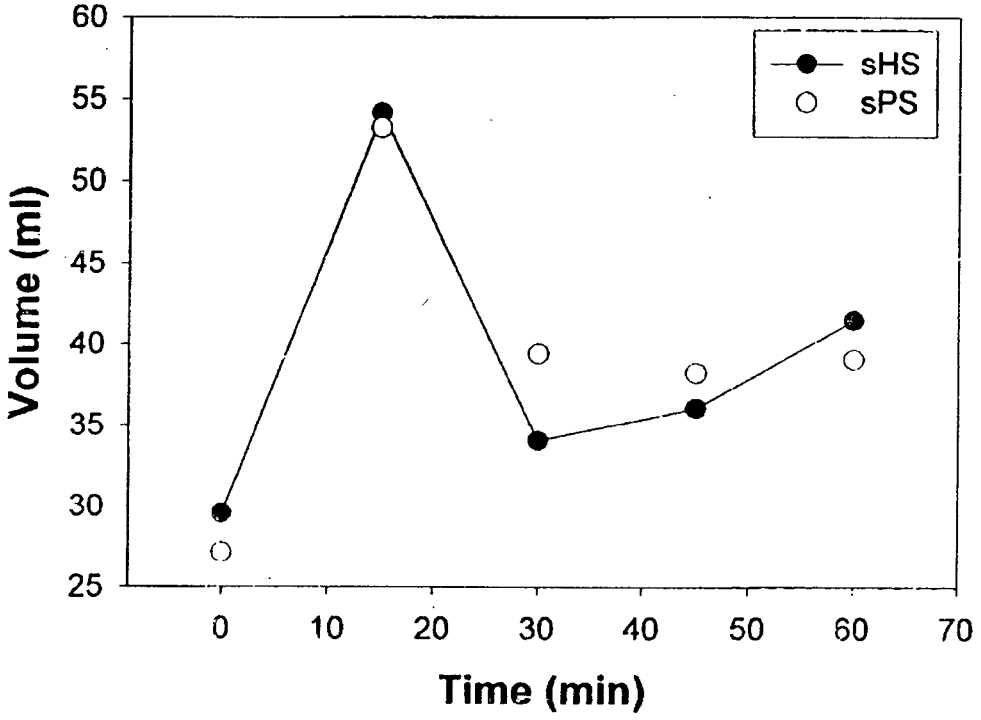

Fig. 4. - Study 98-2: Bicarbonate Concentration
(Depicted are Mean Values)

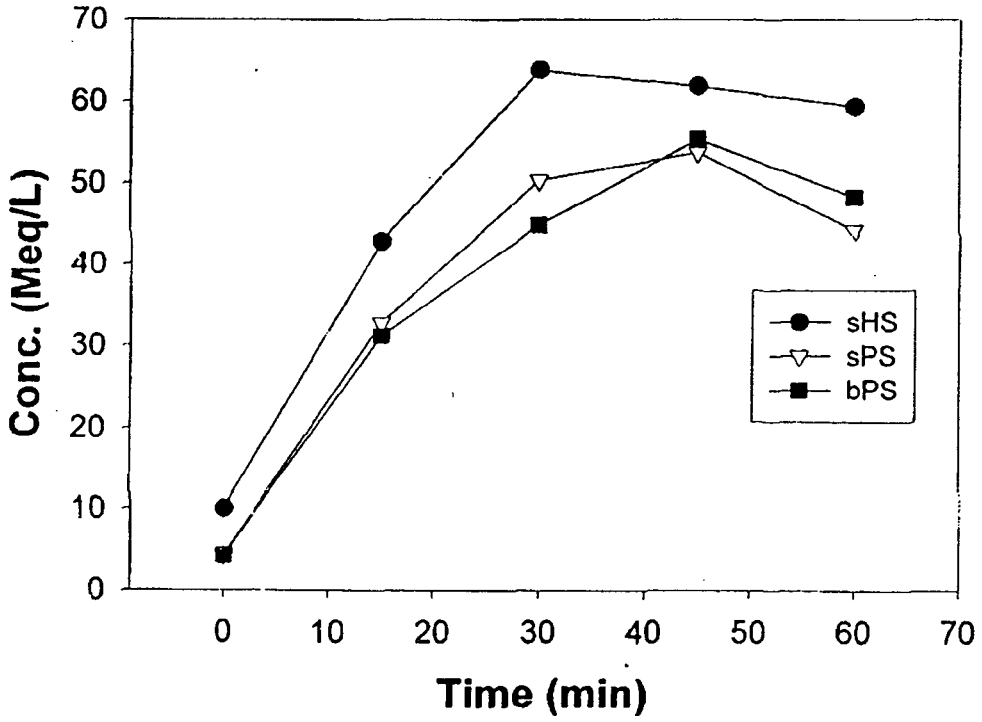

Fig. 5. - Study 99-9: Bicarbonate Concentration
(Depicted are mean values)

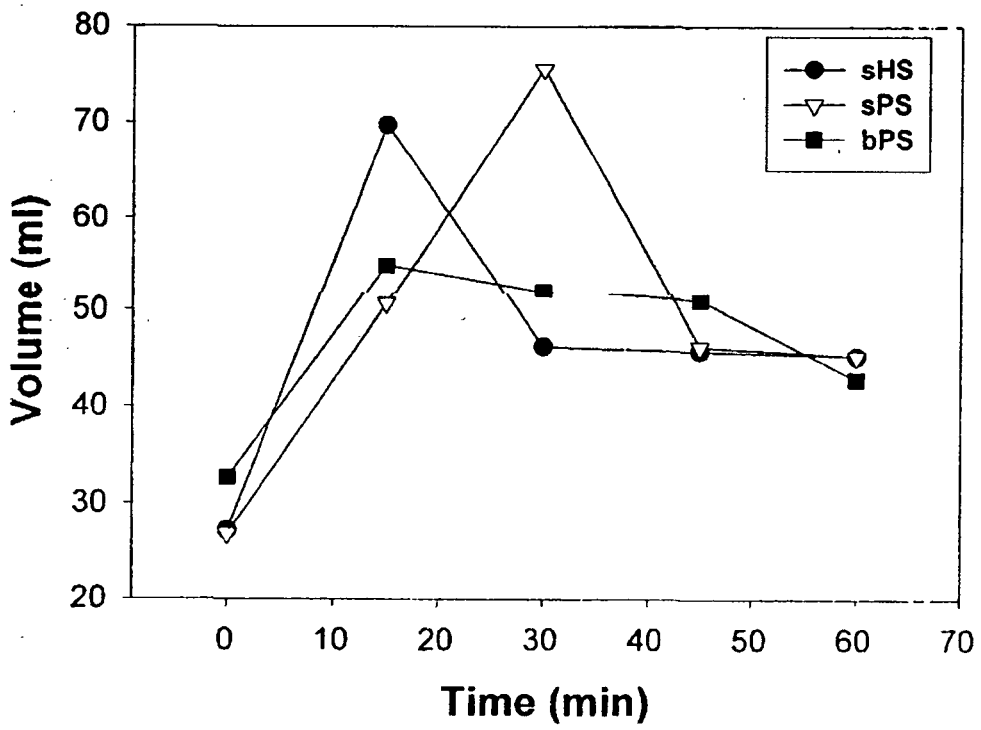

Fig. 6. - Study 99-9: Volume of Pancreatic Secretion (Depicted are mean values)

2. Diagnosis of Gastrinoma

In support of this indication, the sponsor submitted results of studies CRC 99-8 (randomized, controlled crossover comparing the effects of sHS to those of sPS and bPS) and expected to pool these data with those of CRC 97-2 (randomized, single blind, active control, two-way crossover comparison of the effects of sHS to those of sPS) in gastrinoma patients.

In study 99-8, the sequence of administration of the three secretin products was randomized to balance any theoretical period effects. Positive diagnosis of gastrinoma was based on >110 pg/ml increase over baseline in serum gastrin concentrations post-secretin injection. Five patients completed the 3-way crossover. As seen in Table 6 of the MOR by Dr. Barreiro, each SST produced increases in serum gastrin concentration within 5 min., which far exceeded the 110 pg/ml used as a diagnostic paradigm for gastrinoma.

The 3 patients in study CRC 97-2 never received sHS.

In summary, as pointed out by Dr. Barreiro, there was diagnostic agreement for sHS, sPS and bPS in 6 of 6 patients with gastrinoma. In the 3-way comparison of these 6 patients, there was no statistically significant difference for any of the comparisons except for sHS vs sPS at the 15 min. time of observation (p=0.0274). In addition, the reviewer cites results of study CRC 99-10

involving SST in 12 normal volunteers. In these subjects, the serum gastrin concentration responses to both sHS and sPS were **negative for gastrinoma.**

- In general sHS did not produce AEs of concern in gastrinoma patients, although some minor transient AEs noted in Dr. Goldkind's review of NDA 21-209 (June 16, 2000) should, conservatively, be incorporated in the labeling.

- Based on the data submitted by the sponsor, in NDA 21-256, Dr. Barreiro recommends that sHS be approved for the diagnosis of suspected gastrinoma tumors.

- **The MTL agrees with this recommendation.**

  1) The data on sHS **stand on its own**. As shown in Table 6 of Dr. Barreiro's MOR (November 27, 2001), the SST with sHS produced increases in serum gastrin concentration with 5 min. that were higher than the 110 pg/ml threshold used as the diagnostic paradigm for gastrinoma.

  2) In 6 of 6 patients in whom the diagnosis of gastrinoma had been proven and who underwent 3-way crossover comparisons, there was no statistically significant differences for any of the comparisons (sHS vs sPS; sHS vs bPS; and sPS vs bPS) . The exception was the comparison at 15 min. between sHS vs sPS. But this sporadic finding does not negate the **similitude of effects** between sHS and bPS (biological secretin, a diagnostic tool approved for this indication). There was also close similarity between the effect of sHS and sPS (a form of secretin found **approvable** for this indication by Dr. L. Goldkind).

  3) Furthermore, in study CRC 99-10 in healthy volunteers the serum gastrin concentration response to sHS (as well as sPS) was negative for gastrinoma (minor increases, none higher than 110 pg/ml).

3. Facilitation of Pancreatic Duct Cannulation of the Minor Papilla During ERCP in Patients With Pancreas Divisum

In support of this indication, the sponsor submitted results of studies CRC 98-4 (open-label, non-comparative, single arm, multicenter) and CRC 98-4 Amendment (randomized, double-blind, placebo-controlled, crossover, multicenter) in patients with pancreas divisum in whom facilitation of the minor pancreatic duct cannulation was assessed.

In study 98-4, a total of 297 patients were enrolled at 11 medical centers. Results are included in Table 6 of the MOR by Dr. Barreiro. Of the 297, 32 were for cannulation of the **minor papilla** in patients with pancreas divisum. Of these 32, 27 (84%) had successful cannulation of the minor papilla after sHS administration; in 5 patients, the cannulation was unsuccessful and this reflected in the observational statistical analysis summarized in Table 8 of the MOR. This Table is reproduced here (Table 3).

TABLE 3
Study 98-4

Was sHS Useful During Procedure with the Presence of Pancreas Divisum?

OUTCOME	Frequency	Percent	Cumulative Frequency	Cumulative Percent
SUCCESSFUL	27	84.4	27	84.4
UNSUCCESSFUL	5	15.6	32	100.0
Chi-Square Test for Equal Proportions Statistic = 15.125 DF = 1 Prob = 0.001				
This Table corresponds to Table 8 in Dr. M. Barreiro's MOR of November 20, 2001.				

In study 98-4 Amendment, the sequence of receiving sHS or placebo (PL) was determined by a randomization code provided to the research pharmacist at each participating center. Blinded syringes of test medication were provided to study personnel (Appendix B of Dr. Barreiro's MOR). By protocol, an arbitrary 5-min. limit was allowed to attempt cannulation.

- Only 3/27 patients were able to have their minor ducts cannulated prior to randomization and test medication administration.

- Only 2 of the remaining 24 could be successfully cannulated with PL, which was administered as the second treatment after sHS was given.

- 16 of the 24 patients randomized had successful cannulation of the minor duct, 9 after sHS was administered first and 7 after sHS was given second (after PL failed).

- 15 patients received PL.[7] In 12 of these 15, PL was given first and in all 12 cases **cannulation failed.**

- 3 patients received PL second after sHS failed; in 2 of these, cannulation was successful. The MO suspects that this may be a carrying over effect of the sHS preceding PL administration.

- In summary, cannulation time was statistically significantly longer for no treatment and PL than for sHS (Table 11 of the MOR by Dr. Barreiro).

[7] As explained by Dr. Barreiro, the reason only approximately one-half of the enrolled patients received PL was that in the 50% of cases in which sHS was given first (according to randomization), it **almost always worked,** obviating the need to give the second blinded treatment.

- Manual review of the CRFs by the MO failed to reveal any AEs reported during this trial.

- A number of methodological flaws in both protocols were identified by the MOR. These include:

  - An excessive dose of sHS (0.2 μg/Kg B_{wt}) producing pancreatic stimulation for a 60-min. period, far longer than the **needed** production of pancreatic juice for a few seconds, minutes at most.

  - This maximal dose of sHS used, because of the same reasons, negates any randomization or blindness in CRC 98-4 Amendment. The 5-min. period allocated to cannulate the papilla after injection, after which the second injection is given is void, if the first injection was sHS. The patient will continue to produce pancreatic juice for another 55 min., when the endoscopist, according to the protocol, would be working under "the effect" of PL. The MO concluded that, as a consequence of this, all statistical analyses of CRC 98-4 Amendment will have to be redone.

  - Lack of recording prior and concomitant therapy in the CRF. This is a flaw because these medications have effects on smooth muscle. As the MO points out, depending on the doses used, these medications are known to affect the results of manometric studies performed in cases of suspected sphincter of Oddi dysfunction (SOD).

  - Failure of data reporting.

- Because of the reasons listed above, the MOR considers that the sponsor **has failed to demonstrate** that sHS facilitates cannulation of the minor papilla in patients with pancreas divisum.

- **The MTL agrees with the MOR's recommendation.**

  1) In Study 98-4, the proportion of pancreatic divisum patients in whom successful cannulation of the minor papilla was accomplished (84%) confirms empirical observations. Successful cannulation of the Vaterian ampula in 71% of the patients further suggests that sHS may be useful in facilitating these cannulations.

  2) However, the many flaws in the design and execution of study 98-4 Amendment, ennumerated in detail in Dr. Barreiro's MOR, including lack of adequate controls, not accounting for potentially confounding concomitant medications and the failure to use procedures designed to minimize bias, precludes approval of sHS for this indication.

V. SUMMARY REVIEW OF SAFETY (TABLE 4)

As pointed out by Dr. Barreiro in Section V of his MOR, a total of **686** patients (502 in clinical trials and 184 in autism studies) were exposed to intravenously administration secretin.

- No deaths have been reported in association with sHS administration.
- Except as noted below, there were neither serious nor severe AEs reported in association with sHS administration.
- In 3 of the 5 clinical trials in NDA 21-256, comprising a total of 42 patients, no AEs were reported, except as shown below. In the other 2, comprising a total of 38 patients, the following AEs, mostly mild, were seen:

STUDY	AE
CRC 99-8 (gastrinoma) [n=6]	• Mild tingling of hands (n=1) • Moderate stomach distress (n=1)
CRC 98-4 (Facilitation of cannulation) [n=32]	• Mild acute pancreatitis (n=1) (Pt. on multiple I.V. restarts; discharge delayed by 1 day = SAE) • mild vomiting (n=1)
Total number of patients exposed = 80	

- The total number of patients exposed per dose and indication was depicted in Table 15 of Dr. Barreiro's review. This information is summarized in Table 4.

TABLE 4

sHS: Number of Patients Exposed per Dose and Indication

DIAGNOSTIC TEST			AUTISM		
sHS	sPS	bPS	sHS (µg/Kg)		PL
			0.4	0.2	
[n=502]	[n=27]	[n=15]	[n=173]	[n=11]	[n=145]

Included are data from studies CRC 98-3B, 98-3B-2, 99-4, 99-5, 99-6, 98-2, 98-4, 98-4 Amendment, 99-8, 99-9, 99-10 and 2000-1.

	Clinical Trials	Autism	Total
Number of Patients receiving a dose of 0.2 µg/Kg B_{wt}	429	11	440
Number of Patients receiving a dose of 0.4 µg/Kg/ B_{wt}	73	173	246
		G RAND TOTAL	**686**

- 57 of the 173 autism patients receiving 0.4 μg/Kg B_{wt} experienced AEs. These included AEs related to the underlying condition, such as aggressive behavior, agitation, ear pain, fever, hyperactivity, and sleep disturbance, in addition to congestion, diarrhea (loose stools) and rash (Table 15 in MOR by Dr. Barreiro).

- The available information indicates that sHS is safe and apparently well tolerated.

- In order to test for drugs ensistivity, all 686 patients administered sHS were first injected intravenously with 0.2 μg (=0.1 ml) of secretin. There were no untoward reactions in any of the 686 patients exposed. This precautionary measure should be included in the labeling.

VI. MTL'S RECOMMENDATIONS FOR REGULATORY ACTION

1. The indication diagnosis of pancreatic exocrine dysfunction should be **approved**.

   This recommendation is based on results of studies CRC 98-2 and CRC 99-9. The recommended dose is 0.2 μg/Kg B_{wt} I.V. bolus over 1 min.

2. The indication diagnosis of gastrinoma should be **approved**.

   This recommendation is based on results of Study CRC 99-8. The recommended dose is 0.4 μg/Kg B_{wt} I.V. bolus over 1 min.

3. The indication facilitation of j — papilla during ERCP — is **approvable.**

   This recommendation is based on results of studies CRC 98-4 and CRC 98-4 Amendment. Although the 98-4 data confirm emprical observations, the open label nature of the trial was not designed to minimize bias. On the other hand, study 98-4 Amendment did not use proper controls, did not account for potentially confounding concomitant medications and was, all in all, an inadequately designed and not well executed trial.

For this indication to be **approved**, well-designed/well-executed evaluations are needed. The MTL recommends preparation of a protocol with the input of 2 to 3 top experts in this field, Issues to be considered in the design of the trial include: dose response (for this indication only a fraction of the dose used for other indications is needed), blinding, randomization and sequence of administration of test medications and comparator, adequate control, and primary (and secondary) endpoints of efficacy.

It is understood that the recommendation for approval of sHS for its use as a diagnostic test for indications 1. and 2. remains subject to resolution of the outstanding CMC deficiencies in NDA 21-156. With regard to purity, however, it is important to mention that the brand of secretin marketed for more than 20 years, and considered to be safe and effective, identified as **bPS** in this review, was initially manufactured by Kabi. This secretin, later produced and marketed by

Ferring is known to have —— % **impurities**. These impurities, suspected to have some biological activity, are yet to be characterized. But bPS is considered to be **safe and effective**.

VII. LABELING

The labeling revisions proposed by Dr. M. Barreiro in his November 27, 2001 MOR of NDA 21-156 are all acceptable.

Pediatric use

[ ]

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader, HFD-180
Gastrointestinal Drugs

cc:
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/s/

Hugo Gallo Torres
11/28/01 09:43:44 AM
MEDICAL OFFICER

This is the MTL's secondary review of [redacted] Synthetic Human Secretin, NDA 21-256. Approval of a) diagnosis use in pancreatic exocrine dysfunction and b) diagnosis of gastrinoma, is recommended. The facilitat. [redacted] indication is approvable.

DIVISION OF GASTROINTESTINAL AND COAGULATION DRMCG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 21-256

DATE SUBMITTED: March 16, 2000

REFUSED TO FILE: May 11, 2000

DATE RESUBMITTED: June 15, 2001

GENERIC NAME: SYNTHETIC HUMAN SECRETIN (sHS)

PROPOSED TRADE NAME: --

SPONSOR: ChiRhoClin

PHARMACOLOGICAL CATEGORY: Polypeptide Secretagogue

INDICATIONS FILED: 1) Diagnosis of Pancreatic Exocrine
2) Diagnosis of Gastrinoma
3) Facilitation of
Papilla during ERCP

MATERIAL REVIEWED: See Page 7

MEDICAL OFFICER: M. A. Barreiro, MD, MSc

Table of Contents

	Page
I – Table of Contents	2
II – Executive Summary	3
• Summary of Clinical Background	3
• sHS in the Diagnosis of Exocrine Pancreatic	4
• sHS in the Diagnosis of Gastrinoma	5
• sHS in the	6
• Recommendations for Regulatory Action	7
III – Clinical Review	7
A. Overall Data	7
Secretin	8
B. Pancreatic Exocrine Dysfunction	8
Study CRC 98-2	9
Study CRC 99-9	10
C. Diagnosis of Gatrinoma	11
Study CRC 99-8	12
Study CRC 97-2	12
D. Facilitation of Pancreatic Duct Cannulation of the Minor Papilla During ERCP in Patients with Pancreas Divisum	14
Study 98-4	15
Study 98-4 Amendment	16
IV – Integrated Review of Safety	18
A. Methods	18
B. Clinical Trial Safety	19
C. Sponsor's Integrated Summary of Safety	19
V – Special Concerns	20
• Informed Consent and IRB Approval	20
• FD 1572 Form and Curriculum Vitae	20
• Financial Disclosures	20
• Pregnancy Use Information	20
• Pediatric studies	20
VI – Recommendations for Regulatory Action	21
VII. Tables	22 - 35

II - Executive Summary

ChiRhoClin, Inc., the sponsor of sHS, has submitted an NDA requesting approval for the following indications:

1) Diagnosis of Pancreatic Exocrine —
2) Diagnosis of Gastrinoma
3)

This reviewer considers that there is sufficient **clinical information** to grant approval of the first two indications (Diagnosis of Pancreatic Exocrine — and Gastrinoma) and considers approvable the third — providing additional information is submitted.

Summary of Clinical Background

In 1902 Bayliss and Starling demonstrated that an extract of duodenal mucosa of pigs injected into dogs would stimulate pancreatic secretion. This experiment created the concept of "hormone", and was also the first demonstration of the structural homology of the hormone responsible for that action, secretin, across animal species. Since then, secretin has been isolated, purified and, lately, synthesized. Secretin of porcine origin has been used for the study of exocrine pancreatic function for over 40 years. The Secretin Stimulation Test (SST) has become the gold standard for the diagnosis of Chronic Pancreatitis (CP). Many uses have been attempted for the SST. The one that has endured is the diagnosis of CP, mostly alcohol-induced in the Western civilization. Better understanding of pancreatic disease and technological advance have reduced the number of patients with CP in which SST is needed to effect a change in the patient's management plan. Other indications have been found, however. The diagnosis of gastrinoma (Zollinger Ellison Syndrome) and to facilitate identification and cannulation of the Vaterian ampula or the accessory pancreas (Santorini's duct) during ERCP, are two examples.

Biological porcine secretin (bPS) was made available in the US by different laboratories through the years: Boots, Kabi and lately, Ferring. All these preparations included a — — % of impurities, some of which are suspected to be biologically active. For example, injection of bPS to healthy volunteers would produce a slight elevation of gastrin that never reaches diagnostic levels of gastrinoma. In a few cases, a mild, transient drop in blood pressure has been observed . These effects are thought to be due, at least partly, to biologically active compounds present in bPS, rather than secretin-specific effects. As it happens with other biological compounds, the possibility of contamination by animal pathogens is always present

Because of these reasons, the industry has produced synthetic compounds, that, theoretically, would be measured more accurately (in fractions of a gram rather than biological units) and would be devoid of chemical or bacteriological contaminants, improving the safety profile

Synthetic Human Secretin (sHS) tries to meet those needs. sHS has a potency of no less than 5433 clinical units (CU) per mg peptide. sHS contains 16 mcg of purified synthetic human secretin. When reconstituted in 8.0 mL of Sodium Chloride Injection USP, each mL of solution contains 2 mcg of sHS for intravenous use. The pH of the reconstituted solution has a range of 3 to 6.5.

The primary action of secretin is to increase the volume and bicarbonate content of pancreatic juice.

Synthetic human secretin (sHS), synthetic porcine secretin (sPS) and biologically derived porcine secretin (bPS) have been evaluated and compared in the validated cat bioassay used for release of bPS. sHS and sPS were found to have equivalent pharmacological activity in terms of stimulating the exocrine pancreas to secrete juice and bicarbonate. The potency correlation with bPS for both sHS and sPS was 0.2 μg (sHS or sPS) equaled 1 CU (bPS). The biologically activity of sHS and sPS was approximately 5000 CU per as opposed to 3000 CU per mg of bPS, indicative of —— purity of sHS and sPS.

Secretin administered intravenously stimulates gastrin release in patients with gastrinoma, whereas no or very small changes occur in normals. This gastrin response constitutes the basis for the use of secretin as a provocative test in the patients in whom gastrinoma is suspected..

sHS in the Diagnosis of Exocrine Pancreatic —— This indication is supported by two studies:

1) Study CRC 98-2. This is a randomized, crossover study evaluating sPS and sHS for the assessment of exocrine pancreatic function in patients with a diagnosis of CP. Twelve patients with CP previously diagnosed by SST with bPS, received single doses of sHS and sPS of 0.2 mcg/kg, both intravenously in bolus form over one minute. The primary endpoints were determination of pancreatic secretion volume and bicarbonate. Criteria for efficacy was concordance with sPS for CP.

   There was 100% agreement in the diagnostic results for the diagnosis of CP and determination of severity between sHS and sPS.

   There were no AEs in this study.

Comment This study involved a small number of patients. Despite variability of results within patients and between patients, this study demonstrates that both synthetic secretins produce similar results during SST, thus, meeting efficacy criteria of concordance between sHS and sPS. The drug was well tolerated by all patients.

2) Study CRC 99-9. This is a randomized, crossover study evaluating sHS, sPS and bPS for the assessment of exocrine pancreas function in patients with a diagnosis of CP. Four females and two males received a single dose of sHS and sPS of 0.2 mcg/kg, and bPS of 1 CU/kg intravenously over one minute. Each patient underwent three

SSTs separated by at least 24 hours . The pharmacological endpoints were pancreatic secretion volume and bicarbonate concentration. The criteria for efficacy evaluation was diagnostic concordance of sHS with bPS for CP.

All six patients tested positive for CP. There was 100% diagnostic agreement between the three drmcgs.

There were no AEs with the administration of sHS.

Comments. Due to the small number of patients the results should be interpreted as observational in nature. The results, however, all point to the fact that sHS produce an effect similar to that of bPS (a drug already in the market) and sPS (a drug considered approvable by the FDA during a recent review) as a diagnostic tool when evaluating exocrine pancreatic function. Further, sHS was well tolerated by all patients.

sHS in the Diagnosis of Gatrinoma. According to the sponsor this indication is supported by **two** studies, although in reality, the patients received sHS in only **one.**

1) Study CRC 99-8. This is a randomized, controlled, crossover study evaluating sHS, sPS and bPS for the diagnosis of gastrinoma. The dose of sHS and sPS was 0.4 mcg/kg, the dose of bPS was 2 CU/kg. Secretin was administered in bolus form over one minute. The tests were conducted at least 2.5 hours apart. Serum gastrin concentrations were determined at 0, 1, 2, 5, 10, 15 and 30 minutes post-secretin injection. Efficacy variable was a positive diagnosis of gastrinoma based on >110 pg/mL increase over basal levels in serum gastrin concentrations post-secretin injection. The primary efficacy variable was the diagnosis of gastrinoma in patients with documented diagnosis of gastrinoma. Two males and three females were enrolled in CRC 99-8 and completed the three way crossover. One patient couldn't complete the study the first trial because of poor venous access, but was re-enrolled later on and completed all three tests. One patient did not have tissue proven documentation of gastrinoma, but other chemical studies were supportive of the diagnosis. All six patients showed positive secretin stimulation tests. Each secretin test produced increases in serum gastrin concentration within five minutes, which far exceeded the 110 pg/mL used as diagnostic paradigm for gastrinoma. There was tingling of the hands, mild, in patient # 1, and stomach distress, moderate, in patient # 3. There were no hemodynamic changes observed.

2) Study CRC 97-2. Three patients with gastrinoma received bPS and sPS, but no sHS, the drmcg currently under review.

Comments In study CRC 99-8, on the gastrinoma indication, there was diagnostic agreement for sHS, sPS and bPS in six of six patients. There was a significant difference for the comparison between sHS and sPS at 15 minutes (p=0.0274). Of interest, in another study (CRC 99-10) involving 12 normal volunteers, serum gastrin responses were negative for gastrinoma with sPS and sHS.

Again, this is a study in a small number of patients. The performance of secretin tests 2.5 hours after each other was a concern. There are no data in the literature as to the time needed for the physiological recovery of the tumor. This fact did not seem to affect the efficacy or safety results.

sHS in the Facilitation — Papilla during ERCP — In support of this indication, the sponsor submitted results of two studies:

1) CRC 98-4. This is an open label, non-comparative, single arm, multicenter study for the routine clinical use of sHS as a diagnostic agent and to assist in pancreatic duct cannulation The patients received **sHS in the same doses used for SST in CP, that is, 0.2 mcg/kg**. The efficacy variable was the percentage of patients in which secretin helped localized the pancreatic duct opening resulting in successful ERCP cannulation

   Thirty-two patients received sHS for cannulation of the minor papilla in cases of pancreas divisum. Of those, 27 (84%) resulted in successful cannulation after the administration of sHS. Two patients registered AEs: patient # 24 complained of vomiting of mild severity that resolved spontaneously, possibly related to the drug; and patient # 25 registered two AEs: 1) multiple I.V. restarts due to poor veins and 2) mild acute pancreatitis, that prolonged the hospitalization for a day (Serious Adverse Event), resolved satisfactorily, considered unlikely due to the drug.

2) CRC 98-4 Amendment. This study came as a consequence of conversations between the sponsor and the Agency. It was agreed that in order to obtain formal approval and labeling for this indication a randomized, double-blind, placebo controlled, crossover study in 20 patients focused on cannulation of the accessory pancreatic duct would be necessary. The patients received **sHS in the same dose used for SST in CP, that is, 0.2 mcg/kg,** or placebo. The endoscopist supposedly would be blinded to the drug administered. The research pharmacist would dispense the drug following a randomization schedule. The endoscopist would administered the drug, try to cannulate for five minutes (as per protocol) and if unsuccesful would administer the second dose of drug, and try to cannulate for another five minutes.

Comments. In this reviewer's opinion this protocol has significant flaws that make the results invalid:

- The dose of sHS used was excessive. sHS 0.2 mcg/kg produces an output of pancreatic juice that lasts for at least 60 minutes and produces (according to CRC 2000-1) a mean of 260 mL. Secretin always stimulates the pancreas maximally. All it was needed for this study was a trace amount stimulating the pancreas for a few seconds or minutes.

- This maximal dose of sHS negates any randomiztion or blinding in CRC 98-4 Amendment.

- The drugs used during the ERCP procedure, many of which affect smooth muscle, were not listed. As a matter of fact, there was no space allocated in the CRF for that purpose, despite the fact that the sponsor claims that "prior and concomitant therapy will be recorded in the CRF..."

Recommendations for Regulatory Action. This reviewer recommends the following:

1) The proposed sHS is approved for the following indications:

- **Diagnosis of pancreatic exocrine —**
- **Diagnosis of gastrinoma**

2) The sponsor has failed to demonstrate that sHS facilitates — papilla. — The empirical evidence is that secretin is of help in identifying and cannulating the main and accessory papilli. An appropiate research protocol designed in collaboration with the experts in the field should be produced and executed if the sponsor wants approval of this indication.

3) Because diagnostic testing for exocrine pancreatic dysfunction and gastrinoma was performed in the past with purified porcine products containing a significant percentage of biologically active, uncharacterized impurities, studies should be planned to establish new cut-off points with sHS. In order to obtain a sufficiently large patient sample, the Agency should encourage multinational participation. A consensus-type of international conference could be organized jointly with the NIH, as a starting point.

4) The label should reflect the limitations of the data on which these approvals are based.

III - Clinical Review

A. Overall Data

The information was obtained from the Medical Reviews of Synthetic Porcine Secretin (sPS), NDA # 21-209, proposed indication: Gastrinoma, February 2000, NDA # 21-136, proposed indications: 1) For diagnostic use in pancreatic exocrine dysfunction and 2) Facilitation of pancreatic duct cannulation during ERCP, March 2000, all by Dr. L Goldkind. And the May 2000 review by Dr. S. Kress of NDA # 21-209, response to approvable letter dated May 16, 2000.
The information was also obtained from five clinical studies conducted by the sponsor, which are listed below:

- CRC 98-2. Evaluates sHS and sPS in crossover fashion in 12 patients (9 available for this review) with Chronic Pancreatitis (CP).

- CRC 99-8. Evaluated sHS, sPS and Biological Porcine Secretin (bPS) as diagnostic agents in patients with tissue proven gastrinoma (Z-E Syndrome) or Multiple Endocrine Neoplasia Type 1 (pituitary gland, pancreatic islets and parathyroid; MEN-1).

- CRC 99-9. A randomized, crossover study which evaluated sHS, sPS and bPS as diagnostic agents in patients with CP.

- CRC 98-4 an open label, clinical use of sPS as diagnostic agent for CP, pancreatic cancer and gastrinoma and to facilitate ERCP cannulation of the minor papilla in patients with pancreas divisum.

- CRC 98-4 Amendment. A placebo controlled, crossover study of sHS to facilitate cannulation of the minor duct in patients with pancreas divisum during ERCP.

These studies will be evaluated per indication and then compared with those used for the submission of sPS, a drug now considered approvable.

Secretin. This gastrointestinal peptide hormone was first extracted from porcine duodenum by Jorpes and Mutt in 1961. Secretin is released from duodenal mucosa by acidic contents and stimulates the production of bicarbonate rich pancreatic juice. Pharmacological uses of secretin have been investigated since purified product became available in the 1970s.

In 1981 the United States FDA approved secretin manufactured by Kabi. In 1989 Ferring assumed production and marketing, and it was this brand of secretin that has been used as a comparator in all the studies reviewed in this paper, under the abbreviation **bPS.**

Ferring secretin is known to have —— % impurities that have not been characterized, but are suspect to have some biological activity.

This reviewer called Ferring Pharmaceuticals Inc. (888-337-7464) and was informed that Ferring doesn't manufacture secretin since April of 1999. The rights were sold to Repligen Labs (877-737-5443) who informed this reviewer /

Apparently, at the time of this writing, there is no secretin available for diagnostic testing in the USA.

B. Pancreatic Exocrine Dysfunction.

In support of this indication, the sponsor submitted results of studies CRC 98-2 and CRC 99-9.

Study CRC 98-2. This is a randomized, crossover study evaluating sPS and sHS for the assessment of exocrine pancreas function in patients with a diagnosis of Chronic Pancreatitis (CP). A single dose of sPS (0.2 mcg/kg) and sHS (0.2 mcg/kg) administered both intravenously, in bolus form, to 12 patients with proven diagnosis of CP by a previous secretin stimulation test (SST) with bPS. Each patient underwent two SSTs 24 hours apart.

The primary endpoints were pancreatic secretion volume and bicarbonate. Four male and eight female patients, ages ranging from 27 years to 76 (average 59 years), with a diagnosis of CP documented by a prior SST with bPS and by clinical and laboratory analysis consistent with the diagnosis (Table 1). Female patients had to use appropriate contraception. All patients provided informed written consent.

The criteria for efficacy evaluation was the concordance with sPS for CP.

The criteria for pharmacological evaluation was pancreatic secretion volume and bicarbonate concentration, post administration of the test drug during a completed SST.

Efficacy results. The sponsor claims 100% agreement in the diagnostic results for the diagnosis of CP and determination of severity between sPS and sHS, that is, the same nine patients were diagnosed with CP and the same three patients were diagnosed with severe CP.

Pharmacological results. sPS and sHS produced mean values for pancreatic juice volume and bicarbonate concentration at each 15 minute sampling period and for the entire 60 minute sampling period "which were statistically equivalent and numerically almost identical" (see Tables 2, 3).

Safety results. There were no adverse events in this study.

Reviewer comments. The number of cases included in this study is small: nine to document the diagnosis of CP and only three to prove its use in determining severity of the disease. These data can not be pooled with that of other studies because of methodological reasons: for example, study 98-1, did not use sHP and was used to support this same indication for sPS in a different time frame (1999). Study CRC 99-9 used bPS in addition to sPS and sHS, and data from the bPS SST used to first diagnose the patients with CP in CRC 98-2 is not available for computation. Noteworthy is that nine of the 12 patients studied in 98-2 participated in 98-1.

This study, however, despite the large variability of results within patients and in between patients, demonstrates that essentially both synthetic secretin products produce similar results during the SST, thus meeting the efficacy criteria of concordance between sHS and sPS.

The drug was well tolerated by all 12 patients, who registered no adverse events or abnormalities of the vital signs during the SSTS

Study CRC 99-9 A randomized, crossover study evaluating sHS, sPS, and bPS for the assessment of exocrine pancreas function in patients with a diagnosis of CP.

Hypothesis: sPS and sHS will be a safe and effective diagnostic agent for CP and will give the same results as bPS.

Study methods and procedures. Four females and two males with an average age of 52 years (range 35 to 70 years) with documented diagnosis of CP received a single intravenous bolus dose of sPS (0.2 mcg/kg), sHS (0.2 mcg/kg) and bPS (1 CU/kg). Each patient underwent three SST separated by at least 24 hours. Females had to be of non-childbearing potential or using appropriate contracepction. Patients provided written, informed consent.

The primary pharmacological endpoints were pancreatic secretion volume and bicarbonate concentrations.

The criteria for efficacy evaluation was diagnostic concordance with bPS for CP.

The criteria for pharmacological evaluation was pancreatic juice volume and bicarbonate concentration.

Safety evaluation. Adverse events and vital signs were monitored during the course of these studies.

Efficacy results. All six patients tested positive for CP (HCO_3 concentration <80 mEq/L in each aliquot) after stimulation with sHS, sPS and bPS. There was 100% diagnostic agreement between the three drugs. Tables 4 and 5 summarize the results over 15 minute intervals and over 60 minutes.

Safety results. There were two adverse events in two patients, both after administration of bPS, both of short duration that resolved spontaneously. There were no serious adverse events.

The **sponsor's conclusion** is that "sHS, sPS and bPS have statistically equivalent pharmacological effects, and diagnostic efficacy for CP".

Reviewer's comments. The conclusion that all three forms of secretin "have statistically equivalent pharmacological effects" is based on the non-significance of the results both at 15 minute intervals, and pooled at 60 minutes. The sponsor has used this approach, rather than using the preferred confidence interval

approach. Due to the small number of patients these results should be interpreted as observational in nature.

Nevertheless, the description of these experiments and the interpretation of the results is that, in essence, sHS, sPS and bPS produce a similar pharmacological effect and are well tolerated.

sPS was determined "approvable" based on similar observational-type of data in small number of patients. The patients in CRC 98-2 are essentially the same as in 98-1 used as a pivotal study for sPS. 98-2 enlarges the sample by only three patients. Dr Goldkind's (NDA # 21-136, Submission Date: May 14, 1999) and Dr Chen's (NDA # 21-136, Date March 7, 2000, Statistical Review and Evaluation) concerns with sPS are very similar to this reviewer's with sHS. The samples are small and they demonstrate similar pharmacodynamic effects on exocrine pancreatic function. They fail to prove sensitivity or specificity for CP or any other form of exocrine pancreatic dysfunction.

The problem lies in that there are not a large number of patients with exocrine pancreatic dysfunction that merit SST, and the fact that naso-duodenal intubation is an unpleasant procedure, that patients are willing to endure once, but very few would voluntarily subject themselves to repeated intubations and all the associated inconveniences: overnight fasting, no medications before the test, days missed of work for many of them. These factors make enrollment in statistically ideal clinical trials with larger number of subjects and more appropriate controls, almost impossible,

Further, the clinical experience tells us that whenever in medicine we have switched from products obtained from crude animal extracts to purified synthetic derivatives the dosing became more accurate, the side effects decreased and the possibility of contracting unknown animal pathogens is eliminated.
Because the evidence submitted in CRC 98-2 and CRC 99-9 points to the fact that sHS has a similar pharmacological effect as bPS (a marketed drug) and sPS (an approvable drug), that in clinical trials has demonstrated to be safe, that the clinical experience tell us that synthetic compounds are usually equal or more effective than crude organ animal extracts, and safer than animal extracts, and because of the socio-economic reasons listed above, **this reviewer supports the approval of sHS as a diagnostic tool in the evaluation of pancreatic exocrine dysfunction**, providing that all other concerns of the registration process are satisfied.

C. Diagnosis of Gastrinoma.

In support of this indication, the sponsor has submitted results of two studies:

1) CRC 99-8, A randomized, controlled, crossover study evaluating sHS, sPS and bPS for the diagnosis of gastrinoma, pooled with:

2) CRC 97-2 A randomized, single blind, active controlled, two way crossover study evaluating diagnostic efficacy and safety of sHS and sPS and in gastrinoma.

Hypothesis: sHS and sPS will be a safe and effective diagnostic agent for gastrinoma and produce serum gastrin responses similar to bPS.

Objectives: To obtain comparative pharmacological, diagnostic efficacy, and safety data for sHS and sPS compared to bPS as diagnostic agents in patients with a diagnosis of gastrinoma.

Study methods and procedures. Because of the low incidence of gastrinoma the sample size was agreed upon with the FDA (six patients) and was not based on power calculation

The sequence of administration of the three secretin products was randomized to balance any theoretical period effects. The research pharmacist, not involved in the clinical aspects of the study dispensed the doses in blinded syringes. The study personnel were informed of the sequence of administration for each patient after that patient completed the study.

The dose level of bPS was the recommended dose for the SST to evaluate gastrinoma (2 CU/kg). The dose levels of sPS and sHS were 0.4 mcg/kg, which have been shown to be pharmacologically equivalent (cat bioassay and CRC 97-1).

The drugs were administered intravenously, in bolus form, one minute after a trace amount (0.1 ml) was injected to test for unsuspected allergies. The tests were conducted at least 2.5 hours apart.

Pharmacological variables: Serum gastrin concentrations at 0, 1, 2, 5, 10, 15 and 30 minutes post-secretin injection.

Diagnostic variables (efficacy): Positive diagnosis of gastrinoma based on >110 pg/ml increase over basal levels in serum gastrin concentrations post-secretin injection.

Safety variables: Adverse events and vital signs, monitored during the study.

Primary efficacy variable: The diagnosis of gastrinoma in patients with documented diagnosis of gastrinoma. The comparison of results obtained with sHS, bPS and sPS was analyzed.

Diagnostic efficacy variable: The diagnostic outcome for gastrinoma based on >110 pg/ml increase in serum gastrin concentration at any measured time-point past secretin administration was compared for sPS and bPS.

Protocol violations (reported by the sponsor) One patient — was available only one day and had all three determinations the same day, 2.5 hours apart. The sponsor rationalizes that the issue of pharmacodynamic carryover effect was not a consideration because the half life of secretins administered IV is under 5 minutes and 2.5 hours between tests represented over 30 half-lives. A second patient — had two tests separated by 2.5 hours.

Two males and three females were enrolled in CRC 99-8. The ages ranged from 27 to 72 years (average 46.8 years). Three additional patiens (two males and one female) were enrolled in CRC 97-2, their average age was 63 years with a range from 55 to 77 years.. These three patients were studied at another medical center.

Diagnostic efficacy results Five patients completed the three way crossover. The serum gastrin concentrations are listed in Table 6 . One patient (# 1, — didn't have documented tissue diagnosis in the CRF. They all showed positive secretin stimulation tests results for sHS, sPS and bPS. Each secretin test produced increases in serum gastrin concentration within 5 minutes, which far exceeded the 110 pg/ml used as diagnostic paradigm for gastrinoma.

The three patients in study CRC 97-2 never received sHS. Two of them with known gastrinoma received bPS and sPS and tested positive. The third one had tested positive for gastrinoma with sPS, underwent a curative resection of a duodenal tumor and had negative tests subsequently after sPS and bPS
In summary, there was diagnostic agreement for sHS, sPS and bPS in 6 of 6 patients, and between sPS and bPS in 9 of 9 patients overall and in 8 of 8 patients remaining positive for gastrinoma

There were no statistical differences in serum gastrin concentrations between sPS and bPS in these eight patients. In the three way comparison of six patients there was a significant difference for the comparison between sHS and sPS at 15 minutes (p=0.0274)

Of interest, in another study (CRC 99-10) involving 12 normal volunteers, serum gastrin responses were negative for gastrinoma with sPS and sHS. The results for both are listed in Tables 6 and 7.

Safety results. The sponsor reports no adverse events or abnormalities of the vital signs. Manual review of the CRFs demonstrates tingling of the hands in patient #1 of mild severity, and stomach distress in patient #3 reported as of moderate severity. In his review of sPS (NDA 21-209, Submission Date: 14 May, 1999) Dr Goldkind notes a drop of 10 to 20 mm of Hg in blood pressure, without cardiovascular compromise, 10 to 15 minutes after injection of secretin in some

patients. The blood pressure remained within normal limits and fluctuated normally during the course of the test. The clinical significance of this observation is difficult to assess in view of the small patient sample. This fact, however, should be listed in the package insert and be part of any post marketing surveillance program.

Reviewer's Comments. There are several methodological problems with the data:

- The patient sample is small, precluding the performance of group statistical analysis

- The performance of SSTs with only 2.5 hours in between answers the issue of pharmacodynamic carryover. The main issue, however, is the time needed for the physiological recovery of the tumor. There are apparently no data in the literature to produce an estimate.

- Patient # 1 in CRC 99-8 has no documented tissue diagnosis of gastrinoma, although behaved like one during the SSTs.

- The patients in CRC 97-2 did not receive the study dru8g, sHP. Despite these shortcomings, sHP produced similar results to those of bPS, the approved marketed product, and to sPS a product that with similar data, in fact, some of the same patients, was considered approvable in Dr Goldkind 's review (NDA # 21-209, Submission Date: Amcgust 19, 1999).

Because all available observational data points in the direction of sHP being a useful tool in diagnosing gastrinoma, the benignancy, small number, short duration and spontaneous resolution of the adverse events and the fact that a synthetic product will have the chance of producing more accurate and reproducible tests in the future, with a substantial safety margin, **this reviewer recommends that sHS be approved for the diagnosis of suspected gastrinoma tumors**. This, if all other concerns raised during the regulatory process are satisfied.

D. Facilitation of pancreatic duct cannulation of the minor papilla during ERCP in patients with pancreas divisum. ERCP is a technique used for the diagnosis and treatment of diseases of the biliary tract and pancreas. ERCP is an abbreviation for **E**ndoscopic, because it is performed via endoscopic instruments; **R**etrograde, because contrast dye is injected into the ducts against the natural flow of bile and pancreatic juice; **C**holangio, because fluoroscopy and X- rays of the biliary tree are performed and **P**ancreatography, because fluoroscopy and X- rays of the pancreatic ductal system are obtained. The patients usually receive mild sedation with a combination of drugs that include Demerol, Versed and Propofol; the motility of the gut is sometimes inhibited by the administration of glucagon. All these medications are given intravenously, in titrated doses, inmediately

before and during the course of the procedure. Before leaving the endoscopy suite, it is standard of care that patients have to be awake. Sometimes, in order to reverse the sedation, naloxone HCl (for the Demerol effect) and/or flumazenil (Romazicon, for the Versed effect), are administered intravenously at the end of the procedure. These facts have to be taken into consideration when assessing the efficacy and safety of another drug used during the course of an ERCP.

In support of this indication, the sponsor has submitted results of two studies: CRC 98-4 and CRC 98-4 Amendment. They will be reviewed separatedly and they will be commented together at the end.

CRC 98-4. This is an open label, non-comparative, single arm, multicenter study for the routine clinical use of sHS as a diagnostic agent and to assist in pancreatic duct cannulation.

Patients with suspected diagnosis of CP, pancreatic carcinoma, gatrinoma or clinically requiring ERCP with pancreas divisum or difficult duct cannulation, were included in this study. Women of childbearing potential should have a negative pregnancy test. Patients should be off anticholinergic drugs one week before the test. There should be no evidence of acute pancreatitis.

The patients received sHS intravenously at a dose of 0.2 mcg/kg, one minute after a trace amount (0.2 mcg=0.1 ml) was given, also intravenously, to rule out unsuspected secretin allergy. **The dose chosen for this indication is the same used for SST in CP patients**

Scientific Rationale. Patients undergoing ERCP for clinical reasons with pancreas divisum known prior to the procedure or discovered at the time of the ERCP with difficult identification and cannulation of the pancreatic duct received sHS to stimulate opening of the ancillary ampula, assist the endoscopists with identifying its location and cannulating the pancreatic duct.

Hypothesis. sHS would prove safe and effective in routine clinical use to diagnose CP, pancreatic carcinoma, gastrinoma, and to facilitate cannulation of the pancreatic duct during ERCP.

Objectives. To obtain supplemental pharmacological, efficacy, and safety data in standard clinical use for the diagnostic indications approved for bPS.

Efficacy variable. Percentage of cases in which secretin helped localize the pancreatic duct opening resulting in successful ERCP cannulation.

Safety variables. Adverse events.

Efficacy results. A total of 297 patients were enrolled in study CRC 98-4 at eleven medical centers. Of those, 63 patients received sHS to facilitate cannulation during ERCP. Thirty-two were for cannulation of the minor papilla in

patients with pancreas divisum and 31 for other reasons involving the Vaterian (major) ampula, including sphincter of Oddi dysfunction (SOD), pancreatic pseudocyst, duodenal adenomas and post-operative status surgery in the area. Twenty-seven of the 32 patients with pancreas divisum (84%) had successful cannulation of the minor papilla after sHS administration. Twenty-two of the 31 patients (71%) with problems involving the Vaterian ampula had successful cannulations after sHS administration

The general data of the patients who received sHS during an ERCP is listed in Table 8. The observational statistical analysis are listed in Tables 9, 10, 11.

Safety results. Two patients recorded adverse events: Patient # 24 complained of vomiting of mild severity, within two hours of receiving the drug, that resolved spontaneously, possibly related to the drug. Patient # 25 registered two adverse events: 1) Multiple I.V. restarts secondary to infiltration, of mild severity, resolved satisfactorily, unlikely due to the drug. 2) Mild acute pancreatitis, that prolonged his hospitalization (Serious Adverse Event), resolved satisfactorily, considered unlikely due to the drug.

- **CRC 98-4 Amendment.** This amendment to protocol CRC 98-4 came as a consequence of conversations between the sponsor ChiRhoClin Inc. and FDA. It was agreed that although administration of intravenous secretin to facilitate cannulation during ERCP had been common practice around the world for 20 years, to obtain formal approval and labeling of sHS for this indication, a randomized, double-blind placebo controlled crossover study in 20 patients focused on cannulation of the accessory pancreatic duct would be necessary. This is a randomized, double-blind, crossover multicenter study for the use of sHS to facilitate minor pancreatic duct cannulation in patients with pancreas divisum during ERCP.

Hypothesis. sHS would prove safe and effective in routine clinical use to facilitate cannulation of the minor pancreatic duct during ERCP in patients with pancreas divisum.

Objective. To obtain pivotal efficacy and safety data in standard clinical use for the indication of facilitation of minor pancreatic duct cannulation in patients with pancreas divisum during ERCP.

Study methods and procedures. Patients who met criteria received sHS 0.2 mcg/kg or placebo, intravenously, in bolus form, after an initial trace amount (0.2 mcg=0.1 ml) was injected intravenously, to rule out unsuspected allergy to sHS. The dose of 0.2 mcg/kg is the one used during SST.

Patients suspected to have pancreas divisum with difficult identification or cannulation received sHS or placebo in randomized, blinded, crossover fashion to assist the endoscopist with the procedure. The sequence of receiving sHS or

placebo was determined by a randomization code provided to the research pharmacist at each participating center. Blinded syringes of study drug were provided to study personnel.

Prior and concomitant therapy. Medications were to be recorded on the case report form. Other than medications known to possibly cause acute pancreatitis and anticholinergics, there were no restrictions on prior or concomitant medications.

Primary efficacy variable. Percentage of cases in which secretin compared to placebo helped localize the minor pancreatic duct opening resulting in successful ERCP cannulation in patients with pancreas divisum.

Safety variables. Adverse events.

Efficacy results. Twenty-seven patients were enrolled at three medical centers as depicted in Table 12. Only three were able to have their minor ducts cannulated prior to randomization and administration of study drug. Of the remaining 24, only two could be successfully cannulated with placebo, which was administered as the second treatment after sHS was given. Of the 24 patients randomized, 16 had successful cannulation of the minor duct, nine after sHS was administered first and seven after sHS was given second (after placebo failed).

Fifteen patients received placebo. The reason only approximately one-half of the enrolled patients received placebo was that in the 50% of cases in which sHS was given first (according to randomization), it almost always worked obviating the need to give the second blinded treatment. Of the 15 patients who received placebo, in 12 cases it was given first, and in all 12 cases cannulization failed. Three patients received placebo second after sHS failed, and in two of those, cannulation was successful. This may be due to remaining sHS effect, given the arbitrary five minute limit allowed to attempt cannulation given by the protocol. Cannulation time was statistically significantly longer for no treatment and placebo than for sHS, as shown in Table 13 .

Safety evaluation. Manual review of the CRFs failed to reveal any adverse events reported during this study.

Reviewer's comments. The sponsor has tried to provide scientific documentation to an accepted fact of gastrointestinal endoscopy practice: That the injection of secretin intravenously during the course of an ERCP produces a visible outpour (often times a squirting) of pancreatic juice for several minutes, enough for the endoscopist to reset the instrument and with a better angle approach accomplish successful cannulation of either papilla. There were several methodological flaws in both protocols which are summarized as follows:

- The dose of secretin is that used when maximal pancreatic stimulation is desired over a 60 minute period, that allows for collection of several samples to measure volume and bicarbonate concentration. **Secretin, in any amount, always stimulates the pancreas maximally.** The dose of 0.2 mcg/kg is excessive and unnecessary for this purpose, when all is needed is production of pancreatic juice for a few seconds, minutes at most.

- This maximal dose of sHS used, because of the same reasons, negates any randomization or blindedness in CRC 98-4 Amendment. The five minute period allocated to cannulate the papilla after injection, after which the second injection is given is void, if the first injection was sHS. The patient will continue to produce pancreatic juice for another 55 minutes, when the doctor, according to the protocol, would be working under "the effect" of placebo.

- As a consequence of this, the statistical analysis of CRC 98-4 Amendment will have to be reviewed.

- The research protocol states that "prior and concomitant therapy will be recorded in the CRF". The CRF does not have a space for it, and at no time, in any case, the medications used for ERCP procedures listed above were detailed. These medications have effects on smooth muscle. Depending on the doses used, they are known to affect the results of manometric studies performed in cases of suspected SOD.

- The data listings tables (vol 7:24 pages 002128 to 2207) report the indications by number: 1, 2, 3, 4, without clarifying what the numbers mean, with the exception of Data Listing 2, in page 002160. This is a failure of data reporting that complicates the evaluation of results.

CRC 98-4, the open label study, reports successful cannulation of the minor papilla in 27 of 32 patients (84%) and successful cannulation of the Vaterian ampula in 22 of 31 cases (71%). These numbers confirm empirical observations, but the lack of controls precludes official approval and labeling.

Because of the reasons given above **this reviewer considers that the sponsor has failed to demonstrate that sHS facilitates papilla**

IV - Integrated Review of Safety

A. **Methods.** The AE reported by the sponsor in the clinical trials used in this submission were analyzed separately and they are presented in Table 14. The integrated summary of safety apparently submitted by the sponsor is listed in the NDA file Table of Contents as being presented in volume 27. Regrettably, this reviewer has not been able to identify a "volume 27" of this NDA. The largest

compendium of patients and AEs are in the proposed package insert (February 13, 2001 version) and they include only 345 patients. Because of this, the sponsor was contacted and an updated list of AEs that includes information on 686 human subjects exposed to the drug was received on 20 November, 2001. These data will be analyzed separately.

B. Clinical Trial Safety. The results of five clinical trials were submitted in support of three indications requested by the sponsor. The AEs of these studies are summarized in Table 14 below.

Table 14
NDA 21-156
Safety of sHS in Clinical Trials

CLINICAL TRIAL #	INDICATION	# OF PATIENTS EXPOSED	ADVERSE EVENTS
CRC 98-2	CHRONIC PANCREATITIS	12	NONE
CRC 99-2	CHRONIC PANCREATITIS	6	NONE
CRC 99-8	GASTRINOMA	6	1 Pt. Tingling of hands, mild. 1 Pt Stomach distress, moderate
CRC 98-4	ACC. PANCR. CANNULAT.	32	1 Pt. Mult.IV restarts and mild ac pancreatitis (delayed disch. 1 day=SAE) 1 Pt mild vomiting
Crc 98-4 AMEND.	FACILIT. OF CANNULAT.	24	NONE

NOTE: No patients were enrolled in study CRC 97-2 (gastrinoma).

In summary, a total of 80 patients were exposed to sHS in the course of five clinical trials. Four patients experienced five AEs, three mild, one of moderate severity and one SAE: a mild acute pancreatitis that in the opinion of the investigator was not due to study drug, but delayed the hospital discharge for a day.

C. Sponsor's Integrated Summary of Safety. Six hundred and eighty-six patients were exposed to sHS: 502 in clinical studies and 184 in autism studies.

All patients received a testing dose of 0.2 mcg=0.1 mL of sHS intravenously one minute before the main dose was administered, also intravenously. There were no untoward reactions in any of the 686 patients.

Four hundred and forty patients received a dose of 0.2 mcg/kg: 429 in clinical trials and 11 in autism studies.

Two hundred and forty-six patients received a dose of 0.4 mcg/kg: 73 in clinical trials and 173 in autism studies.

Table 15 lists all AEs per dose and per kind of study (autism or diagnostic). The AEs are not listed by severity. No SAEs were reported by the sponsor. The largest number of AEs was observed in the group of patients treated with 0.4 mcg/kg of sHS in the autism studies: 57. The AEs observed in six or more patients were all in this group and included: hyperactivity 22, sleep disturbance 13, diarrhea and agitation 10, cough and aggressive behaviour 9, congestion, fever and rash 7, and ear pain 6.

In summary, as a diagnostic tool, sHS appears to be safe and well tolerated.

V – Special Concerns

- ***Informed consent and Institutional Review Board Approval.*** All clinical trials have been approved by qualified IRBs. All patients had signed an Informed Consent, which had previously been approved by an IRB.

- **Form FD 1572 and Curriculum Vitae.** All investigators have signed FD 1572 forms. CVs, documenting the qualifications of the investigator for the study were attached.

- **Financial disclosures.** Certification/Disclosure Form of Financial Disclosure by Clinical Investigators complying with 21 CFR 314.50 (k) (3) have been submitted for all investigators.

- **Pregnancy use information.** All enrolled females were required to be of non-child bearing potential, (either s/p hysterectomy, at least one year post-menopausal, or using medically approved contraception method) and to have had a negative urine hGC pregnancy test within seven days of participating in the study.

- **Pediatric studies.**

  — sHS was also administered to children participating in the autism studies. Some of that informartion has been published (NEJM – Sandler et al. 341 (24): 1801). In summary, 28 children average age 7.6 years received a single dose of sHS of 0.2 mcg/kg, intravenous, over one minute, without treatment-limiting adverse effects. bPS has been used through the years in the pediatric population, without reported AEs.

VI - Recommendations for Regulatory Action. This reviewer recommends the following:

1) The proposed sHS is approved for the following indications:

- **Diagnosis of pancreatic exocrine** —
- **Diagnosis of gastrinoma**

2) The sponsor has failed to demonstrate that sHS facilitates — papilla —

3) Because diagnostic testing for exocrine pancreatic dysfunction and gastrinoma was performed in the past with purified porcine products containing a significant percentage of biologically active, uncharacterized impurities, studies should be planned to establish new cut-off points with sHS. In order to obtain a sufficiently large patient sample, the Agency should encourage multinational participation. A consensus-type of international conference could be organized jointly with the NIH, as a starting point.

4) The sponsor will be requested to report results — separately.

5) The label should reflect the limitations of the data on which these approvals are based.

/S/

Marcelo Barreiro, M.D.

cc:
HFD-103/FHoun
HFD-180/VRaczkowski
HFD-180/JKorvick
HFD-180/HGallo-Torres
HFD-180/MBarreiro
HFD-180/MMcNeil
N/21256111.0MB

TABLE 1
CRC 98-2
DEMOGRAPHIC CHARACTERISTICS

Pat #	Initials	Date Enrolled	Age	Height (cm)	Weight (kg)	Gender	Race
1		01/28/99	53	140.0	42.2	F	B
2		02/02/99	51	167.5	73.0	F	W
3		02/04/99	57	160.0	58.9	F	W
4		02/09/99	64	178.0	93.2	M	W
5		02/11/99	70	157.5	101.0	F	W
6		02/16/99	61	157.5	58.0	F	B
7		02/23/99	56	183.0	75.9	M	W
8		02/25/99	69	165.0	69.0	M	W
9		03/11/99	56	165.0	84.1	F	W
10		04/08/99	27	178.0	83.64	M	W
11		05/05/99	68	160.0	93.2	F	W
12		06/29/99	76	162.5	61.6	F	W

APPEARS THIS WAY
ON ORIGINAL

TABLE 2
CRC 98-2

PANCREATIC STIMULATION RESULTS FOR 15 MINUTE INTERVALS

Synthetic Porcine Secretin vs Synthetic Human Secretin Study											
TREAT		V_B	BC_B	V_15	BC_15	V_30	BC_30	V_45	BC_45	V_60	BC_60
sHS	Mean	29.58	10.92	54.17	38.08	34.08	55.08	36.08	63.42	41.50	57.33
sHS	STD	34.02	7.84	33.27	20.63	22.35	20.71	25.32	21.01	30.98	15.14
sHS	%CV	115.01	71.86	61.42	54.18	65.58	37.59	70.16	33.13	74.64	26.40
sPS	Mean	27.17	11.58	53.25	40.58	39.42	56.75	38.25	62.17	39.08	54.33
sPS	STD	22.31	11.51	37.49	12.54	23.21	20.08	25.13	20.11	25.19	20.67
sPS	%CV	82.13	99.35	70.40	30.89	58.88	35.39	65.71	32.35	64.46	38.05
	Prob	0.8272	0.8823	0.8997	0.6262	0.5043	0.5878	0.6854	0.5957	0.5878	0.306
sHS = synthetic human secretin											
sPS = synthetic porcine secretin											
B_ = Baseline Corrected											

TABLE 3
RC 98-2

PANCREATIC STIMULATION RESULTS FOR 60 MINUTE SAMPLE

Synthetic Porcine Secretin vs Synthetic Human Secretin Study (CRC98-2)				
TREAT		V_1_60	B_TBC	TBC
SHS	Mean	165.83	9.46	9.73
SHS	STD	101.56	8.00	8.20
SHS	%CV	61.24	84.59	84.27
SPS	Mean	170.00	9.72	9.91
SPS	STD	87.40	7.99	7.96
SPS	%CV	51.41	82.20	80.33
	Prob	0.8013	0.8412	0.8896
BC = bicarbonate concentration (Meq/L)				
V = volume (mL)				
TBC = total bicarbonate (Meq)				

TABLE 4
CRC 99-9

PANCREATIC STIMULATION RESULTS OVER 60 MINUTES AT 15 MINUTE INTERVALS

Synthetic Human Secretin vs Synthetic Porcine Secretin Study vs Biologically Derived Porcine Secretin (Ferring) (CRC99-9)

TREAT		V_B	BC_B	V_15	BC_15	V_30	BC_30	V_45	BC_45	V_60	BC_60
sHS	Mean	27.2	10.0	69.7	43.8	46.2	63.8	45.7	61.8	45.2	59.3
sHS	STD	27.0	13.2	34.4	8.9	35.0	12.9	32.7	14.3	35.1	11.3
sHS	%CV	99.5	131.6	49.4	20.2	75.9	20.2	71.6	23.1	77.6	19.0
sPS	Mean	26.8	4.3	50.7	32.8	75.5	50.3	46.2	53.7	45.2	44.2
sPS	STD	31.2	6.0	29.2	14.9	50.9	15.2	36.4	15.5	23.3	12.9
sPS	%CV	116.4	138.2	57.5	45.5	67.4	30.2	78.9	28.8	51.5	29.3
bPS	Mean	32.7	4.3	55.0	31.2	52.2	44.8	51.0	55.3	42.8	48.3
bPS	STD	25.6	8.0	38.2	9.3	44.3	16.2	30.8	13.2	22.6	20.8
bPS	%CV	78.5	185.6	69.5	30.0	84.9	36.1	60.3	23.8	52.7	43.0
	Prob	0.8687	0.5924	0.5740	0.6248	0.1420	0.3922	0.9981	0.9506	0.8376	0.5908

sHS = synthetic human secretin
sPS = synthetic porcine secretin
bPS = biologically derived porcine secretin
B_ – Baseline Corrected
BC = bicarbonate concentration (mEq/L)
V = volume (mL)

TABLE 5
CRC 99-9

PANCREATIC STIMULATION RESULTS OVER 60 MINUTES

Synthetic Human Secretin vs Synthetic Porcine Secretin Study vs Biologically Derived Porcine Secretin (Ferring) (CRC99-9)

TREAT		V_1_60	BC_1_60	B_TBC	TBC
sHS	Mean	206.7	54.9	12.2	12.2
sHS	STD	119.3	10.2	9.1	9.0
sHS	%CV	57.7	18.7	74.4	73.7
sPS	Mean	217.5	44.4	10.2	10.3
sPS	STD	110.0	12.8	7.6	7.6
sPS	%CV	50.6	28.8	74.8	73.5
bPS	Mean	201.0	44.5	9.6	9.6
bPS	STD	118.6	12.0	6.8	6.6
bPS	%CV	59.0	27.0	70.4	68.5
	Prob	0.7504	0.7265	0.2236	0.2385

BC = bicarbonate concentration (mEq/L)
V = volume (mL)
TBC = total bicarbonate (mEq)

TABLE 6
CRC 99-8

SERUM GASTRIN CONCENTRATIONS (pg/mL) (CRC99-8)

Sub. #	Initials	Drug	Baseline	1 min	2 min	5 min	10 min	15 min	20 min	30 min
4(01)		sHS	1							
4(01)		sPS								
4(01)		bPS								
5(02)		bPS								
5(02)		sPS								
5(02)		sHS								
6(03)		bPS								
6(03)		sPS								
6(03)		sHS								
7(04)		sHS								
7(04)		sPS								
7(04)		bPS								
8(07)		sHS								
8(07)		sPS								
8(07)		bPS								

TABLE 7
CRC 99-10

Results of Gastrin Concentration in 12 Healthy Volunteers After Injection of sHS

GASTRIN CONCENTRATION (pg/mL) FOR sHS

Sub #	0 min.	2 min.	4 min.	10 min.	15 min.	30 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	41.9	46.3	49.8	41.1	41.4	37.3
Std	10.8	11.9	18.0	10.3	6.6	5.6
Min						
Max						
%CV	25.8	25.7	36.1	25.1	16.0	15.0

DATA LISTING 8
FACILITATION OF ERCP CANNULATION OF PANCREATIC DUCT

Sub. #	Site	Initials	Indication	Facilitation of ERCP Cannulation of Pancreatic Duct			Cannulation			Comments
				Divisum	Other	If Other, Specify	Successful	Unsuccessful	If Unsuccessful, Specify	
21	Jow		4	✓			✓			
22	Jow		4		✓	? Pancreas divisum		✓	ND	
23	Fre		4		✓	Surgery	✓			
24	Fre		4		✓	Facilitate pancreatic duct cannulation.	✓			
25	Fre		4	✓			✓			
30	She		4		✓	Failed deep cannulation @ major papilla		✓	Unable to cannulate deeply	
31	She		4		✓	Unable to cannulate major papilla		✓	Unable to locate pancreatic orifice	
48	Tos		4	✓			✓			
49	Tos		4	✓				✓	No pancreatic juice seen at papilla after secretin given	
50	Tos		4	✓			✓			
62	She		4		✓	B II Anatomy; Stenotic Pancreatic Orifice	✓			
64	She		4		✓	Stenotic Pancreatic Orifice	✓			
68	She		4		✓	s/p Whipple Procedure		✓	Unable to locate pancreatic orifice	
70	Ete		4	✓			✓			
71	Ete		4	✓			✓			
72	Ete		4	✓			✓			
73	Ete		4		✓	Previous sphincterotomy		✓	Distorted anatomy due to previous sphincterotomy 1) Additional 8µg given 2) Hard (difficult) to assess if secretin ncreased flow of panc. juice due to distorted anatomy.	

DATA LISTING 8 (Continued)

FACILITATION OF ERCP CANNULATION OF PANCREATIC DUCT

Sub. #	Site	Initials	Indication	Facilitation of ERCP Cannulation of Pancreatic Duct			Cannulation			Comments
				Divisum	Other	If Other, Specify	Successful	Unsuccessful	If Unsuccessful, Specify	
74	Ete		4	✓			✓			
75	Ete		4	✓			✓			Very good response in <1 min from completion of administration.
76	Ete		4	✓			✓			
77	Ete		4	✓			✓			
78	Ete		4	✓			✓			
79	Ete		4	✓			✓			Minor located by probing appropriate area, which was stenotic; pt has Roux-En-Y pancreatojejunostomy with patent anastamosis therefore, lack of visible secretory response could be secondary to flow into bypass rather than minor.
80	Ete		4		✓	Previous secretin for cannulation	✓			
82	Ete		4	✓			✓			
92	Ete		4	✓			✓			
94	Joh		4		✓	No divisum, malignant Obliteral pancreatic duct	✓			
97	Ete		4		✓	Scar tissue impeding deep cannulation	✓			
99	Ete		4	✓			✓			
110	Joh		4	✓				✓	Drug did stimulate, but the endoscopist still could not obtain access.	
120	She		4		✓	Stenotic pancreatic orifice	✓			

0021

DATA LISTING 8 (Continued)
FACILITATION OF ERCP CANNULATION OF PANCREATIC DUCT

Sub. #	Site	Initials	Indication	Facilitation of ERCP Cannulation of Pancreatic Duct			Cannulation			Comments
				Divisum	Other	If Other, Specify	Successful	Unsuccessful	If Unsuccessful, Specify	
121	She		4		✓	Stenotic pancreatic orifice		✓	Unable to identify pancreatic orifice cannulation via minor with partial pancreatogram. No contrast exited major papilla.	
123	She		4	✓			✓			
136	Tos		4	✓				✓	Submucosal injection in the area of minor papilla was given.	
146	She		4	✓			✓			
152	Tos		4		✓	Identification of pancreatic duct for sphincterotomy	✓			
154	Tos		4	✓				✓	No PPJ seen coming from minor papilla	
159	Fre		4		✓	Pancreatic sphincteroplasty for stenosis major papilla	✓			
168	Tos		4		✓	Endoscopic secretin test as part of IRB #139-00	✓			
178	Tos		4		✓	*Per IRB protocol* 139-00	✓			
182	She		4		✓	Pt. Is s/p Whipple procedure for mucinous tumor of pancreas.		✓	Unable to identify pancreaic orifice. Pt. is post Whipple procedure, which makes cannulation & identification of the pancreatic orifice really impossible.	
183	She		4		✓	Difficult cannulating angle	✓			
184	She		4	✓				✓	Difficult guidewire passage. Superficial cannulation successful.	
185	She		4		✓	Moderate stenotic orifice	✓			

002192

DATA LISTING 8 (Continued)
FACILITATION OF ERCP CANNULATION OF PANCREATIC DUCT

Sub. #	Site	Initials	Indication	Facilitation of ERCP Cannulation of Pancreatic Duct			Cannulation			Comments
				Divisum	Other	If Other, Specify	Successful	Unsuccessful	If Unsuccessful, Specify	
187	She		4		✓	Initially unable to locate pancreatic orifice	✓			
189	She		4		✓	Stenotic Pancreatic Orifice s/p sphincteroplasty	✓			
199	Ete		4	✓			✓			
200	Ete		4	✓			✓			But not due to secretins which had no effect. Used methylene blue via major & found stain at minor.
201	Ete		4	✓			✓			
202	Ete		4	✓			✓			
224	Joh		4	✓			✓			
260	Fre		4		✓	Location of pancreatic duct at	✓			
264	Ete		4		✓	Identifying minor papilla		✓	None cannulated	
265	Ete		4	✓			✓			
266	Ete		4		✓	S/p whipple procedure	✓			
267	Ete		4	✓			✓			
270	She		4		✓	PD stricture	✓			
271	She		4		✓	Calcitic pancreatitis with obstruction		✓	Attempt to cannulate minor papilla, or main PD obstructed via major papilla – no orifice seen at minor papilla	
272	She		4		✓	Unable to visualize either pancreatic orifice	✓			Major and minor cannulation unsuccessful
273	She		4		✓	Large periampullary diverticulum.	✓			
288	Tos		4	✓			✓			
291	Joh		4		✓	Whipple resection	✓			
293	Tow		4	✓			✓			

TABLE 9
CRC 98-4

Was sHS useful during procedures?

OUTCOME	Frequency	Percent	Cumulative Frequency	Cumulative Percent
s	49	77.8	49	77.8
u	14	22.2	63	100.0

Chi-Square Test for Equal Proportions

Statistic = 19.444 DF = 1 Prob = 0.001

TABLE 10
CRC 98-4

Was sHS useful during procedure with the presence of Pancreas Divisum?

OUTCOME	Frequency	Percent	Cumulative Frequency	Cumulative Percent
s	27	84.4	27	84.4
u	5	15.6	32	100.0

Chi-Square Test for Equal Proportions

Statistic = 15.125 DF = 1 Prob = 0.001

TABLE 11
CRC 98-4

Was sHS useful during procedure without the presence of Pancreas Divisum?

OUTCOME	Frequency	Percent	Cumulative Frequency	Cumulative Percent
s	22	71.0	22	71.0
u	9	29.0	31	100.0

Chi-Square Test for Equal Proportions

Statistic = 5.452 DF = 1 Prob = 0.020

TABLE 12
CRC 98-4 AMENDMENT

DEMOGRAPHICS

Sub. #	Site	Initials	Indication	Date of Procedure	DOB	Weight (kg)	Age	Gender	Race
1	1		4	06/21/00		68.18	51	F	W/AI
2	1		4	07/11/00		80.0	37	F	W
3	1		4	07/14/00		71.0	48	M	W
4	1		4	09/18/00		81.82	55	F	W
5	1		4	09/20/00		81.82	60	F	W
6	1		4	09/21/00		51.82	27	F	W
7	1		4	10/05/00		88.6	52	M	W
8	1		4	10/06/00		72.73	42	M	W
9	1		4	12/11/00		56.82	28	F	W
17	2		4	09/14/00		110.2	46	F	W
18	2		4	09/27/00		47.25	28	M	W
19	2		4	09/29/00		87.0	56	M	W
20	2		4	10/23/00		105.0	46	F	W
21	2		4	10/31/00		44.0	44	F	W
33	3		4	07/11/00		95.4	48	F	W
34	3		4	07/11/00		44.5	64	F	W
35	3		4	07/12/00		89.1	66	F	B
36	3		4	07/13/00		72.7	47	M	W
37	3		4	07/14/00		79.1	81	F	W
38	3		4	07/19/00		106.5	67	M	W
39	3		4	07/20/00		64.5	47	F	W/AI
40	3		4	07/27/00		72.7	45	M	W
41	3		4	08/07/00		156.0	79	F	W
42	3		4	08/08/00		49.1	47	F	W
43	3		4	11/29/00		80.0	66	F	W
44	3		4	12/19/00		58.2	32	F	W
45	3		4	01/12/01		86.4	52	M	B

TABLE 13
CRC 98-4 AMENDMENT

SUMMARY OF MEAN TIMES FOR CANNULATION ATTEMPTS

Drug (N)	Time* (Mean)	Time* (SD)	p-Value sHS vs.
sHS (24)	3.03	1.88	---
Placebo (15)	4.47	1.41	0.0153
Pre-randomization (27)	4.54	1.25	0.0013

* - Minutes

TABLE 15

ALL ADVERSE EVENTS
SPONSOR'S INTEGRATED SUMMARY OF SAFETY (11/20/01)

Event	Autism			Diagnostic		
	sHS (0.4 µg/kg) N = 173 Incidence	sHS (0.2 µg/kg) N = 11 Incidence	Placebo N = 145 Incidence	sHS N = 502 Incidence	sPS N = 27 Incidence	bPS N = 15 Incidence
Abdominal pain	2	0	0	3	0	0
Aches	1	0	0	0	0	0
Aggressive behavior	9	1	2	0	0	0
Agitation	10	0	6	0	0	0
Anxiety	0	0	0	1	0	0
Bronchitis	1	0	0	0	0	0
Burning in stomach or abdomen	0	0	0	1	3	1
Clammy skin	0	0	0	1	0	0
Cold	1	0	0	0	0	0
Confusion	2	0	0	0	0	0
Congestion	7	0	0	0	0	0
Constipation	1	0	2	0	0	0
Cough	9	0	0	0	0	0
Dark urine	1	0	0	0	0	0
Decreased appetite	3	0	1	0	0	0
Decreased O_2 saturation	0	0	0	1	0	0
Decreased sleep	0	0	1	0	0	0
Depression	2	0	0	0	0	0
Diarrhea (loose stools)	10	2	3	1	0	0
Difficulty sleeping	3	0	1	0	0	0
Dizziness	0	0	1	0	0	0
Drowsiness	2	0	3	0	0	0
Dry mouth	2	0	6	0	0	0
Dry skin	1	0	0	0	0	0
Ear pain	6	0	0	0	0	0
Early removal of Dreiling tube	0	0	0	3	0	0
Eczematoid rash	1	0	0	0	0	0
Emotional lability	4	3	2	0	0	0
Eructation	1	0	0	0	0	0
Erythema	0	0	1	0	0	0
Faintness	0	0	0	1	0	0
Fever	7	0	0	0	0	0
Flu	1	0	0	0	0	0
Flushing	2	0	0	4	0	0

TABLE 15 (Continued)

Event	Autism			Diagnostic		
	sHS (0.4 µg/kg) N = 173 Incidence	sHS (0.2 µg/kg) N = 11 Incidence	Placebo N = 145 Incidence	sHS N = 502 Incidence	sPS N = 27 Incidence	bPS N = 15 Incidence
Sedation	0	0	0	1	0	0
Seizure	1	0	1	0	0	0
Self-injurious behavior	1	2	0	0	0	0
Self-stimulatory behavior	2	1	0	0	0	0
Sinus infection	3	0	0	0	0	0
Skin rash	1	0	0	0	0	0
Sleep disturbance	13	0	1	0	0	0
Slow heart rate (57)	0	0	0	1	0	0
Sore throat	2	0	1	0	0	0
Stomach ache	3	0	0	0	0	0
Stuttering	0	1	0	0	0	0
Sweating	1	0	1	0	0	0
Sweating feet	0	0	0	0	1	0
Sweating hands	0	0	0	0	1	0
Tingling in legs	0	0	0	1	0	0
Tremors	1	0	2	0	0	0
Underactivity	4	0	3	0	0	0
Unresponsiveness	0	0	0	1	0	0
Upset stomach	0	0	0	2	0	0
Vasodilation	2	0	0	0	0	0
Vasodilation in fingers and palms	0	1	0	0	0	0
Vasodilation, transient, of hands bilaterally	0	1	0	0	0	0
Virus	2	0	0	0	0	0
Vomiting	6	0	0	3	0	0
Warm sensation in abdomen	0	0	0	1	0	1
Warm sensation in face	0	0	0	1	0	1
Weight gain	0	0	2	0	0	0
Weight loss	1	0	0	0	0	0
TOTAL AEs	**196**	**20**	**74**	**44**	**5**	**4**

TABLE 15 (Continued)

Event	Autism			Diagnostic		
	sHS (0.4 µg/kg) N = 173 Incidence	sHS (0.2 µg/kg) N = 11 Incidence	Placebo N = 145 Incidence	sHS N = 502 Incidence	sPS N = 27 Incidence	bPS N = 15 Incidence
Fractured limbs	1	0	1	0	0	0
Frequent urination	0	0	1	0	0	0
Headache	3	0	2	0	0	0
Hyperactivity	22	3	2	0	0	0
Hypertriglyceridemia	1	0	0	0	0	0
Hypotension	0	0	0	1	0	0
Increase in aggressive behavior	0	1	0	0	0	0
Increase in self-stimulatory behavior	4	2	4	0	0	0
Increase sound sensitivity	1	0	0	0	0	0
Increased appetite	3	0	2	0	0	0
Increased desire for sweets	1	0	0	0	0	0
Increased hearing sensitivity	1	0	0	0	0	0
Increased heart rate	0	0	0	2	0	0
Increased liver function tests	2	0	1	0	0	0
Increased masturbation	1	0	0	0	0	0
Infiltrated IV	0	0	0	1	0	0
Intermittent total body erythema	0	0	1	0	0	0
Irritability	1	2	2	0	0	0
Lethargy	2	0	0	0	0	0
Mild Pancreatitis	0	0	0	1	0	0
Mood lability	2	0	0	0	0	0
Nausea	1	0	2	11	0	1
Nose congestion	4	0	4	0	0	0
Overactivity	2	0	7	0	0	0
Panic attack (before sHS administration)	0	0	0	1	0	0
Rash	7	0	1	0	0	0
Restlessness	1	0	4	0	0	0
Running nose	3	0	0	0	0	0
Scarlet fever	1	0	0	0	0	0

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Marcelo Barreiro
11/30/01 12:54:36 PM
MEDICAL OFFICER

Hugo Gallo Torres
11/30/01 01:22:07 PM
MEDICAL OFFICER