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# Use of Pancreatic Enzymes in Short Bowel Syndrome

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**ABBREVIATIONS AND DEFINITIONS OF TERMS**

AE	Adverse event
BC	Bomb calorimetry
BMI	Body mass index
CFA	Coefficient of fat absorption
CCK	Cholecystokinin
CNA	Coefficient of nitrogen absorption
Creon™	Creon (pancrelipase) Delayed-Release Capsules
CTRC	Clinical Translational Research Center
DXA	Dual energy x-ray absorptiometry
FFM	Fat free mass
FM	Fat mass
GH	Growth hormone
GLP-2	Glucagon-like-peptide 2
HA	Heptadecanoic acid
IGFBP-3	Insulin-like growth factor binding protein 3
IGF-1	Insulin-like growth factor 1
MBT	Malabsorption blood test
NDS	Nutrition Data System
PA	Pentadecanoic acid
PHI	Personal health information
PIVKA	Proteins induced by vitamin K antagonism or absence
QOL	Quality of life
SAE	Serious adverse event
SBS	Short bowel syndrome
THA	Triheptadecanoic acid

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**ABSTRACT**

Context: Patients with short bowel syndrome (SBS) have a high mortality rate that is mainly attributed to complications from central venous access and parenteral nutrition<sup>1</sup>. The primary goal in clinical management of patients with SBS is to wean off of parenteral nutrition and establish enteral autonomy. This goal can be difficult to achieve due to the significant malabsorption that occurs in SBS. There are few medical therapies that improve absorption in patients with SBS. The impact of pancreatic enzymes on enteral absorption has not been evaluated in this patient population. SBS is a life threatening illness in which it is essential to maximize absorption in order to minimize morbidity and mortality.

Objectives: The objective of this study is to evaluate if enteral absorption improves in subjects with SBS following therapy with pancreatic enzymes. Enteral absorption will primarily be assessed using stool coefficient of fat absorption (CFA). Secondary objectives of the study include measurement of coefficient of nitrogen absorption (CNA) and stool bomb calorimetry (BC) before and after pancreatic enzyme administration. A subset of subjects will also have enteral absorption measured using the malabsorption blood test (MBT) before and after pancreatic enzyme administration.

Study Design: This is an interventional study of subjects with SBS who will be evaluated before and after pancreatic enzyme administration. A subset of subjects will have the MBT performed before and after pancreatic enzyme administration as a measure of enteral fat absorption.

Setting/Participants: This outpatient study will be conducted at CHOP. Approximately, sixteen subjects with SBS between the ages of 4.0 and 17.9 years and ten adult subjects with SBS between the ages of 18 and 75 years will be enrolled. Only adult subjects have the option to be part of the subset that has the MBT.

Study Interventions and Measures: Subjects with SBS will be evaluated both on and off Creon™, a pancreatic enzyme medication. Enteral absorption will be measured before and after pancreatic enzyme administration. Enteral absorption will be measured using three methods: CFA, CNA, and BC. A subset of adult subjects will also have the MBT before and after pancreatic enzyme administration. Subjects with SBS have significant malabsorption and have several proposed mechanisms of functional pancreatic insufficiency. The longterm goal is to determine if pancreatic enzymes improve enteral absorption in patients with SBS, it may allow parenteral nutrition to be weaned and improve both their morbidity and mortality.

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**PROTOCOL SYNOPSIS**


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<b>Study Title</b>	The Use of Pancreatic Enzymes in Short Bowel Syndrome
<b>Funder</b>	AbbVie Inc.
<b>Clinical Phase</b>	Phase II – This is an open-label intervention therapeutic exploratory study
<b>Study Rationale</b>	<p>Patients with short bowel syndrome (SBS) have a high mortality rate that is mainly attributed to complications from central venous access and parenteral nutrition<sup>1</sup>. In 2012, Squires et al<sup>1</sup> published the largest retrospective review to date that described outcomes for patients with SBS at fourteen centers in the United States. The study showed that over a 5-year period, the mortality rate was 27%. Central venous access and parenteral nutrition also expose patients to an increased risk of several morbidities, including gallstones, cholestatic liver disease, glucose instability, deep vein thromboses, bone disease, and emboli. The ultimate goal in clinical management of patients with SBS is to wean off of parenteral nutrition and establish enteral autonomy. This goal can be difficult to achieve due to the significant malabsorption that occurs in SBS. Madsen et al<sup>2</sup> studied a cohort of subjects with short bowel syndrome, high stool output, and high fecal energy losses and demonstrated that they had a low coefficient of fat absorption of about 48%. This study demonstrates how significant malabsorption can be in patients with SBS and therefore highlights the challenge that clinicians face in attempting to minimize parenteral nutrition use. There are few medical therapies that improve absorption in patients with SBS. To date, teduglutide, a glucagon-like-peptide 2 (GLP-2) analog, is the only medication that has been clinically shown to improve intestinal adaptation and allow parenteral nutrition to be weaned in adults<sup>3</sup>. This drug shows great promise, but there are several concerns, such as increased risk of cancer and a loss of response with drug withdrawal.</p> <p>Pancreatic enzymes have been successful in improving enteral absorption in several patient populations, most notably in cystic fibrosis<sup>4,5</sup>. The impact of pancreatic enzymes on enteral absorption has not been evaluated in patients with SBS and will be the main focus of this study. Maximizing absorption to reduce parenteral nutrition needs in this patient population will be essential in reducing morbidity and mortality.</p> <p>The main objective of this study is to demonstrate if therapy with pancreatic enzymes will improve enteral fat absorption in patients with SBS. We hypothesize that patients with SBS are functionally <b>pancreatic insufficient</b> as a result of their intestinal resection for the following reasons: 1) decreased cholecystokinin (CCK) secretion and impaired enteroendocrine hormone secretion, 2) rapid intestinal transit, 3) high intestinal intraluminal volume, and 4) gastric acid hypersecretion.</p> <p>Exploratory aspects of the study also address the changes that nutrient absorption will have on intestinal adaptation and enteroendocrine hormone signaling. In our study, we will measure several hormone and enteroendocrine</p>

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hormone concentrations at baseline and following administration of pancreatic enzymes both as evidence for proper digestion and as markers of intestinal adaptation.

SBS is a life threatening disease process with a paucity of noninvasive therapies that directly improve enteral absorption and improve patient outcome. If pancreatic enzyme medication is found to improve enteral absorption, this study will increase the clinical use of pancreatic enzymes in patients with SBS. This study will also provide further information on the mechanisms of malabsorption in patients with SBS, which could facilitate identification of other therapeutic targets to improve enteral absorption. It will provide the framework for larger studies to improve enteral absorption in patients with SBS.

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**Study Objective(s)**

**Primary:**

The primary objective of this study will be to determine if enteral absorption improves in subjects with SBS following therapy with pancreatic enzymes. Patients with SBS have significant fat malabsorption for several reasons<sup>2</sup>. Lipid malabsorption in SBS occurs due to bowel resection, diluted pancreatic enzymes, altered enteroendocrine hormone signaling, acid hypersecretion, and rapid intestinal transit<sup>6</sup>. Pancreatic enzymes play a major role in enteral fat absorption. We propose that administering pancreatic enzymes to subjects with SBS will improve absorption of enteral nutrition.

**The primary hypothesis of this study is:**

**H1:** Pancreatic enzyme medication will improve enteral fat absorption in subjects with SBS, which will be indicated by an improved stool coefficient of fat absorption (CFA).

**Secondary:**

**A secondary hypothesis of this study will aim to further characterize the effect that pancreatic enzyme medication will have on global nutrient absorption.**

**H2:** Coefficient of nitrogen absorption (CNA) and bomb calorimetry (BC) will detect changes in enteral protein absorption and stool energy losses, respectively, before and after therapy with pancreatic enzymes.

We will address the unique difficulty of measuring enteral fat absorption in subjects with SBS. Fat absorption in a subset of subjects will be measured using the MBT. CCK concentration will also be measured in this subset as an additional area of exploration, as CCK plays a pivotal role in pancreatic enzyme secretion<sup>6</sup>. Additionally, we will explore the effect that improved nutrient absorption will have on intestinal adaptation by measuring changes in markers of intestinal mass and hormone levels.

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**H3:** The MBT will detect changes in enteral fat absorption before and after therapy with pancreatic enzyme medication on a subset of subjects. It will also help characterize the degree of pancreatic insufficiency in subjects. Baseline serum CCK concentration and serum CCK concentration following pancreatic enzyme therapy will also be determined in this subset.

**H4:** By promoting lipid digestion and release of free fatty acids, pancreatic enzymes will promote intestinal adaptation by stimulating endocrine signaling. Specifically, GLP-2, insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), and growth hormone (GH) concentrations will be measured from blood samples before and after treatment with pancreatic enzymes. Plasma citrulline will also be measured as a marker of intestinal mass before and after treatment with pancreatic enzymes.

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<b>Test Article</b>	Creon™, a pancreatic enzyme preparation
<b>Study Design</b>	This study will characterize enteral absorption, including enteral fat absorption, in subjects with SBS. We propose a longitudinal study design to assess enteral absorption before and after pancreatic enzyme medication in subjects with SBS.

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**Inclusion and  
Exclusion:**
**INCLUSION CRITERIA****General Inclusion Criteria**

- History of a small bowel resection
  - If small bowel resection occurred under 18 years of age, subjects must have dependence on parenteral nutrition for at least three months following small bowel resection
  - If small bowel resection occurred at 18 years of age or older, subjects must have 200 centimeters or less of residual bowel length and must have more than 3 bowel movements per day following small bowel resection
- Age 4 years to 75 years
- Usual state of health for the past two weeks with no medication changes
- Able to participate in a study for about four weeks with 2-4 study visits
- Able to take pancreatic enzyme medication orally

**MBT/CCK Subset Inclusion Criteria**

- Age 18 years to 75 years

All available details of estimated bowel length and presence or absence of an ileocecal valve will be taken into account, but there are no inclusion restrictions based on this information.

**EXCLUSION CRITERIA****General Exclusion Criteria**

- Significant disease other than SBS affecting the gastrointestinal tract that impacts absorption or digestion
  - Motility disorders that affect the upper gastrointestinal tract (i.e. chronic pseudo-obstruction, severe gastroparesis) or motility disorders that are poorly controlled
  - Unable to discontinue medications that directly alter fat absorption (i.e. bile acid sequestering agents, orlistat, weight loss medications, ursodeoxycholic acid) for one week prior to the first blood draw for the study until completion of stool collection following study visit 2 based on the preference of the subject or primary gastroenterologist. Permission must be obtained from the primary gastroenterologist before discontinuing medications in this category.
  - Cholestatic liver disease defined as a serum conjugated bilirubin greater than 1.0 mg/dL, chronic renal failure requiring dialysis or listed for kidney transplant, or gout
  - History of a pork allergy
  - Candidate for intestinal transplantation and listed as status 1
  - Women who are pregnant or lactating
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	<ul style="list-style-type: none"> <li>History of fibrosing colonopathy</li> </ul> <b>MBT/CCK Subset Exclusion Criteria</b> <ul style="list-style-type: none"> <li>History of a soy or safflower oil allergy</li> </ul>
<b>Number Of Subjects</b>	<p><b>Non-MBT/CCK Subset:</b> 16 subjects with SBS between the ages of 4 years and 17.9 years</p> <p><b>MBT/CCK Subset:</b> 10 subjects with SBS between the ages of 18 years and 75 years, subjects will have the option not to perform the MBT</p>
<b>Study Location</b>	All study visits will occur at outpatient research offices at the Clinical and Translational Research Center of the Children's Hospital of Philadelphia (CHOP), a pediatric health care center.
<b>Study Duration</b>	Subject participation will last about 3-4 weeks.
<b>Study Phases</b>	<p><u>Study Visit 0:</u> Informed consent, full 24 hour dietary recall if written consent obtained, blood draw if consent obtained and subject weighs less than 55 pounds, subjects may complete informed consent by telephone. If informed consent is obtained via telephone, then a signed informed consent form will be obtained either prior any study procedures, which includes a 24 hour dietary recall.</p> <p><u>Study Visit #1:</u> First study visit at CHOP. Subjects on pancreatic enzymes at baseline will have a three day washout period. Subjects who are not on pancreatic enzymes at baseline will not require a washout period. On the day of the study visit, all subjects will have laboratories drawn and anthropometrics. Those subjects in the MBT/CCK cohort will have a first MBT performed. Subjects who sign the informed consent form at visit 1 will complete a full 24 hour dietary recall instead of study visit 0. All subjects will be given instructions on how to complete a 3-day diet record and a 72-hour stool collection.</p> <p><u>Study Visit #2:</u> Following the initial diet record and stool collection, subjects can start pancreatic enzyme medication at study doses. Study visit #2 will be scheduled for day 5 of pancreatic enzyme medication. On the day of study visit #2, subjects will have laboratories drawn. Those subjects in the MBT/CCK cohort will have a second MBT performed. All subjects will complete a second 3-day diet record and a 72-hour stool collection at home. Following this, pancreatic enzyme medication will be discontinued and those subjects who were on pancreatic enzyme prior to the study will resume their regular dosing.</p> <p><u>Study Visit #3:</u> All subjects will provide their second 3-day dietary record and 72-hour stool collection. This visit will be used to ensure subject well-being and to monitor for adverse events. Subjects may complete this visit by telephone and mail stool samples to CHOP.</p>
<b>Efficacy Evaluations</b>	The efficacy of pancreatic enzyme medication administration (Creon™) will be evaluated in subjects with SBS using CFA as the primary outcome. CNA and BC will be measured as secondary outcomes. Some subjects in the MBT/CCK cohort will also have the MBT as an outcome of the change in enteral fat absorption before and after pancreatic enzyme medication administration.

<b>Pharmacokinetic Evaluations</b>	<u>N/A</u>
<b>Safety Evaluations</b>	Safety will be monitored by adverse events reporting. The frequencies of AEs by type, body system, severity and relationship to study supplement will be summarized. SAEs (if any) will be described in detail.
<b>Statistical And Analytic Plan</b>	<p>The goal of the primary aim of the study is to compare the outcome CFA before and after pancreatic enzyme medication administration in subjects with SBS. The secondary outcomes of CNA and BC will also be compared in subjects with SBS before and after pancreatic enzyme medication administration. Descriptive statistics for CFA, CNA, and BC outcomes (mean, standard deviation, median, range, 95% CI) will be calculated for the SBS cohort before and after pancreatic enzyme medication administration with paired t-tests or Wilcoxon sign rank tests depending on skewness of data.</p> <p>For the MBT outcomes, a moment-based pharmacokinetic (PK) analysis will be performed based on non-compartmental methodology using WinNonLin version 9.1 (Pharsight, Cary, NC). Baseline (<math>C_0</math>) and maximum (<math>C_{max}</math>) plasma concentrations are calculated, and area under the curve from time zero to eight hours (AUC) is calculated using the linear trapezoid method. PK parameters can then be compared between treatment groups using a paired t-test or Wilcoxon signed rank test as appropriate. To describe HA exposure relative to that of PA, the ratio of the HA to PA <math>C_{max}</math> (<math>C_{max}</math> HA/PA) and AUC (AUC HA/PA) is calculated for each subject after molar transformation and dose-normalization of exposure metrics<sup>7</sup>. Alternately, population PK analyses for repeated-measures endpoints can be conducted via nonlinear mixed-effects modeling with a qualified installation of the nonlinear mixed-effects modeling (NONMEM) software, Version VII, Level 2.0 (ICON Development Solutions, Hanover, MD<sup>8</sup>). Using this method, population PK modeling is conducted by simultaneously fitting structural PK models to both PA and HA concentrations<sup>9</sup>.</p> <p>Descriptive statistics (mean, standard deviation, median, range, 95% CI) will also be employed to assess outcomes related to intestinal hormone signaling that controls pancreatic enzyme secretion and intestinal adaptation in <b>H4</b> (glucagon-like peptide 2, insulin-like growth factor 1, insulin-like growth factor binding protein 3, and growth hormone concentrations). All variables will be tested for normality and nonparametric tests used as appropriate. The change in status for these variables before and after pancreatic enzyme medication administration will be explored with paired t-tests and Wilcoxon sign rank tests depending on skewness.</p>

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**MONITORING PLAN**

The Principal Investigator, Dr. Nina Sainath, is ultimately responsible for monitoring data integrity, patient safety, and overall study oversight. The study will be monitored weekly by the PI and Dr. Stallings. The study protocol will be carried out in accordance with OHRP guidelines and requirements. SAEs that are unanticipated, serious, and possibly related to the study will be managed by the PI, Dr. Sainath, as well as her mentor (Dr. Stallings). For subjects with SBS primarily managed at CHOP, members of the Intestinal Rehabilitation Program (Dr. Christina Bales) will be consulted immediately for all SAEs. For subjects with SBS primarily managed at Penn Medicine/HUP, their primary gastroenterologist and co-investigator, Dr. Octavia Pickett-Blakely, will be consulted immediately and will assume medical care. SAEs will be reported to the study sponsor, IRB, CTSC, and all members of the research team in accordance with requirements. Anticipated SAEs or those unrelated to the study will be reported to the same individuals/entities in accordance with requirements. There will be ongoing collection of data on adverse events and compliance to the treatment protocol throughout the study by the PI, Dr. Sainath, which will be reviewed weekly by Dr. Stallings.

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## SCHEDULE OF STUDY PROCEDURES & STUDY TIMELINE

**Table 1. Summary of Study Visits #1 and #2 and Methods**

	All subjects	MBT/CCK Subset		Non-MBT/CCK Subset		All subjects
Assessment	Visit 0	Visit 1	Visit 2	Visit 1	Visit 2	Visit 3
<b>Obtain informed consent</b>	•					
<b>Study Intervention: Administration of Creon™</b>			•		•	
<b>Primary Outcome</b>						
Coefficient of Fat Absorption (stool)		•	•	•	•	
<b>Secondary Outcomes</b>						
Coefficient of Nitrogen Absorption (stool)		•	•	•	•	
Fecal Bomb Calorimetry (stool)		•	•	•	•	
Malabsorption Blood Test (MBT) (PA, HA, HA/PA absorption, pharmacokinetics)		• <sup>#</sup>	• <sup>#</sup>			
Serum prealbumin		•	•	•	•	
Intestinal Adaptation: serum citrulline, IGF-1, IGF BP3, GLP 2, GH, stool pH, gastric pH		•	•	•	•	
Serum CCK		• <sup>#</sup>	• <sup>#</sup>			
Fecal elastase		•		•		
<b>Diet</b>						
24-hour dietary recall	•	• <sup>**</sup>				
3-day Weighed Food Record		•	•	•	•	
<b>Safety</b>						
Complete Blood Count with Differential		•	•	•	•	
Serum Basic Metabolic Panel		•	•	•	•	
Serum Hepatic Function Panel		•	•	•	•	
Adverse Event Monitoring		•	•	•	•	•
<b>Other</b>						
Anthropometry: height, weight, DXA, skinfolds, circumferences		•		•		
Nutrition Labs: serum vitamins A, E, K; 25-OH vitamin D; zinc; selenium; fatty acid profile	• <sup>*</sup>	•		•		
Health History and Medications		•		•		
Home Environment Questionnaire		•		•		
Pancreatic enzyme medication adherence			•		•	•
Quality of life (MOS SF-36 for adults, PedsQL for subjects < 18 years)		•		•		

**\* Nutrition labs will only be drawn at study visit 0 in subjects who weigh less than 25 kilograms**

**\*\* Subjects who sign the informed consent form at the start of study visit 1 will have a 24 hour dietary recall performed at study visit 1 instead of study visit 0**

**# Subjects in the MBT/CCK cohort will have the option not to have the MBT and serum CCK**

**Table 2. Study Timeline**

	Year 1 (2016-2017)											
	May	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	March	Total
Start-up	x											
MBT/CCK Subset												
Baseline		1	0	1	3	3	2					10
Follow-up		0	1	1	3	3	2					10
Non-MBT/CCK Subset												
Baseline		0	0	5	4	4	3					16
Follow-up		0	0	5	4	4	3					16
Total Visits		1	1	12	14	14	10					52
Data Analysis									x	x	x	
Close out /Writing									x	x	x	

**Table 3. Protocol for MBT/CCK subset<sup>#</sup>**

Protocol	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
<b>MBT #1</b>	Wash-out  No PE*	Wash-out  No PE	Wash-out  No PE  - Fast from 8 pm  - No dairy  - No alcohol  - Normal activity	<b>STUDY VISIT #1</b>  <b>MBT at 8 am</b>  - Lunch at 2 pm  - 9 hourly blood draws  <b>LABS</b>  <b>ANTHROS</b>	Home  - Return to usual diet	Diet record (day 1)	- Diet record (day 2)  - 72-hour stool collection (day 1)	- Diet record (day 3)  - 72-hour stool collection (day 2)	- 72-hour stool collection (day 3)  - PE can be started following stool collection	--
<b>MBT #2</b>	PE treatment	PE treatment	PE treatment	PE treatment  - Fast from 8 pm  - No dairy  - No alcohol  - Normal activity	PE treatment  <b>STUDY VISIT #2</b>  <b>MBT at 8 am</b>  - Lunch at 2 pm  - 9 hourly blood draws  <b>LABS</b>	PE treatment  Home  - Return to usual diet	PE treatment  Diet record (day 1)	PE treatment  - Diet record (day 2)  - 72-hour stool collection (day 1)	PE treatment  - Diet record (day 3)  - 72-hour stool collection (day 2)	PE treatment  - 72-hour stool collection (day 3)  - PE can be discontinued following stool collection

\* PE = pancreatic enzymes

<sup>#</sup> subjects in the MBT/CCK subset who elect not to have the MBT will follow the non-MBT/CCK protocol

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**Table 4. Protocol for NON -MBT/CCK subset**

Protocol	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
<b>Phase 1</b>	Wash-out  No PE	Wash-out  No PE	Wash-out  No PE	<b>STUDY VISIT #1</b>  <b>LABS</b>  <b>ANTHROS</b>	Home  - Normal diet	Diet record (day 1)	- Diet record (day 2)  - 72-hour stool collection (day 1)	- Diet record (day 3)  - 72-hour stool collection (day 2)	- 72-hour stool collection (day 3)  - PE can be started following stool collection	--
<b>Phase 2</b>	PE treatment	PE treatment	PE treatment	PE treatment	<b>PE treatment</b>  <b>STUDY VISIT #2</b>  <b>LABS</b>	PE treatment  Home  - normal diet	PE treatment  Diet record (day 1)	PE treatment  - Diet record (day 2)  - 72-hour stool collection (day 1)	PE treatment  - Diet record (day 3)  - 72-hour stool collection (day 2)	PE treatment  - 72-hour stool collection (day 3)  - PE can be discontinued following stool collection

## 1 BACKGROUND INFORMATION AND RATIONALE

### 1.1 Introduction

Short bowel syndrome (SBS) occurs when there is a history of prior bowel resection and the residual functional intestinal mass is insufficient to allow for adequate absorption of fluid, electrolytes, nutrients, and micronutrients provided by an age appropriate diet. There are several etiologies of SBS, which differ between pediatric and adult populations. In adults, the most common causes of SBS include mesenteric ischemia, Crohn disease, malignancy, radiation enteritis, surgical complications, and trauma<sup>6</sup>. In pediatric patients, SBS is most commonly due to necrotizing enterocolitis and congenital anomalies, such as intestinal atresia, gastroschisis, and malrotation<sup>10</sup>.

Patients with SBS have a high mortality rate that is mainly attributed to complications from central venous access and parenteral nutrition<sup>1</sup>. In 2012, Squires et al<sup>1</sup> published the largest retrospective review to date that described outcomes for patients with SBS at fourteen centers in the United States. The study showed that over a 5-year period, the mortality rate was 27%. Central venous access and parenteral nutrition also expose patients to an increased risk of several morbidities, including gallstones, cholestatic liver disease, glucose instability, deep vein thromboses, bone disease, and emboli. The ultimate goal in clinical management of patients with SBS is to wean off of parenteral nutrition and establish enteral autonomy. This goal can be difficult to achieve due to the significant malabsorption that occurs in SBS. Madsen et al<sup>2</sup> studied a cohort of subjects with short bowel syndrome, high stool output, and high fecal energy losses and demonstrated that they had a low coefficient of fat absorption of about 48%. This study demonstrates how significant malabsorption can be in patients with SBS and therefore highlights the challenge that clinicians face in attempting to minimize parenteral nutrition use.

There are few medical therapies that improve absorption in patients with SBS. To date, teduglutide, a glucagon-like-peptide 2 (GLP-2) analog, is the only medication that has been clinically shown to improve intestinal adaptation and allow parenteral nutrition to be weaned in adults<sup>3</sup>. This drug shows great promise, but there are several concerns, such as increased risk of cancer and a loss of response with drug withdrawal.

Pancreatic enzymes have been successful in improving enteral absorption in several patient populations, most notably in cystic fibrosis<sup>4,5</sup>. The impact of pancreatic enzymes on enteral absorption has not been evaluated in patients with SBS and will be the main focus of this study.

Our primary objective is to demonstrate that treating patients with SBS with pancreatic enzymes will improve enteral fat absorption. However, exploratory aspects of the study also address the changes that nutrient absorption will have on intestinal adaptation and enteroendocrine hormone signaling.

SBS is a life threatening disease process with a paucity of noninvasive therapies that directly improve enteral absorption and improve patient outcome. Maximizing absorption to reduce parenteral nutrition needs in this patient population will be essential in reducing morbidity and mortality. This study will also provide further information on the mechanisms of malabsorption in patients with SBS, which could facilitate identification of other therapeutic targets to improve enteral absorption. It will provide the framework for larger studies to improve enteral absorption in patients with SBS.

## **1.2 Name and Description of Investigational Product or Intervention**

Creon™ (pancrelipase) Delayed-Release Capsules), a pancreatic enzyme preparation, is a drug that requires prescription for use. It is approved for exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, or other conditions. In the study, we will use Creon 6™, 6,000 USP units of lipase; Creon12™, 12,000 USP units of lipase; Creon24™, 24,000 USP units of lipase; and Creon36™, 36,000 USP units of lipase.

## **1.3 Findings from Non-Clinical and Clinical Studies**

Creon™ is FDA approved for use in exocrine pancreatic insufficiency due to cystic fibrosis and other etiologies. It has been used anecdotally in patients with SBS and is cited as therapy for patients with SBS by experts in the field<sup>11</sup>. The effect of pancreatic enzymes on enteral absorption in SBS has never been formally studied.

## **1.4 Selection of Drugs and Dosages**

This is a proof of concept study and the use of pancreatic enzymes in short bowel syndrome has not been studied before. As a result, our preference would be to use the highest doses of pancreatic enzyme that are deemed safe for our subjects in order to assess if absorption can be improved.

We have based pancreatic enzyme dosing on typical dosing used by the senior dietitian and a senior physician at the Cystic Fibrosis Center at the Children's Hospital of Philadelphia (CHOP) and as recommended by the most recent consensus statement on pancreatic enzyme dosing in cystic fibrosis<sup>12</sup>. The recommended dosing for meals ranges from 500 – 2500 lipase units/kg/meal. The CF Center at CHOP uses a maximum dose of 2500 lipase units/kg/meal and 1250 lipase units/kg/snack. We will aim to administer about 1500 – 2500 lipase units/kg/meal and 750 – 1250 lipase units/kg/snack in this study (see [Table 5 below](#)). Exact dosing will depend on the subject's complicated enteral feeding regimen. Pancreatic enzyme dosing will be weight based and we will not exceed 10,000 lipase units/kg/day for each patient<sup>12,13</sup>.

We anticipate that several subjects in this study will have a complicated enteral feeding regimen that may be comprised of one or more of the following options: 1) bolus gastrostomy tube feeds, 2)

continuous overnight gastrostomy tube feeds, and 3) continuous gastrostomy tube feeds for 18 -24 hours of the day. Please see [Table 5](#) below for a summary of goal pancreatic enzyme dosing for each of these enteral feeding regimens. Subjects should be able to take pancreatic enzyme medication orally in order to be included in the study even if they rely on a gastrostomy tube or jejunostomy tube.

**Table 5. Goal Pancreatic Enzyme Dosing\***

	Pancreatic Enzyme Dosing
Meal	1,500 – 2,500 lipase units/kg/meal
Snack	750 – 1,250 lipase units/kg/snack
Bolus enteral feeds (typically 1 hour infusion)	1,500 – 2,500 lipase units/kg/meal administered with each bolus <sup>+</sup>
Overnight enteral feeds (typically 8-12 hours)	1,500 – 2,500 lipase units/kg/meal administered at the start and end of the feed
Continuous enteral feeds (typically 20-24 hours)	<ul style="list-style-type: none"> <li>• 1,500 – 2,500 lipase units/kg/meal administered at the start and end of the feed</li> <li>• While awake and during continuous feed, enzymes dosed every 4 hours based on grams of fat in formula (not to exceed 4,000 lipase units/grams of fat/day)</li> </ul>

\* Will not exceed maximum daily enzyme dosing of 10,000 lipase units/kg/day

<sup>+</sup> The dose of enzymes with each bolus depends on the enteral feeding regimen, grams of fat, and the volume and number of boluses

**Bolus feeds:** The dose of enzymes that each subject receives prior to each bolus will depend on the volume and total number of boluses received per day. We will attempt to cover each bolus with a maximum dose of 1500 – 2500 lipase units/kg/meal, but this may be reduced if boluses are smaller in volume or occur frequently.

**Overnight feeds:** This group includes subjects on overnight enteral feeds for 8-12 hours. These subjects will receive one meal dose of Creon™ (1500 - 2500 lipase units/kg) prior to feeds and one meal dose of Creon™ at the end of feeds, consistent with our current practice at CHOP.

**Continuous feeds:** This group includes those subjects on continuous enteral feeds for 20-24 hours of the day. For these subjects, we will dose enzymes every 4 hours while awake based on grams of fat in the formula and based on recommended dosing per grams of fat. Overnight, they will receive one meal dose of Creon™ (1500 – 2500 lipase units/kg) before and after the overnight feed.

We will not exceed 10,000 lipase units/kg/day or 4000 lipase units/grams of fat/day for any subject<sup>13</sup>. Each subject will receive pancreatic enzyme medication for a total of ten days. They will start Creon™ 4 days prior to study visit #2, they day of study visit #2, and then for five days after the visit until they have completed the second stool collection.



## 1.5 Relevant Literature

Pancreatic enzymes have been used in patients with SBS and it is cited as a possible therapy for use in SBS<sup>11</sup>. The main objective of this study is to demonstrate that therapy with pancreatic enzymes will improve enteral fat absorption in patients with SBS. We hypothesize that patients with SBS are functionally **pancreatic insufficient** as a result of their intestinal resection for the following reasons: 1) decreased cholecystokinin (CCK) secretion and impaired enteroendocrine hormone secretion, 2) rapid intestinal transit, 3) high intestinal intraluminal volume, and 4) gastric acid hypersecretion.

Cholecystokinin (CCK) is a hormone released by enteroendocrine cells in the small bowel. CCK is responsible for stimulating pancreatic and gallbladder secretions and inhibiting gastric emptying<sup>6</sup>. These functions together promote absorption. It has been shown that patients with SBS have a decreased CCK response following a meal when compared to healthy controls<sup>14</sup>. This impaired response may occur because bowel resection directly results in the loss of cells that secrete CCK. It also may occur due to the impaired secretion of other enteroendocrine hormones that affect CCK secretion. Decreased CCK production would result in decreased secretion of pancreatic enzymes into the intestinal lumen and thus functional pancreatic insufficiency.

A second proposed mechanism for functional pancreatic insufficiency in SBS is related to the rapid intestinal transit that occurs in this population. The distal small bowel is responsible for the secretion of several enteroendocrine hormones, including peptide YY and GLP-2<sup>6</sup>. In a small study on patients with SBS, Nightingale et al<sup>15</sup> showed that patients who lack a distal small bowel and colon had more rapid intestinal transit compared to a healthy control population. This same study also showed that peptide YY hormone secretion was impaired following a meal in these same subjects compared to healthy subjects. This study suggests that resection of the distal small bowel and colon impairs peptide YY secretion, which results in accelerated intestinal transit. It is often thought that peptide YY and other hormones secreted by the distal small bowel and colon act as an 'intestinal break', slowing down movement of the intestine in order to promote absorption<sup>6,15</sup>. Loss of this 'intestinal break' due to bowel resection is therefore thought to lead to faster movement of food through the intestine. Rapid intestinal transit impairs digestion and absorption, as it does not allow luminal contents adequate time to interface with digestive enzymes and the surface mucosa of the bowel. Thus, exogenous pancreatic enzymes can more readily promote micelle formation in the proximal bowel for prompt lipid absorption.

A third proposed mechanism for functional pancreatic insufficiency in SBS is due to the dilution of pancreatic enzymes in the intestinal lumen. The notion of diluted pancreatic enzymes is supported by the clinical observation that when fecal elastase levels are checked as a measure of pancreatic function in patients with SBS, levels are often low due to dilution in watery stool. Though the pancreas may still secrete enzymes into the duodenum, they are likely to be diluted by the high volume of intestinal contents and therefore be less effective. This increased intraluminal volume is not only due to malabsorption, but also due to a high enteral caloric intake. Patients with SBS often receive a higher amount of enteral calories than required by healthy patients of a similar age.

Finally, gastric acid hypersecretion may contribute to functional pancreatic insufficiency in patients with SBS. Gastric acid hypersecretion, specifically, tends to occur for months following intestinal resection. It is thought to be due to altered enteroendocrine hormone signaling following resection and a loss of inhibition of gastrin that leads to increased gastric acid production<sup>6,16,17</sup>. The effect of gastric acid hypersecretion is two-fold in that it increases the volume of contents in the intestinal

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lumen, which serves to dilute pancreatic enzymes present in the lumen. It also drives the luminal pH in the small bowel down, which results in suboptimal activity of pancreatic enzymes<sup>6,16,17</sup>.

Our primary objective is to demonstrate that treating patients with SBS with pancreatic enzymes will improve enteral fat absorption. We will look to determine if administration of pancreatic enzymes in these subjects with SBS results in a change in CFA, as well as other markers of absorption, including stool bomb calorimetry and coefficient of nitrogen absorption (CNA).

An exploratory aspect of this study includes the use of the malabsorption blood test (MBT) as a measure of enteral absorption. Clinically, it is challenging to measure absorption in patients with SBS and this is typically estimated by monitoring height, weight, and serum micronutrient levels. This study will be one of the first to perform multiple measures of absorption on patients with short bowel syndrome. Currently, the gold standard for gut absorption is the CFA. The MBT will be utilized on a subset of subjects in this study as an additional measure of enteral fat absorption, but also to characterize the degree of pancreatic insufficiency in subjects. In this test, subjects consume a high fat shake that contains pentadecanoic acid (PA), a free fatty acid, and triheptadecanoic acid (THA), a triglyceride. Baseline serum levels of PA and THA are measured and then serial serum levels are checked following consumption of the shake allowing calculations to determine enteral fat absorption to be made. The MBT is unique in that it measures absorption of both a triglyceride and a free fatty acid. Improved pancreatic function should result in improvement of triglyceride absorption specifically, as absorption of free fatty acids does not depend upon lipase.

Exploratory aspects of the study also address the changes that nutrient absorption will have on intestinal adaptation and enteroendocrine hormone signaling. Intestinal adaptation refers to the process of improving and maximizing the absorptive capacity of the residual intestine in patients with SBS. It is clear that intestinal resection alters enteroendocrine hormone signaling<sup>6,18</sup>. Alterations in enteroendocrine hormone signaling impact both intestinal absorption and transit. As mentioned, repletion of one intestinal hormone, GLP-2, does improve absorptive capacity of the small intestine<sup>3</sup>.

Endocrine hormones, such as CCK, stimulate proper digestion of triglyceride for fat absorption, but then free fatty acids also mediate downstream endocrine signaling. It is clear that the type of macronutrient, as well as the phase of digestion are both important contributors in the stimulation of enteroendocrine cells<sup>19</sup>. For example, an undigested lipid does little to stimulate enteroendocrine hormone secretion, whereas free fatty acids and monoacylglycerols bind to specific receptors to stimulate hormone secretion, such as GLP-2. Patients with SBS have impaired secretion of GLP-2, which is associated with poor intestinal growth and absorption<sup>6</sup>. Removal of bowel also results in resection of enteroendocrine cells, which explains part of the change in hormonal signaling. One study<sup>20</sup> demonstrated that rats with a significant bowel resection demonstrated improved small bowel growth and adaptation with exposure to GLP-2 and enteral nutrition together compared to enteral nutrition alone, GLP-2 alone, or parenteral nutrition. Thus, not only do enteric hormones allow for proper digestion and absorption, but proper digestion also stimulates intestinal growth. This study also highlights that the delivery of nutrients into the bowel plays a crucial role in hormone signaling.

Several markers of intestinal adaption exist. Insulin-like growth factor 1 (IGF-1) is thought to play a key role in intestinal growth, specifically in that it likely serves downstream of the action of GLP-2<sup>20,21</sup>. Though it is produced primarily by the liver, IGF-1 is also thought to be produced locally in the intestine. Data on growth hormone and IGF-1 in humans has been conflicting, though a study by

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Goulet et al<sup>21</sup> demonstrated improved absorption and decreased dependence on parenteral nutrition following treatment with growth hormone. These patients had increased plasma levels of citrulline, a measure of total intestinal mass, as well as increased serum IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3) concentrations in association with growth hormone (GH) therapy.

In our proposed study, we will explore how improved nutrient absorption alters intestinal adaptation and enteric hormone secretion. We will measure baseline GLP-2, IGF-1, IGFBP-3, GH, and citrulline serum levels. Following administration of pancreatic enzymes, we will assess if improved digestion of nutrients promotes intestinal adaptation by stimulation of enteroendocrine cells. This would be reflected in an increase in serum levels of GLP-2, IGF-1, IGFBP-3, GH, and citrulline following exposure to pancreatic enzyme medication.

As outlined above, rapid intestinal transit, high intestinal luminal volume that may dilute pancreatic enzymes, acid hypersecretion, and altered enteroendocrine hormone secretion all serve as likely causes of functional pancreatic insufficiency in patients with short bowel syndrome. In the proposed study, we will measure fat absorption in subjects with SBS at baseline and following exposure to pancreatic enzyme medication. If treatment with pancreatic enzymes results in improved enteral absorption, it could allow parenteral nutrition to be decreased. This may substantially improve morbidity and mortality in patients with SBS. Furthermore, pancreatic enzymes are a noninvasive intervention with a good safety profile in other disease processes. It would be easy to incorporate their use into the clinical care of patients with SBS if there was evidence that pancreatic enzymes improve enteral absorption.

## 1.6 Compliance Statement

This study will be conducted in full accordance of all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

## 2 STUDY OBJECTIVES

### 2.1 Primary Aim

2.1.1. The primary aim of this study is to determine if pancreatic enzymes improve enteral fat absorption in subjects with SBS. Enteral fat absorption will be measured as CFA. For each subject, CFA will be compared before and after administration of pancreatic enzyme medication.

### 2.2 Secondary Aims

2.2.1. The **secondary aim** of this proposal is to assess the effect that administration of pancreatic enzymes will have on global absorption. Specifically, CNA and stool BC will be measured to detect changes in enteral protein absorption and stool energy losses, respectively, before and after administration of pancreatic enzymes.

We hope to address the unique difficulty of measuring enteral fat absorption in subjects with SBS. Fat absorption in a subset of subjects will be measured using the MBT. CCK concentration will also be measured in this subset as an additional area of exploration, as CCK plays a pivotal role in pancreatic enzyme secretion<sup>6</sup>. Additionally, we hope to explore the effect that improved nutrient absorption will have on intestinal adaptation by measuring markers of intestinal mass and hormone levels.

2.2.2. We will **explore** the ability of the MBT to detect changes in enteral fat absorption before and after administration of pancreatic enzymes in a subset of patients. This test will also help characterize the degree of pancreatic insufficiency in subjects. Baseline serum CCK concentration and serum CCK concentration following pancreatic enzyme therapy will also be determined in this subset.

2.2.3 A final aim will **explore** if improved lipid digestion and release of free fatty acids due to pancreatic enzymes will promote intestinal adaptation by stimulating endocrine signaling. Specifically, GLP-2, IGF-1, IGFBP-3, and GH concentrations will be measured from blood samples before and after administration of pancreatic enzymes. Plasma citrulline will also be measured as a marker of intestinal adaptation before and after administration of pancreatic enzymes.

### **3 INVESTIGATIONAL PLAN**

#### **3.1 General Schema of Study Design**

##### **3.1.1 Screening Phase**

Potential subjects will be screened using the protocol inclusion and exclusion criteria. Subjects will be recruited from regional academic hospitals and gastroenterology subspecialty centers. Primary recruitment centers will include regional academic hospitals and gastroenterology subspecialty centers. Primary recruitment centers will include: 1) The Children's Hospital of Philadelphia and 2) University of Pennsylvania Medical Center Hospital. Primary recruitment centers may include: 1) Pennsylvania Hospital; 2) Presbyterian Hospital; and 3) Philadelphia Veterans Administration Medical Center. Other likely collaborators and recruitment centers may include: 1) St. Christopher's Hospital for Children and 2) other regional centers. These outside institutions will be involved with recruitment of subjects only and will otherwise not be engaged in the research. Our research team anticipates no difficulty in enrolling well-qualified participants with the proposed sample size (**see Table 2. Study Timeline**). Informed consent will be obtained prior to any study related procedures being performed, and this will include the discontinuation of pancreatic enzyme medication for those participants who are taking this medication at the time of enrollment in the study.

##### **3.1.2 Study Treatment Phase**

All study visits will occur at outpatient research offices of the Clinical and Translational Research Center at The Children's Hospital of Philadelphia (CHOP), a pediatric health care center. Eligible subjects will be enrolled into the study and come to CHOP for 2-4 study visits. Refer to Table 1 for list of assessments and the study timeline (Table 2) for the pace of recruitment.

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### **3.1.3 Open-label treatment with Creon™**

All subjects will receive Creon™ intervention that starts 4 days prior to Study Visit #2. Study visit #2 will be about 2 weeks after Study visit #1. Please refer to Table 1 for list of assessments and the study timeline (Table 2) for the visit schedule.

### **3.2 Allocation to Treatment Groups and Blinding**

This is an open-label intervention therapeutic exploratory study, and not a randomized controlled trial.

### **3.3 Study Duration, Enrollment and Number of Sites**

#### **3.3.1 Duration of Study Participation**

The study duration for all subjects will be up to four weeks.

#### **3.3.2 Total Number of Study Sites/Total Number of Subjects Projected**

The study will be conducted at two investigative site in the United States, the Children's Hospital of Philadelphia and the University of Pennsylvania. Recruitment will occur across regional centers as described above. All study visits will occur at The Children's Hospital of Philadelphia.

Recruitment will stop when 16 subjects with SBS between the ages of 4 and 17.9 years are enrolled and when 10 subjects with SBS between the ages of 18 years and 75 years are enrolled. It is expected that 26 subjects will be enrolled to produce at least 22 evaluable subjects.

### **3.4 Study Population**

#### **3.4.1 Inclusion Criteria**

##### **General Inclusion Criteria for all Subjects**

- History of a prior small bowel resection
  - If small bowel resection occurred under 18 years of age, subjects must have dependence on parenteral nutrition for at least three months following small bowel resection
  - If small bowel resection occurred at 18 years of age or older, subjects must have 200 centimeters or less of residual bowel length and must have more than 3 bowel movements per day following small bowel resection
- Age 4 years to 75 years
- Usual state of health for the past two weeks with no medication changes
- Able to participate in a study for about four weeks with four study visits
- Able to take pancreatic enzyme medication orally

##### **MBT/CCK Subset Inclusion Criteria**

- Age 18 years to 75 years

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All available details of estimated bowel length will be taken into account, but there are no inclusion restrictions based on this information.

### **3.4.2 Exclusion Criteria**

#### **General Exclusion Criteria for all Subjects**

- Significant disease other than SBS affecting the gastrointestinal tract that impacts absorption or digestion
- Motility disorders that affect the upper gastrointestinal tract (i.e. chronic pseudo-obstruction, severe gastroparesis) or motility disorders that are poorly controlled
- Unable to discontinue medications that directly alter fat absorption (i.e. bile acid sequestering agents, orlistat, weight loss medications, ursodeoxycholic acid) for one week prior to the first blood draw for the study until completion of stool collection following study visit 2 based on the preference of the subject or the primary gastroenterologist. Permission must be obtained from the primary gastroenterologist before discontinuing medications in this category.
- Cholestatic liver disease defined as a serum conjugated bilirubin greater than 1.0 mg/dL), chronic renal failure requiring dialysis or listed for kidney transplant, or gout
- History of a pork allergy
- Candidate for intestinal transplant and listed as status 1
- Women who are pregnant or lactating
- History of fibrosing colonopathy

#### **MBT/CCK Subset Exclusion Criteria**

- History of a soy or safflower oil allergy

## **4 STUDY PROCEDURES**

### **4.1 Screening**

Subjects will be screened with support from the clinical sites using the protocol inclusion and exclusion criteria. Clinic staff will inform eligible individuals of the existence of this study and ask for permission from these individuals to share their contact information with the CHOP study staff. The Recruitment Enhancement Core at CHOP will provide assistance with recruitment plan development and also identify individuals with a diagnosis of short bowel syndrome and contact potential participants. We will also use the Penn Analytics Data Center to identify patients with a diagnosis of short bowel syndrome. Once identified, we will contact their provider to inform individuals of the existence of the study either in person, by telephone, or via letter and to obtain permission to share their contact information with the CHOP study staff. Either verbal or in person screening can occur. In the instance of screening over the phone, verbal subject permission will be obtained. In the instance of in person screening, study staff will obtain a signature from the subject. For both instances, screening consent will occur prior to obtaining any information from study subjects. Screening will be performed by medical record review and administration of a

questionnaire with details on medical history. Questionnaires can be completed both in-person or over the telephone. Subjects will be asked to contact the lead investigator, Dr. Sainath, if their enteral feeding regimen changes between screening and Study Visit #1.

All subjects will be enrolled in their usual state of health defined as no hospitalizations, emergency room or unscheduled acute illness clinic visits, and with activity levels and food intake considered typical by the subject for two weeks prior to Study Visit #1.

## 4.2 Study Treatment Phase

Subjects will have 2-4 visits in this study that will all occur at The Children's Hospital of Philadelphia. Study visit 0 will be to obtain informed consent and laboratories may be drawn (see description below). Study Visit #1 will be without pancreatic enzyme medication and Study Visit #2 will occur after they receive Creon™ as their pancreatic enzyme medication therapy. Study visit #3 will be off of study doses of pancreatic enzyme medication, though subjects on pancreatic enzymes at baseline may resume their regular dose. Study visit #3 will be to assess subject well-being, medication adherence, and to drop off stool collected and dietary records.

Study Visit #1 includes anthropometrics and baseline laboratories. A spot stool sample will be collected to determine stool pH. Subjects in the MBT/CCK cohort will have the MBT performed as well and a serum CCK concentration as part of their laboratories. Study Visit #2 includes repeat laboratories, which will not include micronutrient levels. A spot stool sample will be collected to determine stool pH. Subjects in the MBT/CCK cohort will again have the MBT performed and a serum CCK concentration drawn. (refer to study procedures in Table 1).

Study Visit 0: Visit for Consent and HIPAA Authorization for release of medical record information

- Informed Consent will be obtained at study visit 0. Subjects will have the option to complete this study visit via telephone. If subjects are taking pancreatic enzyme medication and will need to discontinue medication 3 days prior to Study Visit #1, a signed, informed consent form will be obtained in person or by mail, fax, or email prior to the beginning of any discontinuation of the medication. If subjects are taking a medication that directly alters fat absorption and will need to discontinue medication one week prior to Study Visit #1, a signed, informed consent form will be obtained prior to the beginning of any discontinuation of the medication. Medications that alter fat absorption will not be discontinued without the permission of the primary gastroenterologist. We will obtain a signed, informed consent form for all subjects in the MBT/CCK cohort prior to initiation of fasting or dietary changes for study visit 1. HIPAA Authorization forms from the subjects' institutions will be obtained and will be signed in person or obtained by mail/fax/email.
- Instructions in preparation for study procedures will be given in person at study visit 0. If this visit is conducted via telephone, instructions will be given via at that time.
- At study visit 0, a 24 hour dietary recall will be completed once written consent is obtained in order to allow for detailed calculations of pancreatic enzyme medication dosing. If informed consent is obtained via telephone, a signed, informed consent form will be obtained prior to completing a 24 hour dietary

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recall. If signed, informed consent is obtained at study visit 1, completion of a 24 hour dietary recall will occur at study visit 1.

- At study visit 0, once consent has been obtained, subjects less than 25 kilograms will have laboratories drawn to check micronutrient levels. Subjects who weigh less than 25 kilograms must come to CHOP for study visit 0, but will have the option of completing informed consent via telephone. The informed consent form will be signed prior to having laboratories drawn at study visit 0.

There are four protocols for Study Visit #1. The first protocol is for subjects with SBS who are naïve to pancreatic enzyme medication, that is, they have not received pancreatic enzyme medication prior to Study Visit #1. The second protocol for Study Visit #1 is for subjects with SBS who are currently taking pancreatic enzyme medication and will require a pancreatic enzyme medication washout period, that is, they will not take pancreatic enzyme medication for three days prior to Study Visit #1 (a “pancreatic enzyme medication washout” period). The third protocol is for subjects who are part of the MBT/CCK cohort who will have the MBT during Study Visit #1 and who are naïve to pancreatic enzyme medication. The fourth protocol is for subjects who are part of the MBT/CCK cohort and will have the MBT during Study Visit #1 and who also require a pancreatic enzyme medication washout. All subjects will be prescribed Creon™ as their pancreatic enzyme medication therapy and will receive this therapy for Study Visit #2. Please note that subjects eligible for the MBT/CCK subset will have the option to decline the MBT. If this occurs, these subjects will follow the same protocol as those in the non-MBT/CCK subset.

### **Study Visit #1: Protocol for non-MBT/CCK Subjects who have not Received Pancreatic Enzyme Medication Prior to Study Visit #1**

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#### **Day 1-7 - Home**

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- Those subjects who are on a medication that directly alters fat absorption will discontinue this medication after permission is obtained from their primary gastroenterologist. Study team must have a signed, informed consent form prior to discontinuation of medication.
- Subject’s normal diet

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#### **Day 8 – CHOP Visit to CTSC Outpatient Lab and NGL**

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- Sign informed consent form if study visit 0 conducted via telephone for those subjects who do not have to discontinue medication or have labs at study visit 0
- 24-hour dietary recall for those subjects who sign the informed consent form at study visit 1
- Urine pregnancy test for pre-menopausal females
- Subject’s normal diet
- Baseline blood draw: Fat soluble vitamins (A, D, E, K)\*, pre-albumin, serum zinc\*, selenium\*, fatty acid profile\*, citrulline, IGF-1, IGF BP3, GLP-2, GH, CBC, CMP, hepatic function panel
- Anthropometry (height, weight, skinfolds, circumferences)
- Whole body DXA



- 
- Spot stool sample will be collected for stool pH and fecal elastase. Subjects who are unable to produce a sample at the visit will collect and freeze a stool sample at home on one occasion on Day 8, 9, or 10.
  - If subject has a G tube, spot gastric pH will be checked
  - Questionnaires: Health History and medications, Home Environment, Quality of Life (MOS SF-36 or PedsQL)
  - Instructions will be given for collection and shipping for: stool collection (72-hour fecal fat and nitrogen analysis and bomb calorimetry), 3-day weighed food records, and adverse events diary
  - Prescribe Creon™ and dispense to subjects
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#### **Day 9 - Home**

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- Maintain adverse events diary
  - Subject's normal diet
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#### **Day 10 - Home**

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- Subject's normal diet
  - 3-day weighed food record begins
  - Food record – Day 1
  - Maintain adverse events diary
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#### **Day 11 - Home**

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- Subject's normal diet
  - Food record – Day 2
  - Stool collection begins (72-hour fecal fat, 72-hour fecal nitrogen, and bomb calorimetry), store frozen until brought to CHOP.
  - 72-hour stool – Day 1
  - Maintain adverse events diary
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#### **Day 12 - Home**

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- Subject's normal diet
  - Food record – Day 3
  - 72-hour stool – Day 2
  - Maintain adverse events diary
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#### **Day 13 - Home**

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- Subject's normal diet
  - 72-hour stool – Day 3
  - Maintain adverse events diary
-

- These laboratories will be drawn at study visit 0 if the subject weighs less than 25 kg

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**Study Visit #1: Protocol for non-MBT/CCK Subjects who are Receiving Pancreatic Enzyme Medication Prior to Study Visit # 1 and require a Washout Period**

Participants discontinuing pancreatic enzyme medication will be without this medication for the nine days encompassing Visit 1.

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**Day 1-4 - Home**

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- Those subjects who are on a medication that directly alters fat absorption will discontinue this medication after permission is obtained from their primary gastroenterologist. Study team must have a signed, informed consent form prior to discontinuation of medication.
- Subject's normal diet

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**Days 5, 6, & 7**

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- Discontinue pancreatic enzyme medication (Washout) Subject's normal diet

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**Day 8 – CHOP Visit to CTSC Outpatient Lab and NGL**

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- Sign informed consent form if study visit 0 conducted via telephone for those subjects who do not have to discontinue medication or have labs at study visit 0
- 24-hour dietary recall for those subjects who sign the informed consent form at study visit 1
- Urine pregnancy test for pre-menopausal females
- Subject's normal diet
- Baseline blood draw: Fat soluble vitamins (A, D, E, K)\*, pre-albumin, serum zinc\*, selenium\*, fatty acid profile\*, citrulline, IGF-1, IGF BP3, GLP-2, GH, CBC, CMP, hepatic function panel
- Anthropometry (height, weight, skinfolds, circumferences)
- Whole body DXA
- Spot stool sample will be collected for stool pH and fecal elastase. Subjects who are unable to produce a sample at the visit will collect and freeze a stool sample at home on one occasion on Day 8, 9, or 10.
- If subject has a G tube, spot gastric pH will be checked
- Questionnaires: Health History and medications, Home Environment, Quality of Life (MOS SF-36 or PedsQL)
- Instructions will be given for collection and shipping for: stool collection (72-hour fecal fat and nitrogen analysis and bomb calorimetry), 3-day weighed food records, and adverse events diary
- Prescribe Creon™ and dispense to subjects

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**Day 9 - Home**

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- Subject's normal diet

- 
- Maintain adverse events diary
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**Day 10 - Home**

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- Subject's normal diet
  - 3-day weighed food record begins
  - Food record – Day 1
  - Maintain adverse events diary
- 

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**Day 11 - Home**

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- Subject's normal diet
  - Food record – Day 2
  - Stool collection begins (72-hour fecal fat, 72-hour fecal nitrogen, and bomb calorimetry), store frozen until brought to CHOP.
  - 72-hour stool – Day 1
  - Maintain adverse events diary
- 

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**Day 12 - Home**

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- Subject's normal diet
  - Food record – Day 3
  - 72-hour stool – Day 2
  - Maintain adverse events diary
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**Day 13 - Home**

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- Subject's normal diet
  - 72-hour stool – Day 3
  - Maintain adverse events diary
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\* These laboratories will be drawn at study visit 0 if the subject weighs less than 25 kg

**Study Visit # 1: Protocol for MBT/CCK Subjects who have not Received Pancreatic Enzyme Medication Prior to Study Visit #1**

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**Day 1-6 - Home**

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- Those subjects who are on a medication that directly alters fat absorption will discontinue this medication after permission is obtained from their primary gastroenterologist. Study team must have a signed, informed consent form prior to discontinuation of medication.
  - Subject's normal diet
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**Day 7 – Home**

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- Subject's normal diet except for no dairy intake
  - No alcohol intake
  - Normal daily activity
  - Fast overnight starting at 8pm
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#### **Day 8 – CHOP Visit to CTSC Outpatient Lab and NGL**

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- Urine pregnancy test for pre-menopausal females
  - Insert heparin catheter
  - Baseline blood draw: baseline MBT draw, Fat soluble vitamins (A, D, E, K), pre-albumin, serum zinc, selenium, fatty acid profile, citrulline, IGF-1, IGF BP3, GH, CBC, CMP, hepatic function panel, baseline CCK, baseline GLP-2
  - Administer MBT study meal (breakfast)
  - MBT – hourly blood sample for 8 hours
  - Blood sample for CCK concentration at 1 hour
  - Blood sample for GLP-2 concentration at 1 hour and 2 hours
  - After hour 6, a low fat study lunch
  - Anthropometry (height, weight, skinfolds, circumferences)
  - Whole body DXA
  - Spot stool sample will be collected for stool pH and fecal elastase. Subjects who are unable to produce a sample at the visit will collect and freeze a stool sample at home on one occasion on Day 8, 9, or 10.
  - If subject has a G tube, spot gastric pH will be checked
  - Questionnaires: Health History and medications, Home Environment, Quality of Life (MOS SF-36 or PedsQL)
  - Instructions will be given for collection and shipping for: stool collection (72-hour fecal fat analysis and bomb calorimetry), 3-day weighed food records, and adverse events diary
  - Prescribe Creon™ and dispense to subjects
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#### **Day 9 – Home**

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- Subject's normal diet
  - Maintain adverse events diary
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#### **Day 10 - Home**

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- Subject's normal Diet
  - Maintain adverse events diary
  - 3-day weighed food record begins
  - Food record – Day 1
- 

#### **Day 11 - Home**

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- 
- Subject's normal Diet
  - Food record – Day 2
  - Stool collection begins (72-hour fecal fat, 72-hour fecal nitrogen, and bomb calorimetry), store frozen until brought to CHOP.
  - 72-hour stool – Day 1
  - Maintain adverse events diary
- 

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**Day 12 - Home**

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- Subject's normal diet
  - Food record – Day 3
  - 72-hour stool – Day 2
  - Maintain adverse events diary
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**Day 13 - Home**

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- Subject's normal diet
  - 72-hour stool – Day 3
  - Maintain adverse events diary
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**Study Visit #1: Protocol for MBT/CCK Subjects who are Receiving Pancreatic Enzyme Medication Prior to Study Visit # 1 and require a Washout Period**

Participants discontinuing pancreatic enzyme medication will be without this medication for the nine days encompassing Study Visit # 1.

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**Day 1-4 - Home**

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- Those subjects who are on a medication that directly alters fat absorption will discontinue this medication after permission is obtained from their primary gastroenterologist. Study team must have a signed, informed consent form prior to discontinuation of medication.
  - Subject's normal diet
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**Days 5 & 6**

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**Discontinue pancreatic enzyme medication (Washout)**

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**Day 7**

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- Discontinue pancreatic enzyme medication (Washout)
  - Regular lunch/dinner except for no dairy intake
  - No alcohol intake
  - Normal daily activityFast overnight starting at 8pm
-

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**Day 8 – CHOP Visit to CTSC Outpatient Lab and NGL**


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- Urine pregnancy test for pre-menopausal females
- Insert heparin catheter
- Baseline blood draw: baseline MBT draw, Fat soluble vitamins (A, D, E, K), pre-albumin, serum zinc, selenium, fatty acid profile, citrulline, IGF-1, IGF BP3, GH, CBC, CMP, hepatic function panel, baseline CCK, baseline GLP-2
- Administer MBT study meal (breakfast)
- MBT – hourly blood sample for 8 hours
- Blood sample for CCK concentration at 1 hour
- Blood sample for GLP-2 concentration at 1 hour and 2 hours
- After hour 6, a low fat study lunch
- Anthropometry (height, weight, skinfolds, circumferences)
- Whole body DXA
- Spot stool sample will be collected for stool pH and fecal elastase. Subjects who are unable to produce a sample at the visit will collect and freeze a stool sample at home on one occasion on Day 8, 9, or 10.
- If subject has a G tube, spot gastric pH will be checked
- Questionnaires: Health History and medications, Home Environment, Quality of Life (MOS SF-36 or PedsQL)
- Instructions will be given for collection and shipping for: stool collection (72-hour fecal fat analysis and bomb calorimetry), 3-day weighed food records, and adverse events diary
- Prescribe Creon™ and dispense to subjects

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**Day 9 - Home**


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- Subject's normal diet
- Maintain adverse events diary

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**Day 10 - Home**


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- Subject's normal diet
- 3-day weighed food record begins
- Food record – Day 1
- Maintain adverse events diary

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**Day 11 - Home**


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- Subject's normal diet
- Food record – Day 2
- Stool collection begins (72-hour fecal fat, 72-hour fecal nitrogen, and bomb calorimetry), store frozen until brought to CHOP.
- 72-hour stool – Day 1
- Maintain adverse events diary

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**Day 12 - Home**


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- Subject's normal diet
  - Food record – Day 3
  - 72-hour stool – Day 2
  - Maintain adverse events diary
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**Day 13 - Home**


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- Subject's normal diet
  - 72-hour stool – Day 3
  - Maintain adverse events diary
- 

### **4.3 Subjects who are on medications that directly alter fat absorption prior to the study**

Subjects who were on a medication that directly alters fat absorption will have stopped the medication 7 days prior to study visit #1. This will only occur with the permission of their primary gastroenterologist. Subjects must sign an informed consent form in person or send it via email, fax, or mail prior to discontinuation of medication. They will remain off the medication through the end of treatment with pancreatic enzyme medication. Once they complete the second stool collection and treatment with pancreatic enzyme medication as outlined below, they can resume this medication.

### **4.4 Open-Label Treatment with Creon™**

Subjects will receive open-label treatment with Creon™ as their pancreatic enzyme medication therapy and will receive this therapy for nine days encompassing Study Visit #2. There are two protocols for Study Visit #2. The first protocol is for subjects in the non-MBT/CCK cohort and the second protocol is for subjects in the MBT/CCK cohort. Please note that subjects who are eligible for the MBT/CCK subset and decline the MBT will follow the same protocol as the non-MBT/CCK subset.

### **Study Visit #2: Pancreatic Enzyme Medication Treatment Protocol for Subjects in the non-MBT/CCK Subset**

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**Days 1 -4**


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- Pancreatic enzyme medication treatment
  - Subject's normal diet
- 

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**Day 5 – CHOP Visit to CTSC Outpatient Lab and NGL**


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- Subject's normal diet
  - Pancreatic enzyme medication treatment
-



- 
- Blood draw: pre-albumin, citrulline, IGF-1, IGF BP3, GLP-2, GH, CBC, CMP, hepatic function panel
  - Spot stool sample will be collected for stool pH
  - If subject has a G tube, spot gastric pH will be checked
  - Adherence to pancreatic enzyme medication and Adverse Events Questionnaires
  - Instructions will be given for collection and shipping for: stool collection (72-hour fecal fat, 72-hour fecal nitrogen, and bomb calorimetry), 3-day weighed food records, and adverse events diary
- 

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#### **Day 6 - Home**

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- Pancreatic enzyme medication treatment
  - Subject's normal diet
  - Maintain adverse events diary
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#### **Day 7 - Home**

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- Pancreatic enzyme medication treatment
  - Subject's normal diet
  - 3-day weighed food records begins
  - Food record – Day 1
  - Maintain adverse events diary
- 

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#### **Day 8 - Home**

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- Pancreatic enzyme medication treatment
  - Subject's normal diet
  - Food record – Day 2
  - Stool collection (72-hour fecal fat, 72-hour fecal nitrogen, and bomb calorimetry), store frozen until brought to CHOP.
  - 72-hour stool – Day 1
  - Maintain adverse events diary
- 

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#### **Day 9 - Home**

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- Pancreatic enzyme medication treatment
  - Subject's normal diet
  - Food record – Day 3
  - 72-hour stool – Day 2
  - Maintain adverse events diary
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#### **Day 10 - Home**

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- Pancreatic enzyme medication treatment
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- 
- Subject's normal diet
  - 72-hour stool – Day 3
  - Maintain adverse events diary
- 

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#### **Day 11 - Home**

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- Subjects who had discontinued a medication that directly alters fat absorption for this study can resume this medication as it was prescribed by their primary physician

### **Study Visit #2: Pancreatic Enzyme Medication Treatment Protocol for Subjects in the MBT/CCK Subset**

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#### **Days 1, 2, & 3**

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- Pancreatic enzyme medication treatment
  - Subject's normal diet
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#### **Day 4**

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- Pancreatic enzyme medication treatment
  - Subject's normal diet except for no dairy intake
  - No alcohol intake
  - Normal daily activity
  - Fast overnight starting at 8pm
- 

#### **Day 5 – CHOP Visit to CTRC Outpatient Lab and NGL**

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- Pancreatic enzyme medication treatment
  - Insert heplock catheter
  - Blood draw: baseline blood draw for MBT, pre-albumin, citrulline, IGF-1, IGF BP3, GH, CBC, CMP, hepatic function panel, baseline CCK, baseline GLP-2
  - Administer MBT study meal (breakfast)
  - MBT – hourly blood sample for 8 hours
  - Blood sample for CCK concentration at 1 hour
  - Blood sample for GLP-2 concentration at 1 hour and 2 hours
  - After hour 6 a low fat study lunch
  - Adherence to pancreatic enzyme medication and Adverse Events Questionnaires
  - Instructions will be given for collection and shipping for: stool collection (72-hour fecal fat, 72-hour fecal nitrogen, and bomb calorimetry), 3-day weighed food records, and adverse events diary
  - Spot stool sample will be collected for stool pH
  - If subject has a G tube, spot gastric pH will be checked
-

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**Day 6 - Home**

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- Pancreatic enzyme medication treatment
  - Subject's normal diet
  - Maintain adverse events diary
- 

**Day 7 - Home**

---

- Pancreatic enzyme medication treatment
  - Subject's normal diet
  - 3-day weighed food records begins
  - Food record – Day 1
  - Maintain adverse events diary
- 

**Day 8 - Home**

---

- Pancreatic enzyme medication treatment
  - Subject's normal diet
  - Food record – Day 2
  - Stool collection (72-hour fecal fat, 72-hour fecal nitrogen, and bomb calorimetry), store frozen until brought to CHOP
  - 72-hour stool – Day 1
  - Maintain adverse events diary
- 

**Day 9 - Home**

---

- Pancreatic enzyme medication treatment
  - Subject's normal diet
  - Food record – Day 3
  - 72-hour stool – Day 2
  - Maintain adverse events diary
- 

**Day 10 - Home**

---

- Pancreatic enzyme medication treatment
  - Subject's normal diet
  - 72-hour stool – Day 3
  - Maintain adverse events diary
- 

**Day 11 - Home**

---

- Subjects who had discontinued a medication that directly alters fat absorption for this study can resume this medication as it was prescribed by their primary physician

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### Study Visit #3: Follow-Up Visit for All Subjects

Subjects will have the option to complete this visit via telephone. Questions on adverse events and medication adherence will be asked via telephone. Stool collection and diet records can be mailed or dropped off.

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#### Days 1

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- Adverse events monitoring
- Final medication adherence questionnaire
- Drop of final 72-hour stool collection and 3-day diet record

### 4.5 Unscheduled Visits

Due to the complexity of the study, no unscheduled visits will be permitted.

### 4.6 Subject Completion/Withdrawal

For subjects who were naïve to pancreatic enzyme medication at the start of the study, at the end of participation in the study (all collections are complete for Study Visit #2) Creon™ will be discontinued and they will and resume their usual care without pancreatic enzyme medication. For subjects who were receiving pancreatic enzyme medication prior to the start of the study, at the end of participation in the study (all collections are complete for Study Visit #2), Creon™ will be discontinued and they will resume their usual care and will resume the pancreatic enzyme product and dose they were receiving before the study began.

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigators for lack of adherence to study treatment or visit schedules, or adverse events. The Investigators or the Sponsor may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF. All subjects withdrawn from the study will receive a follow up phone call weekly for one month.

We expect investigator-based subject withdrawal to be rare. Subjects who experience an unexpected increase in ostomy or stool output during or following a baseline study will require additional monitoring of serum electrolytes and stools or ostomy output as needed. Those subjects who require changes to their parenteral nutrition for greater than three days or initiation of intravenous hydration and electrolyte repletion for greater than three days will not have a repeat MBT. These subjects will not require withdrawal from the study if both they and their primary care team for SBS agree to continued participation. Once electrolytes are stable, they will continue the study.

If a subject withdraws from the study for any cause, baseline data will be used for analysis.

## 5 STUDY EVALUATIONS AND MEASUREMENTS

### 5.1 Screening and Monitoring Evaluations and Measurements

#### 5.1.1 Medical Record Review

Variables that will be abstracted from the medical chart (paper or electronic):

- History of a prior small bowel resection
  - If small bowel resection occurred under 18 years of age, subjects must have dependence on parenteral nutrition for at least three months following small bowel resection
  - If small bowel resection occurred at 18 years of age or older, subjects must have 200 centimeters or less of residual bowel length and must have more than 3 bowel movements per day following small bowel resection
- Date of birth - Age 4 years to 75 years
- Sex
- SBS diagnosis: estimated length of residual bowel, number and purpose of operations, presence or absence of ileocecal valve
- Most recent enteral nutrition and parenteral nutrition regimen
- Medical comorbidities that affect the gastrointestinal tract and impact absorption or digestion
- Current diagnosis of a motility disorder (i.e. chronic pseudo-obstruction, severe gastroparesis)
- Current diagnosis of cholestatic liver disease defined as a serum conjugated bilirubin greater than 1.0 mg/dL
- Current listing status for intestinal transplant
- History of pancreatic enzyme use
- History of a pork, soy, or safflower oil allergy
- History of gout, chronic renal failure requiring dialysis or listed for kidney transplant, or fibrosing colonopathy
- All medications, particularly medications that alter fat absorption (weight loss medications, bile acid sequestering agents, or ursodeoxycholic acid)
- All allergies
- History of use of pancreatic enzymes
- Hospitalizations in the past 2 weeks
- Emergency room visits or unscheduled sick visits in the last month

#### 5.1.2 Laboratory Evaluations

Serum 25-dihydroxyvitamin D and pre-albumin will be assessed at CHOP laboratories. PIVKA II (Sarah Booth, Tuft's University, Medford, MA) and/or undercarboxylated osteocalcin % (UCOC %) will be assessed for vitamin K status (Caren Gundberg, Yale University, New Haven, CT). Prealbumin, zinc, serum retinol (vitamin A),  $\alpha$  tocopherol (vitamin E), and selenium will be assessed at CHOP Laboratories using standard techniques. A fatty acid profile will be assessed by Mayo Medical Laboratories (Rochester, MN). This will provide data on baseline malabsorption and nutritional

status resulting from short bowel syndrome that may be improved with pancreatic enzyme medication in subjects. Safety measures include results from serum basic metabolic panel (BMP), hepatic function panel, and complete blood count with differential (CBC) performed at CHOP Laboratories using standard techniques. The hepatic function panel will provide serum albumin, total protein, bilirubin, and liver enzymes to provide additional liver and nutritional status information. Serum citrulline, IGF-1, IGF BP3, GLP-2, GH, and CCK levels (MBT/CCK subset only) will be assessed by the CTRC Core Laboratory at CHOP. All individuals from institutions outside of CHOP will receive only coded, not readily identifiable, samples for analyses and are not otherwise engaged in human subjects' research.

#### **5.1.2.1 Pregnancy Testing**

A urine pregnancy test will be performed for pre-menopausal female subjects who are 9 years of age or older.

#### **5.1.3 Other Evaluations and Measures**

Dietary intake: A twenty-four hour dietary recall will be obtained after written, informed consent is obtained. This may be completed at study visit 0 or study visit 1. Information on parenteral nutrition and enteral nutrition will be obtained.

Three day weighed food records will be obtained at baseline and while on PERT. Calories, macronutrient content, and micronutrient content will be calculated based on dietary records. All subjects will be provided with scales, spoons, and other supplies needed for accurate collection of dietary data. Analysis of the dietary records will be conducted with the assistance of the CTRC staff and Bionutrition Unit. In particular, dietary intake will be analyzed using Nutrition Data System (NDS) for Research software version 2012 developed by the National Coordinating Center (NCC, University of Minnesota, Minneapolis, MN)

Anthropometric Assessment: Height and weight will be measured for each subject and BMI will be calculated. For subjects under 20 years of age, height, weight, and BMI Z scores will be calculated using growth charts from the Centers for Disease Control and Prevention (CDC)<sup>22</sup>. Anthropometric techniques will be measured using the methodologies described by Lohman et al<sup>23</sup>. Weight (0.1 kg) will be measured on a digital electronic scale (Seca, Munich, Germany) and height (0.1 cm) will be measured using a stadiometer (Holtain, Crymch, UK). In order to assess subcutaneous fat stores, skinfold thickness of the triceps, biceps, subscapular, and suprailiac areas will be measured (0.1 mm) with a skinfold caliper. Total body composition, total free fat mass (FFM) and fat mass (FM) and percent body fat (%FAT), will be assessed by the skinfolds using prediction equations adapted for children, adolescents, and adults<sup>50, 51</sup>. Mid upper arm circumference will be measured with a fiberglass tape (0.1 cm). Upper arm muscle Z scores and fat area Z scores will be determined for each subject. All anthropometric assessments will be performed once at the study visit #1.

Body Composition: Body composition will be assessed with dual-energy x-ray absorptiometry (DXA) (Delphi A, Hologic, Inc., Bedford, MA) for subjects only at study visit #1. DXA uses very low-dose x-ray exposures (3 mrem) and measurements are rapid, making this a suitable technique for use in children. We will attempt to obtain a DXA scan in subjects of all ages. Standard positioning and clothing techniques are used. Quality control scans are performed daily using a simulated L1-L4 lumbar spine made of hydroxyapatite encased in epoxy resin, and a whole body composition phantom. A difference of >1.5% from the standard will be deemed out-of-range requiring servicing by the manufacturer. The scans will be analyzed to generate traditional DXA measures: whole body

Area, BMC and areal-BMD (gm/cm<sup>2</sup>). In our institution, the in vitro CV is less than 0.6% and the in vivo coefficient of variation in adults is less than 1%. A urine pregnancy test will be performed on female subjects who are pre-menopausal prior to the scan. Pregnant subjects will not be scanned and will leave the study.

Gastric and Stool pH: Stool pH will be measured at study visit #1 and #2 as a screen for gastric acid hypersecretion. Gastric pH will be measured study visit #1 and #2 if subjects have a gastrostomy tube or a nasogastric tube. This will be performed by the CTRC Core Laboratory at CHOP.

Fecal elastase: Pancreatic function will be assessed by fecal elastase-1 at study visit #1 only to determine the level of pancreatic enzyme activity in the stool<sup>24</sup> (Joli Diagnostics, Williamsville, NY). Subjects will be provided with the stool collection kit and proper instructions and supplies, and samples will be collected during the day of the visit if possible. If subjects are unable to produce a stool sample at study visit #1, they will be given supplies to collect a stool sample at home within two days following the visit. This stool sample will be frozen and returned on the day of study visit #2. The stool sample will be stored at -20°C, and analyzed with a monoclonal enzyme-linked immunosorbent assay (ARUP Laboratory, Salt Lake City, UT).

Home Environment and Health Questionnaire: The questionnaire will be administered via interview by the research staff at Study Visit #1, and will consist of two sections. The Health History section has general questions about the subject's health history including documentation of medical history, recent hospital admissions and illnesses, medication, history of pancreatic enzyme supplementation, parenteral nutrition, and nutrient supplement use. A Home Environment section describes aspects of environment, such as education and income level, whether on Medicaid/Medicare and household size to describe the demographic characteristics. In addition to subjects' contact information (name, address, phone numbers); contact information from two additional contacts will be collected to maintain contact with the subject in the event that the subject cannot be contacted at their primary residence.

Quality of Life Questionnaires: In order to assess the health-related quality of life (QOL), validated questionnaires will be administered to all subjects at Study Visit #1. For all subjects 18 years of age and older, the Medical Outcomes Study 36-Item Short-Form Health Survey (MOS SF-36), a standardized, validated health survey will be administered. The MOS SF-36 covers physical functioning, bodily pain, general health perception, vitality, social functioning, emotional and mental health domain<sup>25</sup>. For subjects between 4 and 17.9 years of age, the Pediatric Quality of Life Inventory (PedsQL™) is a validated health survey that will be administered. For subjects who are 4 years old, a parent or legal guardian only will complete a proxy-report. For subjects between the ages of 5 and 17.9, both the subject and the parent or legal guardian will complete a survey. The PedsQL™ addresses physical, emotional, social, and school functioning<sup>26</sup>.

Adherence: Adherence to pancreatic enzyme medication for subjects will be assessed at Study Visit #2 and #3 and by phone calls. This time will also be used to trouble-shoot any barriers to adherence, and also to collect information on adverse events experienced during the course of the study.

Adverse Events Diary: Subjects will be asked about all adverse events at Study Visit #1, Study Visit #2, and Study Visit #3 and asked to rate by intensity (mild, moderate, severe). Serious adverse events will be reported as per various policies in a timely manner to CHOP IRB, and CTRC.

## 5.2 Efficacy

### 5.2.2. Diagnostic tests, Scales, Measures

**Coefficient of fat absorption (CFA):** The coefficient of fat absorption (CFA %) will be calculated based on a 72 hour stool and a 3-day weighed diet record collection performed after both Study Visit #1 and #2. Collection of stool will begin 24 hours after dietary records are started. All subjects will remain on their normal diet during stool collection. This includes the normal meals, snacks, and tube feeds that they typically receive. All subjects will receive a home collection kit and detailed instructions on stool collection. Stool collections will be performed at home and returned to CHOP upon completion. Subjects who are in diapers can either use plastic wrap to line the diaper or a urine collection bag secured around the anus for stool collection. They will then transfer stool from the plastic wrap or the collection bag to a stool collection container. All materials, including hand gloves, will be provided to ensure safe and accurate stool collection. All stool will be frozen until the time of analysis. Total fat content of the stool will be determined by a gravimetric method (Mayo Medical Laboratories, Rochester, MN). Total dietary intake of fat will be determined from the 3-day weighed food records. CFA % will be calculated based on determining the grams of fat consumed and the grams of fat excreted<sup>27</sup>. CFA % will be compared for each subject before and after administration of pancreatic enzymes.

**Coefficient of nitrogen absorption (CNA):** The coefficient of nitrogen absorption (CNA %) will be calculated based on a 72 hour stool and a 3-day weighed diet record collection performed both at Study Visit #1 and #2. Collection of stool will begin 24 hours after dietary records are started. All subjects will remain on their normal diet during stool collection. This includes the normal meals, snacks, and tube feeds that they typically receive. Subjects will receive materials and instructions for proper stool collection. All samples will be collected at home and returned to CHOP. Stool will be frozen until the time of analysis. Total nitrogen content of stool will be determined by a gravimetric method (Mayo Medical Laboratories, Rochester, MN). Total dietary intake of nitrogen will be determined from a 3-day weighed food record. CNA % will be calculated based on grams of nitrogen consumed and grams of nitrogen excreted<sup>27</sup>. CNA % will serve as a measure of protein absorption. CNA % will be compared for each subject before and after administration of pancreatic enzymes.

**Bomb calorimetry (BC):** Bomb calorimetry is a measure of energy loss in stool. This will be determined based on a 72-hour stool collection (Covance Labs, Madison, WI) performed on each subject before and after administration of pancreatic enzymes. All subjects will remain on their normal diet during stool collection. This includes the normal meals, snacks, and tube feeds that they typically receive. All samples will be collected at home, returned to CHOP, and frozen until the time of analysis. BC measures the heat of combustion of a reaction and in particular, measures the energy given off by a stool sample that is burned<sup>28</sup>. As a result, it provides a measure of fecal energy loss in kcal/g stool. The energy loss from stool will be compared in each subject before and after administration of pancreatic enzymes.

**Malabsorption blood test (MBT):** This test will be performed on the MBT/CCK cohort only. These subjects will have the option to decline the MBT. The MBT is a measure of intestinal fat absorption and pharmacokinetic analyses yields primary outcomes from this test. The MBT involves consumption of an 8 ounce (oz) test meal that contains about 580 calories, 32.4 g of fat, and 50% calories from fat. Specifically, the fats contained in the test meal are pentadecanoic acid (PA), a free fatty acid, and triheptadecanoic acid (THA), a triglyceride with three molecules of heptadecanoic



saturated fatty acids bound to glycerol. THA requires hydrolysis by pancreatic lipase in the intestinal lumen prior to intestinal absorption. The MBT test meal is administered after the subject has fasted for 12 hours and eliminated dairy from the diet for 24 hours. The meal is prepared just prior to consumption and is composed of 64 g vanilla Scandishake (Axcen, Scandipharm, Birmingham, AL), 6 oz Silk light **vanilla** soy milk, **0.5 ounces of Hershey's chocolate syrup**, 10 milliliters microlipid (www.nestle-nutrition.com), PA, and THA. An indwelling catheter is placed in the subject prior to consumption of the meal. Blood is drawn at baseline (0 hour) and then following ingestion of the test meal at Hour 1, 2, 3, 4, 5, 6, 7, and 8. The meal should be consumed within 5 minutes following the baseline blood draw. From the samples of blood, serum PA and heptadecanoic acid (HA) levels are assessed by gas-liquid chromatography (GC). After the blood draw at Hour 6, subjects are provided a 1000 kcal, low fat (12 g) lunch meal. They are also able to consume zero-calorie and caffeine-free beverages without limit during the MBT.

Subjects in the MBT group who elect to have the MBT will have a MBT at baseline and again following administration of pancreatic enzymes. If subjects are on pancreatic enzymes prior to study enrollment, after consultation with their medical team, they will be asked to discontinue pancreatic enzymes three days before their study visit #1 until the end of the first 72 hour stool collection. For the second MBT that will be performed on pancreatic enzymes, subjects will take enzymes for 4 days and the MBT will be scheduled on day 5. Following this, they will continue to take pancreatic enzymes until the second 72-hour stool collection is complete. Please see **Table 3** for details of the MBT protocol. Subjects in the non-MBT group will not have a MBT performed.

Plasma samples to measure PHA and TA levels will be analyzed by GC. Using methods from Bligh and Dyer, total lipids are extracted from 200 µl of plasma<sup>7,29</sup>. Fatty acids are methylated in the lipid extract and fatty acid methyl esters are then extracted into isooctane. 1 µl of sample is then injected into a GC column for analysis using a Hewlett-Packard 5890 series II gas chromatograph with a programmable cool on-column capillary inlet, flame ionization detector (FID), and HP7673 auto sampler/injector. Chromatographic data collection and analysis is via a serial connection to a computer that runs ChromPerfect Spirit™ chromatography data system (Justice Laboratory Software, Denville, NJ). The column used is a CP-Sil 88 for FAME, 100 m (L) x 0.25 mm (ID) x 0.25 µm (film thickness) (Agilent Technologies, Inc., Santa Clara, CA) with a 1 m (L) x 0.53 mm (ID) deactivated precolumn. Calibration curves are generated based on injections of methyl PA, methyl HA, and methyl tridecanoate injections. Inter-assay variability (%CV) for the measurement of PA in samples with low, medium, and high concentrations (1.30, 2.99, and 6.70 mg/dL) has been shown to be 2.9%, 2.6%, and 3.1%, respectively<sup>7</sup>. Inter-assay variability for the measurement of HA (0.56, 1.29, and 3.05 mg/dL) in the samples has been shown to be 2.6%, 4.0%, and 3.9%, respectively<sup>7</sup>.

Primary outcomes for the MBT include pharmacokinetic analyses of PA and HA, which includes comparison of the absorption curves, maximum plasma concentration ( $C_{max}$ ), area under the curve, percent absorption of plasma PA and HA concentrations, and the HA/PA ratio between each subject in the MBT cohort before and after administration of pancreatic enzymes.

### 5.3 Safety Evaluation

Safety will be monitored by adverse events reporting. The frequencies of AEs by type, body system, severity and relationship to study supplement will be summarized. SAEs (if any) will be described in detail.

## 6 STATISTICAL CONSIDERATIONS

### 6.1 Primary Endpoint

The primary aim of this study is to determine if pancreatic enzymes improve enteral fat absorption in subjects with SBS. Enteral fat absorption will be measured as CFA. For each subject, CFA will be compared before and after administration of pancreatic enzyme medication.

### 6.2 Secondary Endpoint

The **secondary aim** of this proposal is to assess the effect that administration of pancreatic enzymes will have on global absorption. Specifically, CNA and stool BC will be measured to detect changes in enteral protein absorption and stool energy losses, respectively, before and after administration of pancreatic enzymes.

An additional **secondary aim** includes that we will **explore** the ability of the MBT to detect changes in enteral fat absorption before and after administration of pancreatic enzymes in a subset of patients. This test will also help characterize the degree of pancreatic insufficiency in subjects.

A final **secondary aim** will **explore** if improved lipid digestion and release of free fatty acids due to pancreatic enzymes will promote intestinal adaptation by stimulating endocrine signaling. Specifically, GLP-2, IGF-1, IGFBP-3, and GH concentrations will be measured from blood samples before and after administration of pancreatic enzymes. CCK will also be measured in the MBT/CCK Cohort only before and after administration of pancreatic enzymes. Plasma citrulline will also be measured as a marker of intestinal adaptation before and after administration of pancreatic enzymes.

### 6.3 Statistical Methods

Analysis will begin with descriptive analyses of the study sample using means, standard deviations, medians, and ranges for continuous variables, and frequency distributions for categorical variables. Descriptive statistics and exploratory graphing such as frequencies, means, standard deviations, box plots, and scatter plots will be used to assess the normality of the data in terms of the presence of skew and/or outliers.

#### 6.3.1 Efficacy Analysis

**Statistical Analysis: H1, H2, and H3:** Descriptive statistics for CFA, CNA, and BC outcomes (mean, standard deviation, median, range, 95% CI) will be calculated for the SBS cohort before and after PERT administration with paired t-tests or Wilcoxon sign rank tests depending on skewness of data. For the MBT outcomes, a moment-based pharmacokinetic (PK) analysis will be performed based on non-compartmental methodology using WinNonLin version 9.1 (Pharsight, Cary, NC). Baseline ( $C_0$ ) and maximum ( $C_{max}$ ) plasma concentrations are calculated, and area under the curve from time zero to eight hours (AUC) is calculated using the linear trapezoid method. PK parameters can then be compared between treatment groups using a paired t-test or Wilcoxon signed rank test as appropriate. To describe HA exposure relative to that of PA, the ratio of the HA to PA  $C_{max}$  ( $C_{max} HA/PA$ ) and AUC (AUC HA/PA) is calculated for each subject after molar transformation and dose-normalization of exposure metrics<sup>7</sup>. Alternately, population PK analyses for repeated-measures endpoints can be conducted via nonlinear mixed-effects modeling with a qualified installation of the nonlinear mixed-effects modeling (NONMEM) software, Version VII, Level 2.0 (ICON

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Development Solutions, Hanover, MD<sup>8</sup>. Using this method, population PK modeling is conducted by simultaneously fitting structural PK models to both PA and HA concentrations<sup>9</sup>.

In exploratory analyses, we will compare the estimates of percent fat absorption from the MBT with both the CFA% from the 72-hour fecal fat and diet analysis and the BC results (energy loss in the stool). We will compare the methods for detection of fat malabsorption as measured by CFA% and BC with fat absorption as measured by MBT for the subjects before and after pancreatic enzyme medication use. A correlation analysis will be conducted to evaluate the performance of the MBT relative to that of the CFA%. HA and PA  $C_{max}$ , AUC, and HA/PA ratios will be plotted against CFA% or BC caloric loss to explore the relationship between the two tests. Any relationships observed in the plots will be further explored using correlation analysis and appropriate regression analysis as dictated by the observations.

Descriptive statistics (mean, standard deviation, median, range, 95% CI) will also be employed to assess outcomes related to intestinal hormone signaling that controls pancreatic enzyme secretion and intestinal adaptation in **H4** (glucagon-like peptide 2, insulin-like growth factor 1, insulin-like growth factor binding protein 3, and growth hormone concentrations). All variables will be tested for normality and nonparametric tests used as appropriate. The change in status for these variables before and after PERT administration will be explored with paired t-tests and Wilcoxon sign rank tests depending on skewness.

### 6.3.1 Safety Analysis

Safety will be monitored by adverse events reporting. The frequencies of AEs by type, body system, severity and relationship to study supplement will be summarized. SAEs (if any) will be described in detail.

## 6.4 Sample Size and Power

Sample Size Considerations: The primary hypothesis (**H1**) of this study is: 1) the CFA will detect changes in fat absorption with PERT administration in subjects with SBS. The sample size selected for the SBS cohort (n=26) is based upon our previous experience in cystic fibrosis (CF) and chronic pancreatitis (CP) in detecting changes over time before and after administration of PERT. Although few studies of fecal fat loss in subjects with SBS have been conducted, losses of about 48% of fat intake in the stool have been reported<sup>2</sup>. For the CFA outcome, our experience has been in CF and pancreatic insufficiency (PI), with average CFA of 81±14% in one study<sup>30</sup> and 83±10% in another<sup>31</sup> when subjects were on PERT. In comparison, healthy subjects have CFA ≥93%. From the literature for CP, a number of clinical trials have used CFA to describe fat malabsorption in subjects with CP and confirmed PI before and after administration of PERT. Ramesh et al<sup>32</sup> found an increase in CFA from 66.7±14.0% before PERT to 88.9±5.2% after PERT (change of 22.7±12.2%) in adults with CP from India. Thorat et al<sup>33</sup>, in a randomized controlled trial in India, saw CFA increase from 66.5±14.1 to 86.1±7.5% in those taking PERT compared to an increase from 67.0±14.0 to 72.9±11.5% for placebo, a treatment effect of 13.7% (95% CI: 9.1, 18.2) after 1 week of PERT. Drawing from the literature on CP in the absence of information for SBS, the change in CFA for subjects with CP and confirmed PI before and after PERT administration has ranged from 8 to 23% with the SD of that change ranging from 12 to 18%, but averaging at 14%. 22 subjects will have 80% power to detect a difference in means of 9% (increase in CFA% from 85 to 94% after PERT administration), assuming a SD of differences of 14%, using a paired t-test with  $\alpha = 0.05$  two-sided significance level.

A secondary hypothesis (**H2**) in the study is: 2) the CNA and BC will detect changes in enteral protein absorption and stool energy losses, respectively, with PERT administration in subjects with SBS. There is limited data on CNA in SBS. One study<sup>2</sup> found that subjects with SBS had a CNA of about 47%. From the literature on CF, Trapnell et al<sup>5</sup> reported an increase in CNA from  $49.9 \pm 1.9\%$  to  $85.1 \pm 1.9\%$  after administration of PERT. Borowitz et al<sup>4</sup> reported a similar increase in both CFA and CNA following PERT, with CNA specifically increasing from as low as 57% to 74.6% following administration of PERT. Ramesh et al<sup>32</sup> studied adults patients with CP and demonstrated that PERT resulted in a significant increase in CNA from  $79 \pm 8.9\%$  to  $85.5 \pm 3.8\%$  (change of  $6.5 \pm 7.9\%$ ). Similar to CFA, for CNA, 22 subjects will have 80% power to detect a difference in means of 9% (increase in CNA% from 85 to 94% after PERT administration), assuming a SD of differences of 14%, using a paired t-test with  $\alpha = 0.05$  two-sided significance level.

For the BC method, there is limited information for typical variability in calories lost in stool in either healthy subjects or those with malabsorption diagnoses. It has been reported that patients with SBS can have fecal energy losses as high as  $1609 \pm 561$  kcal/day<sup>2</sup>. Using 72-hour stool assessments, Wierdsma et al<sup>28</sup> has recently reported an average daily energy loss of  $213 \pm 66$  kcal in 23 healthy adults. If we assume that approximately 200 kcal/day are lost in the stool of healthy subjects, 21 subjects in each group will have 80% power to detect a difference in means of 50 kcal (the difference in BC between a healthy group mean of 200 and a CP group mean of 250 kcal lost in stool) assuming that the common SD is 56 using a t-test with  $\alpha = 0.05$ . For BC, 22 subjects will have 80% power to detect a difference in means of 36 (decrease from 250 to 214 kcal/day in the stool), assuming a SD of differences of 56, using a paired t-test with  $\alpha = 0.05$  two-sided significance level.

We expect no more than 20% attrition in this study given a relatively short time period between study visit #1 and study visit #2. By enrolling 26 subjects with SBS, we can account for attrition and also allow for the possibility of greater variability in the CFA, CNA, and BC outcomes within the SBS cohort for which we have had no previous experience.

Assessment of fat malabsorption using the MBT method (**H3**) will be conducted on a subset of 10 subjects and is exploratory. We have previous experience in CF and PI with detecting differences in the pharmacokinetic parameters  $C_{max}$  and AUC for HA and the HA/PA ratio<sup>7</sup>, and in detecting the percent change in HA absorption (from pharmacokinetic modeling) compared to healthy subjects<sup>9</sup>, and in detecting changes in subjects with CF before and after pancreatic enzyme administration<sup>7,9</sup>. We have demonstrated differences in the magnitude of MBT outcomes (exposure metrics) indicating the degree of fat absorption in these subjects with varying treatment regimens of approximately 0.5 in both  $C_{max}$  and AUC HA/PA ratios with a standard deviation of  $\sim 0.7$ . Differences of this magnitude were significant with samples of 16 subjects or less. Given the small sample size of this subset of subjects with SBS ( $n=10$ ) and the known moderate variability within subjects in PA and HA with CF and PI<sup>7,9</sup>, the use of the MBT method to detect fat malabsorption in SBS is considered an exploratory aim, and will inform future studies once effect sizes in the MBT outcomes are determined.

## 6.5 Interim Analysis

An interim analysis is now planned to help inform decisions on the number of subjects needed to adequately power the study.

## 7 STUDY MEDICATION

### 7.1 Description

CREON (pancrelipase) Delayed-Release Capsules (Creon™), a pancreatic enzyme preparation, is a drug that requires prescription for use. It is approved for use for exocrine pancreatic insufficiency due to various etiologies at the current dose.

#### 7.1.1 Packaging

Creon36™ capsules containing 36,000 lipase units (LU) each, Creon24™ capsules containing 24,000 lipase units (LU) each, Creon12™ capsules containing 12,000 lipase units (LU) each, and Creon6™ capsules containing 6,000 lipase units (LU) each will be provided (AbbVie, Inc.) to subjects with SBS. A 12 day supply of Creon™ will be provided for ten days of use. The exact daily dose for each subject will depend on their specific enteral nutrition regimen. Subjects will return unused capsules to the study team at the end of the study, and will be provided with mailing envelopes for this purpose.

#### 7.1.2 Labeling

Storage will be at CHOP in room temperature (below 77° F) and dry conditions (humidity less than 70%). This facility is temperature controlled and continuously monitored.

#### 7.1.3 Dosing

This is a proof of concept study and the use of pancreatic enzymes in short bowel syndrome has not been studied before. As a result, our preference would be to use the highest doses of pancreatic enzyme that are deemed safe for our subjects in order to assess if absorption can be improved.

We have based pancreatic enzyme dosing on typical dosing used by the senior dietitian and a senior physician at the Cystic Fibrosis Center at the Children's Hospital of Philadelphia (CHOP) and as recommended by the most recent consensus statement on pancreatic enzyme dosing in cystic fibrosis<sup>12</sup>. The recommended dosing for meals ranges from 500 – 2500 lipase units/kg/meal. The CF Center at CHOP uses a maximum dose of 2500 lipase units/kg/meal and 1250 lipase units/kg/snack. We will aim to administer about 1500 – 2500 lipase units/kg/meal and 750 – 1250 lipase units/kg/snack in this study (see [Table 5 below](#)). Exact dosing will depend on the subject's complicated enteral feeding regimen. Pancreatic enzyme dosing will be weight based and we will not exceed 10,000 lipase units/kg/day for each subject<sup>12,13</sup>.

We anticipate that several subjects in this study will have a complicated enteral feeding regimen that may be comprised of one or more of the following options: 1) bolus gastrostomy tube feeds, 2) continuous overnight gastrostomy tube feeds, and 3) continuous gastrostomy tube feeds for 18 -24 hours of the day. Please see [Table 5 below](#) for a summary of goal pancreatic enzyme dosing for each of these enteral feeding regimens. Subjects should be able to take pancreatic enzyme medication orally in order to be included in the study even if they rely on a gastrostomy tube or jejunostomy tube.

**Table 5. Goal Pancreatic Enzyme Dosing\***

	Pancreatic Enzyme Dosing
Meal	1,500 – 2,500 lipase units/kg/meal
Snack	750 – 1,250 lipase units/kg/snack
Bolus enteral feeds (typically 1 hour infusion)	1,500 – 2,500 lipase units/kg/meal administered with each bolus <sup>+</sup>
Overnight enteral feeds (typically 8-12 hours)	1,500 – 2,500 lipase units/kg/meal administered at the start and end of the feed
Continuous enteral feeds (typically 20-24 hours)	<ul style="list-style-type: none"> <li>• 1,500 – 2,500 lipase units/kg/meal administered at the start and end of the feed</li> <li>• While awake and during continuous feed, enzymes dosed every 4 hours based on grams of fat in formula (not to exceed 4,000 lipase units/grams of fat/day)</li> </ul>

\* Will not exceed maximum daily enzyme dosing of 10,000 lipase units/kg/day

<sup>+</sup> The dose of enzymes with each bolus depends on the enteral feeding regimen, grams of fat, and the volume and number of boluses

**Bolus feeds:** The dose of enzymes that each subject receives prior to each bolus will depend on the volume and total number of boluses received per day. We will attempt to cover each bolus with a maximum dose of 1500 – 2500 lipase units/kg/meal, but this may be reduced if boluses are smaller in volume or occur frequently.

**Overnight feeds:** This group includes subjects on overnight enteral feeds for 8-12 hours. These subjects will receive one meal dose of Creon™ (1500 - 2500 lipase units/kg) prior to feeds and one meal dose of Creon™ at the end of feeds, consistent with our current practice at CHOP.

**Continuous feeds:** This group includes those subjects on continuous enteral feeds for 20-24 hours of the day. For these subjects, we will dose enzymes every 4 hours while awake based on grams of fat in the formula and based on recommended dosing per grams of fat. Overnight, they will receive one meal dose of Creon™ (1500 – 2500 lipase units/kg) before and after the overnight feed.

We will not exceed 10,000 lipase units/kg/day or 4000 lipase units/grams of fat/day for any subject<sup>13</sup>. Each subject will receive pancreatic enzyme medication for a total of ten days. They will start Creon™ 4 days prior to study visit #2, they day of study visit #2, and then for five days after the visit until they have completed the second stool collection.

#### **7.1.4 Treatment Compliance and Adherence**

Adherence will be systematically assessed using the following methods: 1) A supply of Creon™ that is sufficient for 12 days will be prescribed for all subjects at Study Visit #1 by Dr. Nina Sainath, the Lead Investigator and will be dispensed to the subjects by Dr. Sainath. All subjects will be asked to begin taking Creon™ capsules four days prior to their scheduled visit to CHOP for Study Visit #2. 2) Subjects will be asked to complete an Adherence Survey, a semi-structured interview to document adherence to taking the Creon™ over ten days at Study Visit #2 and Study Visit #3. Adherence at

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Study Visit #3 may be assessed by telephone or in person. We will maintain regular contact with subjects via telephone, text message, or email to ensure that each subject has an adequate supply of Creon™ and to obtain a cursory assessment of barriers to adherence so that we can develop individualized strategies to overcome these barriers. 3) Subjects will be provided with calendars on day 0 as a scheduling aid for study visits and a reminder to adhere to taking Creon™. 4) Subjects will return unused Creon™ capsules at the end of the study to the study team in a mailing envelope provided.

#### **7.1.5 Drug Accountability**

Records of Creon™ receipt and disposition for each dose used in the study will be maintained by the study team. Records of receipts and dispensing records will be examined during the course of the study. The purpose of these records is to ensure regulatory authorities that the Creon™ will not be distributed to any person who is not a study subject under the terms and conditions set forth in this protocol. Creon™ will be prescribed for all subjects in the study by Dr. Sainath, the Lead Investigator, and dispensed to the subjects by Dr. Sainath. Creon™ may not be used for any purpose other than that described in this protocol. At study completion, all left over Creon™ will be returned to the study team and this will be used as one estimate of adherence. Once the dataset is closed, leftover Creon™ will be destroyed by the Lead Investigator.

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## **8 SAFETY MANAGEMENT**

### **8.1 Clinical Adverse Events**

Clinical adverse events (AEs) will be monitored throughout the study.

### **8.2 Adverse Event Reporting**

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

### **8.3 Definition of an Adverse Event**

An adverse event is any untoward medical occurrence in a subject who has participated in the research protocol. The occurrence does not necessarily have to have a causal relationship with the research activities. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the research activities.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

### **8.4 Definition of a Serious Adverse Event (SAE)**

An SAE is any adverse experience occurring that results in any of the following outcomes:

- death
- a life-threatening event (at risk of death at the time of the event)
- requires inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect in the offspring of a subject

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

#### **8.4.1 Relationship of SAE to investigation or other intervention**

The relationship of each SAE to the study activities will be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

### **8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems**

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research



involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study activities will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

### 8.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

## 8.6 Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting will be consistent with regulatory and sponsor requirements. All serious adverse events experienced by a study subject receiving Creon™ will be reported to the AbbVie, Inc. within 24 hours of learning of the event regardless of the relationship of the event to Creon™, the AbbVie product. The PI and the Lead Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie. For medical emergencies, we will follow the CHOP procedures for medical emergencies that may occur for adult visitors to CHOP.

## 9 STUDY ADMINISTRATION

### 9.1 Treatment Assignment Methods

This is an open-label intervention therapeutic exploratory study. All subjects will receive Creon™. This is not a randomized controlled trial.

### 9.2 Data Collection and Management

We will establish a database to store study data using standard software (e.g. RedCap). The database will be designed to perform automatic computations, such as exact age based upon birth date and date of exam, and averaging anthropometric measures, which are recorded in triplicate. Reports containing the number of subjects enrolled and data entered for each subject are generated and reviewed each month by the PI and the Lead Investigator. The PI, or study staff, will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. Following data entry, all primary and secondary endpoint data will be verified

against original source documents. Data verification will be performed by someone other than the individual originally collecting and entering the data.

All subjects will be assigned a unique identification number that will be used to insure strict confidentiality. The databases are secured with password protection to insure confidentiality and security. The informatics manager receives only coded information which is entered into the database under those identification numbers. Electronic communication with outside collaborators involves only coded, not readily identifiable, information. A master list containing private health information (PHI) and subject ID number will be kept separate from the data forms and the database that will only have a study ID number. The master list will be on a separate computer (password protected). Copies of the master list with PHI will also be stored on the CHOP secured server. All source documents including case report forms, laboratory results, and subject study binders will be kept in secured locations. The file cabinets and the study-specific room will be locked with access to study personnel only, and the outer hallway is also locked with limited access to CHOP research personnel.

Routine backup to the main study database, files created for analyses, and analysis programs will be completed. The main study database will be archived on a daily basis and stored on a CHOP secured server. The Informatics Core of the CTRC will create case report forms, set up the database in RedCap, and provide oversight for data entry and quality assurance for this study.

### **9.3 Confidentiality**

Medical history information will be obtained at baseline. All of the materials collected are for research purposes only, and data will be kept in strict confidence. No information will be given to anyone without permission from the subject. This will be stated in the consent form.

Confidentiality is assured by use of identification codes. All data, whether generated in the laboratory or at the bedside, will be identified with an identification code unique to the subject.

To maintain confidentiality, private health information will be collected, accessed and stored in accordance with Institutional policies and HIPAA guidelines, including the use of multilevel password protection and enforcement of system user privileges on the database. To minimize the risk of disclosure, all direct identifiers will be removed as soon as possible and codes will be substituted for personal identifiers. PHI collected for this study will be kept up to five years after final publication. Records of individuals are stored with ID numbers and a code with no discernible personal identifiers. Code lists and data files will be stored in separate, secure locations. Data will be accessed and stored on password-protected computers. To maintain confidentiality, codes will be used in the database, presentations and publications. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

### **9.4 Regulatory and Ethical Considerations**

#### **9.4.1 Data and Safety Monitoring Plan**

The study will be monitored weekly by the Principal Investigator, Dr. Sainath, as well as by Dr. Stallings. The study protocol will be carried out in accordance with OHRP and NIH guidelines and requirements. SAEs that are unanticipated, serious, and possibly related to the study will be managed by the Principal Investigator (Dr. Sainath), as well as by Dr. Stallings. For subjects with SBS primarily managed at CHOP, members of the Intestinal Rehabilitation Program (Dr. Christina Bales ) will be consulted immediately for all SAEs. For subjects with SBS primarily managed at Penn Medicine/HUP, their primary gastroenterologist, Dr. Octavia Pickett-Blakely, will be consulted immediately and will assume medical care. SAEs will be reported to the study sponsor, IRB, CTRC,

and all members of the research team in accordance with requirements. Anticipated SAEs or those unrelated to the study will be reported to the same individuals/entities in accordance with requirements. There will be ongoing collection of data on adverse events and compliance to the treatment protocol throughout the study by the PI, Dr. Sainath, which will be reviewed weekly by Dr. Stallings.

#### 9.4.2 Risk Assessment

The most common side effects associated with taking the pancreatic enzyme Creon™ in clinical trials were abdominal pain, hyperglycemia, hypoglycemia, frequent abnormal bowel movements, flatulence, vomiting, dizziness, sore throat and cough. Irritation of the inside of the mouth may occur if Creon™ is not swallowed completely. Additionally, subjects in diapers are at risk of diaper dermatitis due to Creon™ if diapers are not changed frequently and a heavy barrier cream is not utilized. Increase in blood uric acid levels (hyperuricemia), and severe allergic reactions (pork allergy) including trouble with breathing, skin rashes or swollen lips, although rare, may occur. Although it has never been reported, it is possible for a person to get a viral infection from taking pancreatic enzyme products that come from pigs. Fibrosing colonopathy and colonic strictures is a rare, serious adverse reaction associated with chronic high-dose pancreatic enzyme use over a prolonged period of time with enzyme doses in excess of 6,000 LU/kg body weight per meal or 10,000 LU/kg/day in patients with cystic fibrosis. Doses of Creon™ prescribed for this study will not exceed 10,000 LU/kg/day or 4000 LU/grams of fat/day for any subject.

There are risks associated with discontinuing pancreatic enzyme medication for subjects with SBS who have noted clinical improvement on pancreatic enzymes. These include feelings of indigestion, stomach cramping after meals, gas, foul smelling, floating stools, light-colored, orange or yellow stools, frequent or loose stools, or weight loss. Some participants in the study may be at increased risk for these symptoms.

- The participants receiving pancreatic enzyme medication prior to enrolling in the study who will discontinue use prior to the first study visit (Study Visit #1) may be at risk for signs and symptoms of fat malabsorption (described above) for nine days of the study. These nine days include the three days prior to Study Visit #1 (washout period), the day of Study Visit #1 to CHOP, and the five days of specimen collection after Study Visit #1. These participants will resume their pancreatic enzyme product and dose for the period of time between the end of the nine days encompassing Study Visit #1 and the start of the three days prior to Study Visit #2 when they will switch to Creon™ at doses prescribed based on the study protocol. Therefore, they will not be at increased risk for the signs and symptoms of fat malabsorption during the time between visits or during the ten days encompassing Study Visit #2 as they will be taking pancreatic enzyme medication throughout this period. When the study is completed, these participants will discontinue Creon™ and resume their usual care and resume their usual pancreatic enzyme product and dose.
- The participants who are naïve to pancreatic enzyme medication prior to entering the study, will take Creon™ for the ten days encompassing Study Visit #2 of the study, that is, four days prior to the protocol visit to CHOP, the day of the visit, and then five days after the visit until all specimen collections have been completed. If these participants have undiagnosed reduced pancreatic function and reduced fat absorption, they may have increased risk for the signs and symptoms of fat malabsorption upon discontinuation of

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Creon™ at the end of the study. If their pancreatic function and fat absorption is normal, withdrawal from Creon™ at the end of the study will not increase their risk for these symptoms.

Approximately ten adult subjects with SBS will have the option to have the MBT at both Study Visit #1 and Study Visit #2. During this test, a high fat supplement will be administered enterally. Subjects with poor absorption are therefore at risk of developing indigestion, abdominal pain or cramping, increased flatus, and frequent or loose stools. Ostomy output and stool output may increase and if estimated to be greater than 50 milliliters/kilogram/day, subjects may require serum electrolyte monitoring. If dehydration or severe electrolyte abnormalities occur, mainly acidosis (serum bicarbonate level less than 20 mmol/L) or hypokalemia (serum potassium less than 3.5 mmol/L), subjects will be hospitalized. Subjects who are primarily followed at The Children's Hospital of Philadelphia by Dr. Christina Bales, subjects less than 18 years, or subjects followed by pediatric gastroenterologists will be admitted to CHOP for monitoring, hydration, and electrolyte repletion. Subjects who are primarily followed at adult institutions will be discussed with Dr. Octavia Pickett-Blakely. Dr. Pickett-Blakely will assume their care and they will be hospitalized at the Hospital of the University of Pennsylvania.

The procedures in this study involve the potential risks related to the drawing of blood. The risks of drawing blood are rare, and minimal. There is a small risk of pain, infection and local irritation associated with insertion of an intravenous heparin catheter. However, this is considered a minimal risk and skilled research staff will insert the intravenous catheter. In subjects who have central venous access and are under 18 years of age, we will give their parents/legal guardians the option of having blood drawn from their central line instead of a venipuncture. Skilled research staff will take all necessary precautions to avoid risk of infection. Each subject with SBS in the MBT/CCK subset will have approximately 136cc (approximately 9 tablespoons) of blood drawn at study visit #1 and about 111 cc (approximately 7-8 tablespoons) of blood drawn at study visit #2. Subjects in the non-MBT/CCK subset who weigh 25 kilograms or more will have approximately 50 cc (approximately 3-4 tablespoons) of blood drawn at study visit #1 and approximately 25 cc (approximately 1-2 tablespoons) of blood drawn at study visit #2. **Subjects in the non-MBT/CCK subset who weigh less than 25 kilograms will have approximately 26 cc (approximately 1-2 tablespoons) of blood drawn at study visit 0 and approximately 25 cc (approximately 1-2 tablespoons) of blood drawn at both study visit #1 and study visit #2.**

There is minimal risk associated with the low radiation exposure from the DXA scan. Radiation exposure is estimated to be no more than 3.0 µSv (depending on age and size) per visit, well below everyday background exposure (approximately 8.2 µSv). DXA instruments are regularly monitored for safety, and only experienced pediatric research personnel will conduct these tests.

Anthropometric measurements and pregnancy testing pose minimal risk to the subjects. There is minimal risk associated with sharing dietary intake, demographic information, health history and medical information.

Collection and storage of stool is associated with a small risk of fecal contamination. However, for safety and convenience, subjects will be provided with proper stool collection instructions and supplies (gloves, disposable collection containers, storage freezer container).

Private health information will be collected, accessed and stored according to HIPAA guidelines, including the use of multilevel password protection and enforcement of system user privileges on the database. To minimize the risk of disclosure, all direct identifiers will be removed as soon as possible and codes will be substituted for personal identifiers. Records of individuals are stored

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with ID numbers and a code with no discernible personal identifiers. Code lists and data files will be stored in separate, secure locations. Data will be accessed and stored on password-protected computers. To maintain confidentiality, codes will be used in the database, presentations and publications.

#### **9.4.3 Potential Benefits of Study Participation**

We cannot ensure a direct benefit to the subjects as a result of participating in this study. Participants may benefit from knowing that they will contribute to a clinical research study that is important to the health of people with SBS in the U.S. and around the world.

#### **9.4.4 Risk-Benefit Assessment**

The research we propose is justified, considering that the risk associated with participation is minimal compared to the potential and anticipated benefits. The benefits of participation clearly outweigh the risks, in view of the potential positive benefits of the study to the larger population of people living with SBS.

### **9.5 Recruitment Strategy**

It is expected that subjects will be recruited by word of mouth and at the recommendation of the subjects' SBS Care Team. The Recruitment Enhancement Core at CHOP will provide assistance with identifying individuals with a diagnosis of short bowel syndrome and contacting potential participants. Interested individuals can contact the study team. We will also use the Penn Analytics Data Center to identify and contact patients with a diagnosis of short bowel syndrome. Once identified, we will contact their provider to inform individuals of the existence of the study and to obtain permission to share their contact information with the CHOP study staff.

### **9.6 Informed Consent and HIPAA Authorization**

Once a subject has expressed interest in participating a CHOP-based research team member will contact the subject via telephone and continue the introduction of the study to subjects. Verbal consent and HIPAA authorization for phone screening will be obtained prior to the collection of health information to determine eligibility. If screening occurs in person in the clinical care setting, participants will sign the screening consent prior to the collection of any health information to determine eligibility. Assent will not be obtained for pediatric subjects between 7 and 17.9 years on the screening consent form. A HIPAA Authorization form from the subjects' institutions for obtaining non-CHOP medical records, will be signed in person or obtained by mail/fax/email. All members of the team will be available (in person, by phone or email) to discuss the details and answer any study related questions as they arise. Once interest and eligibility are determined, procedures to set up enrollment will begin. At entry into the study, all subjects will be asked to review the study consent form. Dr. Sainath or other member of the clinical research team will meet with the subject or discuss via telephone to confirm the subject understands the study, and to answer any questions that the subject might have. A physician-level study team member will be available to answer any questions of issues that may arise. After all study-related questions are answered and subjects have had time to consider their decision, Dr. Sainath or a member of the clinical research team will obtain fully informed, consent from the adult subjects or from the parents/legal guardians of pediatric subjects. If informed consent is obtained via telephone, then a signed informed consent form will be obtained either prior to having laboratories drawn at study visit 0 for those subjects who weigh less than 25 kilograms, prior to discontinuation of any medications as part of the study protocol, prior to obtaining a 24-hour dietary recall by telephone,

at the start of study visit 1 prior to any other study procedures scheduled that day, or prior to any dietary changes or fasting in preparation for study visit 1. If informed consent is obtained via telephone, a copy of the consent form will be provided to the subject or parent/guardian via email, fax, or mail prior to the informed consent process. In order for the consent process to be completed by phone, Dr. Sainath or a member of the clinical research team must speak to both parents/guardians if the subject is under 18 years and must also speak to the subject if the subject is 7 years or older. This may require multiple phone calls or a conference call. Informed consent for non-English speaking subjects will only be completed in person with an interpreter. Dr. Sainath or a member of the clinical research team will obtain assent for pediatric subjects between the ages of 7 year and 17.9 years. Adult subjects will be given a printed copy of the signed, informed consent and the legal guardians of pediatric subjects less than 18 years will be given a printed copy of the signed, informed consent.

### **9.6.1 Waiver of Documentation of Consent/ Alteration of HIPAA Authorization**

A waiver of documentation of consent will be sought for the verbal screening component of the study when potential participants are approached by phone. The rights and welfare of the subject will not be adversely affected because during the verbal consent process it is explained to the subject that we are recording their health information to determine eligibility for the study. The research could not practicably be carried out without this waiver as it is not practicable to approach and screen all potential participants in person. A waiver of assent of pediatric subjects between the ages of 7 and 17.9 years will be sought for the screening component of the study, as pediatric subjects may not be available when parents or legal guardians of potential participants are approached by phone. An alteration of HIPAA authorization will be sought for the screening component of the study. The use and disclosure of protected health information for the purposes of screening for eligibility involves no more than minimal risk to the privacy of participants, as the identifiers will be protected from improper use and disclosure, identifiers will be destroyed at the earliest opportunity consistent with the conduct of the study, and protected health information will not be reused or disclosed to any other person or entity, except as required by law for authorized oversight of the research project. The research could not practicably be conducted without access to and use of the protected health information collected during screening to determine eligibility.

Study staff stress during the verbal consent that the screening is voluntary, but necessary if they wish to participate, and that they can decline and stop the process at any point. Screening may also take place in person in which case the participant will sign the screening consent prior to the collection of health information to determine eligibility, and a waiver of documentation of consent will not apply. **Verbal consent/HIPAA authorization may be obtained for screening.** A written informed consent will be obtained prior to main study entry. This will occur at study visit 0 either in person or by telephone. Subjects or their legal guardian will sign an informed consent form prior to having laboratories drawn at study visit 0 for those subjects who weigh less than 25 kilograms, prior to discontinuation of any medication as part of the study protocol, prior to completing a 24-hour dietary recall by telephone, prior to study procedures at study visit 1, or prior to dietary changes or fasting in preparation for study visit 1. Discontinuation of pancreatic enzyme medication for those

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participants who are taking this medication at the time of enrollment in the study will not occur prior to obtaining written, informed consent

## **9.7 Payment to Subjects**

### **9.7.1 Payments to subject**

All participants who are part of the MBT/CCK cohort and have the MBT performed at Study Visit #1 and Study Visit # 2 will be compensated \$200 for Study Visit #1 and \$175 for Study Visit #2 for time and effort associated with each study visit: Visit 1 Visit 2. All subjects will be compensated \$25 for Study Visit #3 for time and effort associated with this last study visit. Subjects who complete study visit #3 by phone will receive payment once their stool samples are received either in person or by mail. Subjects in the MBT/CCK cohort will receive a total of \$400 (\$200 for Study Visit #1, \$175 for Study Visit #2, and \$25 for Study Visit #3)

Pediatric subjects who are part of the non-MBT/CCK cohort and who are between the ages of 9 and 17.9 years will be directly compensated for their efforts. Parents or legal guardians of subjects in the non-MBT/CCK cohort and who are between the ages of 4 and 8.9 years will be compensated for their child's participation. Adult subjects who are eligible for the MBT/CCK cohort and decline the MBT will follow the non-MBT/CCK protocol and will be compensated the same amount as non-MBT/CCK subjects who are between the ages of 9 and 17.9 years. All participants who are part of the non-MBT/CCK cohort will be compensated \$100 for Study Visit #1 and \$75 for Study Visit #2 for time and effort associated with each study visit: Visit 1 Visit 2. All participants will be compensated \$25 for Study Visit #3 for time and effort associated with this last study visit. Subjects who complete study visit #3 by phone will receive payment once their stool samples are received either in person or by mail. Subjects in the non-MBT/CCK cohort or their parent/legal guardian will receive a total of \$200 (\$100 for Study Visit #1, \$75 for Study Visit #2, and \$25 for Study Visit #3).

## **10 PUBLICATION**

The research data obtained through the study outlined in this protocol will be shared with the research community, both through oral presentation at scientific meetings, and in written form, as published manuscripts. Reported factual material (primary data on which summary statistics and tables are based), commonly accepted in the scientific community as necessary to document and support research findings, will be provided in a timely fashion upon request by members of the scientific community to the lead investigator and the Principal Investigator for a period of three years following acceptance for publication. The CHOP investigator will have access to the complete study data.

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