NCT02706483

An Open-Label, Long-Term Safety and Tolerability Study of Plecanatide in Patients with Irritable Bowel Syndrome with Constipation (IBS-C)

Sponsor:	**Synergy Pharmaceuticals Inc.** **420 Lexington Avenue, Suite 2012** **New York, NY 10170** [redacted]
Clinical Research Organizations:	**ICON Clinical Research Inc.** **2100 Pennbrook Parkway** **North Wales, PA 19454** **United States** **Chiltern International Inc.** **1241 Volunteer Parkway Suite 95** **Bristol, TN 37620** **United States**
Medical Monitor:	[redacted]
Sponsor Protocol No.:	**SP304203-06**
IND No.:	**115,118**
Study Drug Name:	**Plecanatide**
Date/Version of Protocol:	**July 21, 2016 / Version 3.0** **October 28, 2015 / Version 2.0** **September 14, 2015 / Version 1.0**

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and with other applicable regulatory requirements.

SIGNATURE PAGE

DECLARATION OF SPONSOR

Title: An Open-Label, Long-Term Safety and Tolerability Study of Plecanatide in Patients with Irritable Bowel Syndrome with Constipation (IBS-C).

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the guidelines on Good Clinical Practice.

DECLARATION OF THE INVESTIGATOR

Title: **An Open-Label, Long-Term Safety and Tolerability Study of Plecanatide in Patients with Irritable Bowel Syndrome with Constipation (IBS-C).**

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator Brochure, electronic Case Report Forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB/IEC, except where necessary to eliminate an immediate hazard to the patients.

I confirm that I have read and will follow the above-named protocol. I understand it, and I will work according to the principles of Good Clinical Practices (GCP) as described in the United States Code of Federal Regulations (CFR) parts 50, 54, 56, and 312, and the International Conference on Harmonization (ICH) document "Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance." Further, I will conduct the study in keeping with local legal and regulatory requirements and principles of the Declaration of Helsinki as currently endorsed by regional regulatory health authorities.

Responsible Investigator of the local study center

_____ _____
Signature Date

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Name (block letters)

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Title (block letters)

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Institution (block letters)

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Phone number

PROTOCOL SYNOPSIS

Study Title	An Open-Label, Long-Term Safety and Tolerability Study of Plecanatide in Patients with Irritable Bowel Syndrome with Constipation (IBS-C)
Sponsor	Synergy Pharmaceuticals Inc.
Study Number	SP304203-06
Study Centers	Approximately 250 sites in the United States
Objectives	Primary objective: To evaluate long-term safety and tolerability of plecanatide administered once daily for the treatment of IBS-C. Additionally, patients' assessments of their disease severity, adequacy of treatment and desire for treatment continuation will be collected.
Methodology	Multi-center, open-label, long-term safety study
Number of Patients and Population	Up to 1500 male and female patients with IBS-C who are either: 1) Study Completers - completed phase 3 double-blind plecanatide study SP304203-04 or SP304203-05 and did not experience a Serious Adverse Event deemed related to study drug, or 2) Eligible Screen Failures - failed screening in study SP304203-04 or SP304203-05 due to diary noncompliance (exclusion criterion 24 of the core study) or due to another reason, and in all cases, is allowed to enter this study by notification from Sponsor or delegate; confirmation of active IBS-C via ROME III modular questionnaire is required. 3) Early withdrawal from SP304203-04 or SP304203-05 due to lack of efficacy and completed an early withdrawal visit (Visit EW). 4) Patient completed plecanatide study SP304-20212, i.e, had an End-of-Study Visit and did not experience a Serious Adverse Event deemed related to study drug, or 5) Patient was randomized and did not complete study SP304-20212, but (a) completed an early withdrawal visit, and (b) did not have an SAE and (c) the reason for early withdrawal was not a drug-related AE and (d) is allowed to enter this study with written approval from Sponsor or delegate 6) Plecanatide study-naive Patients – patients that did not previously participate in any plecanatide study
Study Termination	The study will end when its enrollment, regulatory and study drug exposure objectives have been met. Consequently, not all enrolled patients will receive 53 weeks of treatment.
Study Drug	Plecanatide 6 mg tablets
Rescue Medication	Bisacodyl (Dulcolax®) 5 mg tablets
Treatment Duration	Up to 53 weeks (1 year)
Study Design	This is a phase 3, multicenter, open-label, long-term safety and tolerability study of 6 mg daily dose of plecanatide administered orally. Patients who are Study Completers or Eligible Screen Failures whose eligibility is confirmed at the end of their participation in the double-blind plecanatide studies SP304203-04 or SP304203-05 will, ideally, start participation in this open-label trial on the day of or within 4 weeks of last dose of study drug in SP304203-04 or SP304203-05 or, for eligible screen failures, on the day of or within 4 weeks of the end of their

	participation in SP304203-04 or SP304203-05 study (Short Interval Patients). If the patient is plecanatide study-naive, participated in the SP304-20212, or more than 4 weeks has elapsed since the patient's last dose of study drug in the SP304203-04 or SP304203-05 study, or more than 4 weeks has elapsed since the end of an eligible screen failure's participation in SP304203-04 or SP304203-05, the patient will need to undergo additional screening assessments in order to be considered for enrollment into this trial (Long Interval Patients). Beginning on Day 1, patients will take an oral dose of study drug QD for up to 53 weeks. Dose adjustments of study drug are not permitted in this study. Patients who interrupt study treatment for adverse events, intercurrent illness or other issues may continue in the study with the approval of the Principal Investigator and the Medical Monitor when the reason for interruption has been adequately reviewed and the patient is deemed appropriate to continue treatment. Bisacodyl (Dulcolax®) 5 mg tablets will be supplied as rescue medication (RM) for the study. Safety and tolerability assessments and patients' self-assessment of disease severity will be performed according to the Schedule of Assessments. Patients who discontinue early from the study will undergo an Early Withdrawal (EW) visit within 5 days after stopping study drug. Patients who prematurely withdraw from study treatment will not be eligible to participate in this or any other plecanatide study in the future. Upon study termination by the Sponsor, patients will undergo an End of Treatment (EOT) visit.
Criteria for Evaluation	
Safety and Tolerability	Evaluation of the safety of once daily (QD) plecanatide over up to 53 weeks of dosing will be based on the occurrence of treatment-emergent adverse events (TEAEs) and assessment of: vital signs, clinical laboratory tests, physical examinations and electrocardiograms. Tolerability will be assessed by treatment interruptions due to diarrhea or other AEs, AE-free days, and continued participation in the trial.
Statistical Methods	A formal Statistical Analysis Plan (SAP) will be written and include details of all statistical methods to be used to analyze the long-term safety and tolerability of plecanatide.

LIST OF STUDY PERSONNEL

Sponsor	[redacted] Executive Vice President and Chief Medical Officer Synergy Pharmaceuticals Inc. 420 Lexington Avenue, Suite 1609 New York, NY 10170 [redacted]
Medical Monitor	[redacted]
SAE Reporting	ICON Clinical Research Medical and Safety Services [redacted]
Central Laboratory	ACM Medical Laboratory, Inc. 160 Elmgrove Park Rochester, New York 14624
Drug Manufacturer	UPM Pharmaceuticals 6200 Seaforth Street Baltimore, MD 21224
Drug Packaging and Distribution	Sharp Packaging Solutions 7451 Keebler Way 7339 Industrial Blvd Allentown, PA 18106

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERM

AE	Adverse event
AGA	American Gastroenterological Association
ALT / SGPT	Alanine transaminase / serum glutamic pyruvic transaminase
AST / SGOT	Aspartate aminotransferase / serum glutamic oxaloacetic transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical [Classification System]
ß-HCG	Beta-human chorionic gonadotropin
BM	Bowel movement
BSFS	Bristol Stool Form Scale
CFR	Code of Federal Regulations
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence interval
CIC	Chronic Idiopathic Constipation
cGMP	Cyclic guanosine monophosphate
CMH	Cochran-Mantel-Haenszel (test)
CRO	Contract Research Organization
CSBM	Complete spontaneous bowel movement
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOS	End of Study
EOT	End of treatment
ET	Early termination
EW	Early withdrawal
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GC-C	Guanylate cyclase
GCP	Good Clinical Practice
GI	Gastrointestinal
IB	Investigator’s Brochure
IBS	Irritable Bowel Syndrome
IBS-SSS	Irritable Bowel Syndrome Severity Scoring System
IBSQoL	Irritable Bowel Syndrome Quality of Life
IBS-C	Irritable Bowel Syndrome with Constipation

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug (application)
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web-based Response System
LLN	Lower limit of normal
LOCF	Last observation carried forward
MCG	Microgram
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
Med DRA	Medical Dictionary for Regulatory Activities
MG	Milligram
MH	Medical History
PDUFA	Prescription Drug User Fee Act
PE	Physical examination
PGA	Patient Global Assessment
PI	Principal Investigator
PIN	Personal Identification Number
PP	Per-Protocol (Population)
QD	Once daily
QoL	Quality of Life
RM	Rescue Medication
SAE	Serious adverse event
SAP	Statistical analysis plan
SBM	Spontaneous bowel movement
SD	Standard deviation
SOC	System organ class
SP-304	Previous designation for Plecanatide
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHODD	World Health Organization Drug Dictionary

1 OVERALL DESIGN AND PLAN OF THE STUDY

This is a multi-center, open-label study of plecanatide in patients with IBS-C. Patients will receive up to 53 weeks of study drug. This clinical trial is designed to evaluate the long-term safety and tolerability of plecanatide in patients enrolling from the phase 2 safety and efficacy SP304-20212 study or phase 3 safety and efficacy studies SP304203-04 and SP304203-05 as well as plecanatide study-naive patients that have not previously enrolled in any plecanatide study. The SP304203-04 and SP304203-05 are studies that will feed into SP304203-06 and will be referred to as the "core studies" in the remainder of this document.

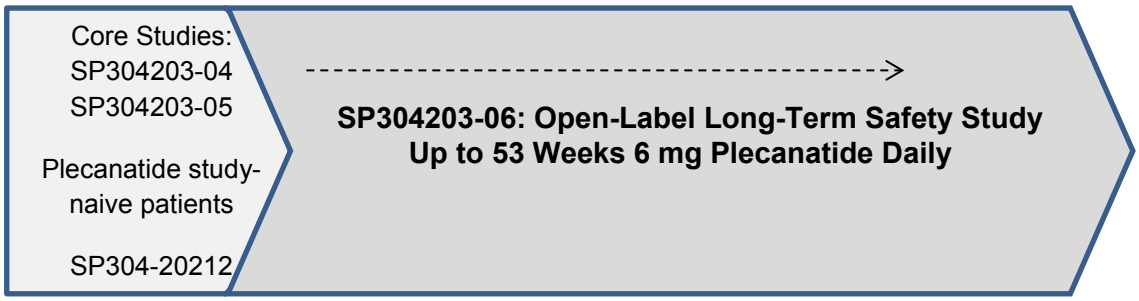
In addition to assessment of safety and tolerability of the once-daily 6 mg oral dose of plecanatide, patients' self-assessment of disease severity and adequacy of treatment will be performed. The desire for treatment continuation will be assessed for each patient at their last visit in the study.

This clinical trial will be conducted in approximately 250 centers in the US that have participated in the core studies. Patients will be evaluated for eligibility at the end of their participation in the double-blind plecanatide core studies and, ideally completers will enroll in this open-label trial SP304203-06 on the day or within 4 weeks of the last dose in the core studies (Short Interval Patients).

For plecanatide study-naive patients, SP304-20212 patients, and any patient that needs a colonoscopy (as outlined in Appendix 3), or when more than 4 weeks have elapsed since the last study drug dose in the core studies, the patient will need to undergo additional screening assessments in order to be considered for enrollment into this trial (Long Interval Patients).

The overall study plan is presented in Figure 1.

Figure 1: Study Design



For Study Completers---after completing the requirements of the end-of-study visit (Visit 6) in the core studies, qualifying patients will be given the option to enter the SP304203-06 Study, ideally enrolling into SP304203-06 on the same day, where they will receive treatment with 6 mg plecanatide in an open-label fashion for up to 53 weeks.

For Eligible Screen Failure patients and patients that withdrew early due to lack of efficacy from SP304203-04 or SP304203-05 (the core studies) - sites will be notified of eligible patients who meet eligibility criteria through IWRS or Medical Monitor or designee for possible enrollment into the study. Sites should also request notice of eligibility.

Short Interval Patients: Patients enrolling from the core studies (a) less than or equal to 4 weeks from the last dose of study drug or (b) less than or equal to 4 weeks from Visit 2 for patients that are Eligible Screen Failure patients: The patient's participation in this trial will start at the Baseline/Day 1 Visit, as per the schedule of assessments in **Table 3**. After written informed consent is obtained, patients will receive

their assigned study drug and will take their first dose at the clinical site. Patients will continue to take a single oral dose of study drug once daily for up to 53 weeks.

Long Interval Patients: All patients enrolling that are (a) plecanatide study-naive, (b) SP304-20212 (Phase 2) patients, (c) greater than 4 weeks from the last dose of study drug in the core study or (d) greater than 4 weeks from Visit 2 for patients that are Eligible Screen Failure patients in the core study: These patients will additionally require the Screening Visit, as per the schedule of assessments in **Table 4**. Written informed consent will be obtained at the screening visit. Consented patients will then undergo screening procedures to determine eligibility for further participation. Patients eligible to continue on to Day 1 will then receive their assigned study drug and will take their first dose at the clinical site. Patients will continue to take a single oral dose of study drug once daily for up to 53 weeks.

If there is doubt about whether a patient is a Short Interval Patient or a Long Interval Patient, they should be considered a Long Interval Patient and a Screening Visit performed. The performance of a Screening Visit, even if not strictly required, will not be considered a protocol deviation.

Safety and tolerability assessments and patients' self-assessment of disease severity and adequacy of treatment will be performed at Weeks 4, 12, 24, 36 and 53, as specified in the schedule of assessments (**Table 3 or Table 4**, as applicable). The desire for treatment continuation will be assessed for each patient at their last visit in the study.

Dose adjustments are not permitted during this study. Bisacodyl (Dulcolax®) 5 mg tablets will be supplied as rescue medication (RM).

Patients who interrupt study treatment for adverse events, intercurrent illness or study drug supply issues may continue in the study with the approval of the Principal Investigator and the Medical Monitor when the reason for interruption has been adequately reviewed and the patient deemed appropriate to continue treatment.

2 INTRODUCTION

2.1 Background

2.1.1 Overview of Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) is characterized by recurrent episodes of abdominal pain and discomfort with associated alterations in bowel habits. The altered bowel habits may include diarrhea, constipation or a mixed pattern of diarrhea and constipation. Abdominal discomfort or pain is a universal feature required for the diagnosis of IBS, and the presence of the predominant abnormal bowel pattern leads to the subtyping of IBS: diarrhea-predominant (D-IBS), constipation-predominant (C-IBS), or mixed IBS (M-IBS). Of the approximately 30 million individuals in North America who meet the diagnostic criteria for IBS, approximately one-third experience constipation during episodes of disease activity [1]. The remaining patients are equally subdivided among the other two subtypes [2]. IBS is a chronic condition, and may start in adolescence with a 2-3:1 predominance in females as compared to males. The most widely accepted definition for the diagnosis of IBS is the Rome III criteria and includes recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with 2 or more of the following: 1) improvement with defecation, 2) onset associated with a change in frequency of stool, and 3) onset associated with a change in form (appearance) of stool. The IBS-C subtype is further characterized by stool pattern such that ≥ 25% of defecations are hard or lumpy stools and < 25% of defecations are loose or watery stools [3]. This study focuses on patients with IBS-C.

Several underlying mechanisms have been implicated in the pathophysiology of IBS, although much remains poorly understood [3, 4]. The pain that patients with IBS experience is believed to be due to

visceral hypersensitivity. In these patients visceral stimuli which are usually normal or not bothersome (in non-IBS patients) are perceived as painful. Psychosocial stressors, genetic factors, altered intestinal microbiota, and altered brain-gut interaction have been theorized to exacerbate or lead to symptoms of IBS. Infection and post-infectious inflammation have also been postulated to lead to the development of IBS or symptoms of IBS [5]. According to the Rome III criteria, a patient has to have continuous or intermittent symptoms of abdominal discomfort for at least 6 months before the diagnosis of IBS can be considered [6].

IBS-C is a multi-symptom disease and the goal of therapy is to provide treatment that alleviates its multiple symptoms. Currently, in clinical practice, treatments are typically focused on the treatment of the individual symptoms of IBS-C. If a patient has predominantly constipation symptoms, the patient is usually prescribed a fiber supplement or a laxative. If bloating and distension occur, the patient may be prescribed an antispasmodic or dietary modification. If a patient complains of abdominal pain, the patient may receive tricyclic anti-depressants although there is no FDA approved treatment for pain associated with IBS-C.

2.1.2 Plecanatide Mechanism of Action

Plecanatide, a synthetic hexadecapeptide designed to mimic the actions of uroguanylin, is currently being developed by Synergy Pharmaceuticals Inc. (Synergy) for treatment of IBS-C and CIC.

Uroguanylin (UG) and guanylin (GN) are endogenous peptide agonists of receptor guanylate cyclase-C (GC-C) that is expressed on the luminal surface of epithelial cells lining the gastrointestinal (GI) tract mucosa. These receptor agonists, including plecanatide, bind and activate GC-C receptor to stimulate the intracellular production of cyclic guanosine monophosphate (cGMP), resulting in decreased Na^+ reabsorption through Na^+/H^+ exchange and activation of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). Activation of CFTR and the subsequent enhancement of transepithelial efflux of chloride and bicarbonate ions lead to influx of water into the intestinal lumen [7]. This fluid secretion is expected to facilitate bowel movements.

In addition to being a secretagogue, plecanatide has demonstrated anti-inflammatory activity in the mouse DSS colitis model [8, 9]. This anti-inflammatory activity may be beneficial for treatment of IBS-C.

2.1.3 Clinical Experience

In a recently completed double-blind trial, plecanatide has been shown to increase significantly the frequency of complete spontaneous bowel movements (CSBMs) and to improve symptoms in patients with IBS-C; it was safe and well-tolerated. Plecanatide has also been shown to increase the frequency of bowel movements (BMs) in patients with Chronic Idiopathic Constipation (CIC) in a double-blind trial. Effects on stool consistency and reduction of the time to first bowel movement were also seen.

Four clinical studies have been completed with plecanatide to date. They are summarized in **Table 1**.

Table 1: Summary of completed, placebo-controlled, clinical trials with plecanatide

Phase	Population	N	Duration	Doses (mg)
1	Healthy volunteers	71	Single-dose	0.1-48.6
2a	Patients with CIC	78	14 days	0.3, 1.0, 3.0, 9.0
2b	Patients with CIC	951	12 weeks	0.3, 1.0, 3.0
2b	Patients with IBS-C	424	12 weeks	0.3, 1.0, 3.0, 9.0
3	Patients with CIC	1,346	12 weeks	3.0, 6.0
3	Patients with CIC	1,337	12 weeks	3.0, 6.0
3	Patients with CIC	2,369	Up to 72 weeks	6.0

The Phase I study (SP304101-08) was a single dose escalation study in 71 healthy subjects receiving doses of 0.1, 0.3, 0.9, 2.7, 5.4, 8.1, 16.2, 24.3, or 48.6 mg plecanatide (n=53) or placebo (n=18). The study reported no systemic absorption at any dose and no serious adverse events (SAEs) or withdrawals due to adverse events (AEs). Diarrhea was the most common AE in the study reported by 8 of 53 (15.1%) plecanatide subjects and 3 of 18 (16.7%) placebo subjects. The occurrence of diarrhea did not appear to be dose-related. Other AEs occurring in 2 or more subjects included: abdominal discomfort, nausea, and vomiting [10].

The Phase 2a study in patients with CIC (SP304201-09) was a 14-day, repeat-dose, placebo-controlled, oral dose-escalation study to determine the safety of plecanatide. Seventy-eight patients were enrolled in this study and randomized to receive one of four plecanatide doses: 0.3 mg, 1.0 mg, 3.0 mg, and 9.0 mg or placebo. Each dose cohort consisted of 20 patients (15 active; 5 placebo). After each cohort was completed, a safety review was conducted prior to initiating the next dose cohort. There were no SAEs or withdrawals due to AEs for any of the patients who received plecanatide during this study. Adverse events occurring in 2 or more subjects included: headache, flatulence, and elevated lipase. None of the 58 patients treated with plecanatide in this study had diarrhea. The majority of AEs were mild or moderate in severity and transient in nature [11].

The Phase 2b study in patients with CIC (SP304-20210) was a large, 12-week, multicenter, dose-ranging study [12]. This randomized, double-blind, placebo-controlled study was initiated in October 2011 (first dose) and completed in December 2012 (last patient, last visit). A total of 951 patients were randomized at 113 clinical site in the US. Randomization was 1:1:1:1 to plecanatide (0.3, 1.0, or 3.0 mg) or placebo. In this study, 948 patients received study drug (712 plecanatide) and 946 patients had at least one study assessment and were included in the modified Intent-to-Treat (mITT) population. In the high (3.0 mg) dose group (n=237), the proportion of patients who were Overall Responders (19%) was statistically significantly greater than in patients treated with placebo (10.7%) (p=0.009).

Among secondary endpoints there were statistically significant changes from baseline (as compared to placebo) that were dose-related in the frequency of CSBMs, stool consistency (higher Bristol Stool Form Scale (BSFS) score), and straining with the greatest change and degree of statistical significance at the 3.0 mg dose group. The median times to first SBM were statistically significantly shorter for all doses of plecanatide compared to placebo (27.3 hours) with the shortest median time to first SBM of 12.5 hours at the 3.0 mg dose. Statistically significantly different (from placebo) changes in patient global assessments and the PAC-SYM and PAC-QOL scales were also seen over the 12 weeks of treatment at the 1.0 and 3.0 mg doses. In general, plecanatide was safe and well tolerated.

Diarrhea was the most common adverse event, which increased with increasing dose to an incidence of 9.7% in the 3.0 mg dose group. Of the cases of diarrhea in patients treated with plecanatide, 0.7% overall were considered severe and in patients receiving 3.0 mg, only one case (0.4%) was considered severe. The other most common TEAEs occurring in at least 2% of patients were headache, abdominal pain, nausea, abdominal distension, urinary tract infection, flatulence, and upper respiratory infection. SAEs were uncommon, occurring in only nine study patients, and none were considered related to study drug. Overall, approximately 5.5% of patients on 3.0 mg of plecanatide withdrew due to adverse events compared to 3.4% on placebo. Three percent of patients at the 3.0 mg dose withdrew participation due to diarrhea compared to 0.4% on placebo. There were no clinically significant changes in laboratory tests, ECGs, or vital signs. Further details can be found in the Investigator's Brochure that contains additional information on plecanatide.

The most recently completed study was a 12-week, multicenter, dose-ranging study (SP304-20212) in patients with IBS-C [Data on file, Synergy Pharmaceuticals]. This randomized, double-blind, placebo-controlled study was initiated in January 2013 (first dose) and completed in March 2014 (last patient, last visit) at 94 sites in the United States. In this study, 428 patients received study drug (342 plecanatide) and 423 patients had at least one study assessment and were included in the modified Intent-to-Treat (mITT) population. The mITT population was the primary analysis population for all efficacy parameters. Randomization was 1:1:1:1:1 to plecanatide (0.3, 1.0, 3.0 or 9.0 mg daily) or placebo.

The plecanatide 3.0 mg dose was selected as one of the doses for phase 3 based on achieving statistically significant improvement in the study's primary endpoint and key secondary endpoints assessed in the topline analyses, which included change from baseline versus placebo over 12 weeks in: CSBM frequency (1.29 placebo vs. 2.74, p=<0.001), worst abdominal pain intensity (-1.4 [-24.5%] placebo vs.-2.0 [-33.9%], p=<0.05) and stool consistency (BSFS) (1.01 placebo vs. 2.49, p=<0.001). Importantly, plecanatide 3.0 mg dose also showed a statistically significant difference from placebo in the overall FDA responder endpoint (21% placebo vs. 41.9%, p=<0.05). An Overall Responder for the FDA endpoint fulfills both ≥30% reduction in worst abdominal pain and an increase of ≥1 complete spontaneous bowel movements (CSBMs) from baseline in the same week for at least 50% of the weeks (i.e. 6/12 weeks).The treatment effects of plecanatide occurred within the first week. Plecanatide was safe and well tolerated with no treatment-related serious adverse events. The most common event was diarrhea, which occurred in 9.3 percent of the 3.0 mg plecanatide-treated patients.

Three large Phase 3 clinical trials with plecanatide in patients with Chronic Idiopathic Constipation (CIC) have been completed: (SP304203-00, SP304203-01, SP304203-03), and two Phase 3 studies in Irritable Bowel Syndrome with Constipation (IBS-C) are ongoing: (SP304203-04, SP304203-05).

2.2 Rationale and Objectives

IBS-C is a chronic medical condition with few treatment options. Many patients either fail to achieve an adequate response or cannot tolerate the existing treatments. Therefore, new treatment options that offer similar or better levels of clinical benefit are needed. Clinical studies of plecanatide in patients with IBS-C and CIC suggest that it is well-tolerated and may improve bowel frequency while decreasing abdominal pain.

The primary objective of this study is to evaluate the long-term safety and tolerability of plecanatide administered once daily for the treatment of IBS-C. In addition, patients' assessments of disease severity and adequacy of treatment will be collected. Desire for treatment continuation will be assessed for each patient at their last visit in the study.

2.2.1 Rationale for the Dose Selection

The once a day 6 mg dose of plecanatide selected for this study is based upon observations from prior plecanatide studies. Doses of 3 and 9 mg/day given for 12 weeks were shown to be safe and effective in a Phase 2 trial of patients with IBS-C, with 3 mg dose demonstrating clinically significant efficacy. The 6 mg daily dose is being evaluated in the core studies and is anticipated to provide desired efficacy with minimal treatment-related side effects. Administration of 6 mg plecanatide for longer-term treatment in this patient population is warranted and will support the highest intended dose in this indication.

2.3 Risk-Benefit Assessment

Based on previously completed clinical studies in patients with IBS-C and CIC, the anticipated benefits of treatment with 6 mg/day of plecanatide for 53 weeks are expected to outweigh the potential risks. Plecanatide has demonstrated no detectable systemic absorption (with a 1 to 10 ng/ml limit of detection). Moreover, the safety profile for 9 mg plecanatide administered daily for 12 weeks was quite acceptable; a dose of 6 mg is expected to be at least as safe and well tolerated. Study patients will be carefully monitored for TEAEs at scheduled study visits.

2.4 Criteria for Evaluation of the Study

The safety, tolerability and exploratory endpoints are described below. For information concerning the analyses of these endpoints, see Section 8.

2.4.1 Safety and Tolerability Endpoints

Safety and tolerability will be measured by the number and nature of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), withdrawals due to adverse events (AEs), treatment interruptions due to diarrhea or other AEs, AE-free days, and the percentage of patients remaining in the study at each week. Other clinically significant changes in vital signs, clinical laboratory assessments, physical examinations and ECGs will be assessed.

2.4.2 Exploratory Endpoints

Patients' assessments of disease severity and adequacy of treatment will be collected by self-administered questionnaires completed by the patient at every study visit, ideally prior to any other study assessments (see Appendix 1 for details).

2.5 Study Design

An open-label, single-arm design with up to 53 weeks of treatment with plecanatide 6 mg QD (the highest dose being evaluated in the core studies) was chosen in accordance with the ICH E1 exposure guideline for drugs intended for chronic use. This study will provide additional data related to the chronic use of plecanatide at the dose intended for clinical use in patients with IBS-C. (See Figure 1)

2.6 Planned Sample Size and Number of Study Centers

It is planned to recruit approximately 1500 patients at approximately 250 clinical sites in the US for this study. See Section 8.2 for a discussion of sample size. Patients will be enrolled in this multi-center, outpatient study by gastroenterologists, family practitioners, internists and general medicine practitioners who have been qualified as Investigators. The study will end when its enrollment, regulatory and study drug exposure objectives have been met. Consequently, not all enrolled patients will receive 53 weeks of treatment.

3 STUDY POPULATION

The study population consists of male and female adult patients with Irritable Bowel Syndrome with Constipation (IBS-C). Patients must meet all of the study entry criteria listed below to be enrolled.

Every effort should be made to ensure that the patient's participation in this trial begins as soon as participation in the plecanatide ("core") study SP304203-04 or SP304203-05 has ended. Ideally, the first visit of this trial (SP304203-06) will occur on the same day as the core study's end-of-study visit (Visit 6) for patients completing the study. For qualifying screen-failure patients, the first visit of this trial will also ideally occur on the same day as the core study's Visit 2. For qualifying patients that withdrew early due to lack of efficacy, the first visit of this trial will also ideally occur on the same day as the core study's EW Visit. In addition, plecanatide study-naive patients and patients that participated in the Phase 2 study SP304-20212 will be considered for enrollment after completing screening to determine eligibility.

3.1 Inclusion Criteria

Patients with documented diagnosis of IBS-C must meet ONE of the following:

1. Completed plecanatide study SP304203-04 or SP304203-05, were compliant with the previous study's requirements, and did not experience any Serious Adverse Event (SAE) deemed related to study drug during the course of the previous study.
2. Failed screening in study SP304203-04 or SP304203-05 due to diary noncompliance (exclusion criterion 24 of the core study) or due to another reason, and in all cases, is allowed to enter this study by notification from Sponsor or delegate; confirmation of active IBS-C via ROME III modular questionnaire is required.
3. Withdrew early from SP304203-04 or SP304203-05 due to lack of efficacy and completed an early withdrawal visit (Visit EW) in the core study.
4. Completed plecanatide study SP304-20212
5. Completed an early withdrawal visit in SP304-20212 study and reason for withdrawal was not a drug related AE
6. Never participated in a plecanatide study (plecanatide study-naive patient) 18 to 85 years of age (inclusive) with IBS-C as defined by Rome III criteria (See ROME III modular questionnaire for IBS in Appendix 2).

Note: Details of how to use the Rome III questionnaire and the scoring system is provided in Appendix 2. At the clinical site patients will be given simple instructions on how to complete the form only; authorized personnel will review them for completeness only, to ensure that all questions have been answered. At no time will study staff correct or suggest changes of patient entries. The patient-reported responses to the questionnaire will be reviewed by the investigator or designee, who will use the scoring table provided in Appendix 2 for documentation of patients' eligibility. The questionnaire and the scoring chart will be kept as part of the patient's source documents.

3.2 Exclusion Criteria

For patients entering from one of the core studies presence of any of the following will exclude the patient from enrollment:

1. Patient is unwilling or unable to: participate in the study for the required duration, understand and sign the informed consent form (ICF) and undergo all protocol related tests and procedures throughout the study.
2. Female patient of childbearing potential with a positive urine pregnancy test on Day 1.

3. Male and female patients of childbearing potential who do not agree to continue to use the method of birth control used in the core double-blind plecanatide study or another acceptable form of birth control for the duration of this clinical trial.
4. Patient has experienced a significant negative change in health status during the course of participation in the core double-blind plecanatide study or after completion of the study.
   Note: Any question or concern with regard to a patient's general health status or a potentially significant change in the patient's general health status during their participation in study SP304203-04 or SP304203-05 should be referred to the Medical Monitor for a medical opinion as to the suitability of the patient for participation in this clinical trial.
5. In the opinion of the Investigator or Medical Monitor, it is not in the patient's best interest to participate in the study. The reason(s) for the patient's exclusion must be specified.
6. Use of Linzess® (linaclotide) or Amitiza® (lubiprostone) within 15 days of the Baseline Visit.
7. Patient has not met the colonoscopy requirements outlined by the AGA Institute for his or her particular risk group as they relate to colon cancer screening and/or surveillance. (See Appendix 3)

For plecanatide study-naive patients and patients that participated in SP304-20212 presence of any of the following will exclude the patient from enrollment:

1. Patient is unwilling or unable to: participate in the study for the required duration, understand and sign the informed consent form (ICF), and undergo all protocol related tests and procedures throughout the study.
2. Female patient is of childbearing potential with a positive urine pregnancy test on Day 1
3. Female patient is lactating.
4. Male and female patients of childbearing potential who do not agree to continue to use an acceptable method of birth control for the duration of this clinical trial.

   Acceptable methods of birth control include:

   a. Hormonal contraceptive (e.g., oral contraceptive, implanted or injected hormonal contraceptive) at least 2 months prior to enrollment.
   b. Use of double-barrier contraception (e.g., condom plus diaphragm, spermicide or intrauterine device).
   c. Surgical sterilization (men who have had a vasectomy or women with bilateral oophorectomy, hysterectomy or tubal ligation).
   d. Maintain a monogamous relationship with someone who is surgically sterile or is not of child-bearing potential (e.g., post-menopausal).
   e. Note: Abstinence is not considered an acceptable form of contraception for the purposes of this study.

   Post-menopausal is defined as without menses for at least 12 consecutive months before screening and have an elevated Follicle-Stimulating Hormone (FSH) consistent with menopause.
   Women who are still menstruating must be able to differentiate their abdominal symptoms associated with IBS-C from those associated with their menses.

5. In the opinion of the Investigator or Medical Monitor, it is not in the patient's best interest to participate in the study. The reason(s) for the patient's exclusion must be specified.
6. Use of Linzess® (linaclotide) or Amitiza® (lubiprostone) within 15 days of the Baseline Visit.
7. Patient reports participation in a clinical study or use of an investigational drug treatment within 30 days of Screening. Participation in an observational study (i.e., registry where no study drug is administered) will be allowed.

8. Patient has a BMI < 18 or > 40 kg/m2.
9. Patient has not met the colonoscopy requirements outlined by the AGA Institute for his or her particular risk group as they relate to colon cancer screening and/or surveillance (See Appendix 3).
10. Patient has unexplained and clinically significant "alarm symptoms" such as lower GI bleeding, iron-deficiency anemia, weight loss or systemic signs of infection.
11. Patient has any pre-existing medical condition (based on medical history or PE or laboratory evaluations) that is considered clinically significant enough to potentially interfere with study assessments or the patient's participation in and completion of the study. The Investigator must get approval from the Sponsor's Medical Monitor or designee before randomizing any patient who has what the Investigator considers clinically-significant medical history, signs, symptoms, or test results during the Screening Period of the study. These include but are not limited to:
    a. History of or current clinically significant cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine or gastrointestinal disease. Gastrointestinal diseases and conditions include inflammatory disorders (e.g., ulcerative colitis or Crohn's Diseases), familial adenomatous polyposis, structural abnormality of the GI tract that can affect GI motility or defecation, surgery to remove or bypass any portion of the GI tract
    b. History of or current cancer (other than basal cell or squamous cell carcinoma of the skin) unless the malignancy has been in a complete remission without maintenance chemotherapy for at least 5 years prior to Visit 1.
    c. Any concomitant medical illness that is predominantly characterized by chronic abdominal pain
    d. Major surgery, i.e., requiring general anesthesia within 6 months of the Screening Visit, or abdominal laparoscopic procedure within 60 days of the Screening Visit.
    e. Determined at screening visit, patient has any abnormal laboratory value that is considered clinically significant by the Investigator. Any laboratory value that is ≥ 3x the upper limit of normal (ULN) must be reviewed for potential clinical significance by the Sponsor's Medical Monitor or designee and cleared for randomization (if otherwise eligible).
12. Current clinically significant active viral hepatitis.
13. History of or infection with HIV.
14. Positive urine screen for opiates

3.3 Concomitant Medications

Any medication the patient takes other than the study drug, including herbal and other non-traditional remedies, is considered a concomitant medication. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage and indication. Any change in the dose or regimen of a concomitant medication must be recorded in the eCRF.

3.3.1 Prohibited Concomitant Medications

All prescription, non-prescription, or herbal therapies used to treat constipation or facilitate bowel movements are prohibited during the study, except the Sponsor-supplied rescue medication (see Section 3.3.2).

The following concomitant medications and supplements are prohibited during the study:

- Resolor® (prucalopride)
- Opioids intended for chronic use
- Amitiza® (lubiprostone)
- Linzess®/Constella® (linaclotide)

- Lactulose
- Laxatives, except the Sponsor-supplied rescue medication (RM)

Note: There is no indication of any specific safety risk when these generally prohibited agents are used concomitantly with plecanatide; however, appropriate medical caution should be exercised when agents that may aggravate underlying constipation are taken or when agents with similar physiological outcomes (i.e., increased BM frequency) are used together.

3.3.2 Permitted Concomitant Medications

Bisacodyl (Dulcolax®) 5 mg tablets will be supplied as rescue medication (RM) for the study. Patients must only use the Dulcolax® supplied by the Investigator during the study. See Sections 4.4.7 and 6.2 for more information on RM. Drugs given to treat AEs will be allowed.

4 VARIABLES AND METHODS OF ASSESSMENT

4.1 Demographics and Baseline Characteristics

Demographic data, medical history (including ongoing AEs) and previous/concomitant medications recorded in the eCRF of the previous plecanatide core study will be replicated in the eCRF for this open-label study when the patient signs the informed consent and is enrolled into this open-label study. New information or clinically-significant changes since the core trial will be solicited from all patients for appropriate updates to the eCRF for this open-label study.

4.1.1 Disease and Medical History

A complete medical history and GI disease history will be recorded for all plecanatide study-naive and SP304-20212 patients. Source documentation for previous treatment, diagnosis, and interventions, where available, should be included in the patient's medical record to facilitate source documentation verification. The outcome of the medical history assessment may be recorded as part of the worksheet for evaluation of eligibility and can be added to the patient's medical records.

4.2 Colonoscopy

A colonoscopy is not required to make a diagnosis of IBS or IBS-C. However, there are two clinical settings where a colonoscopy is required during the screening period:

1) If a patient has not completed a recommended colonoscopy based on the colon cancer screening and surveillance colonoscopy intervals outlined by the AGA, then a study-related eligibility colonoscopy can be authorized (see note) but *must be completed within first 21 days following screening (Visit 0)*. See **Appendix 3** for a brief summary of the AGA guidelines for colonoscopy screening and surveillance for prevention of colorectal cancer.

OR,

2) If the patient satisfies all other Inclusion/Exclusion criteria at Screening Visit and has an unexplained and clinically significant "alarm" sign(s) or symptom(s) at Visit 1 and the Investigator determines that a colonoscopy is required to adequately assess the "alarm" sign or symptom, then a study related eligibility colonoscopy can be requested (see note) but *must be completed within 21 days following screening (Visit 0)*.

Note: If a colonoscopy is to be conducted as part of this study under either of the clinical scenarios outlined above, it will require sponsor or Medical Monitor approval, via the colonoscopy approval form. Once sponsor/medical monitor approval has been received, the procedure must be completed within 21 days following screening (Visit 0) and results must be reviewed and all findings must be negative for the presence of cancer or any of the GI conditions detailed in the exclusion criteria before the patient can be enrolled into the study.

4.3 Patient Reported Outcomes

The following patient questionnaires will be administered at the scheduled study visits:

- Patient Rating of Relief of IBS Symptoms
- Treatment Satisfaction Assessment
- Treatment Continuation Assessment

The self-administered questionnaires will be conducted during the scheduled study visits (as specified in Section 5.2), preferably prior to any other study assessments. Completion of the questionnaires takes 1 to 5 minutes. The items of the questionnaires are depicted in Appendix 1.

4.4 Safety Variables

4.4.1 Collection of Adverse Events

Adverse event (AE) collection for the study will begin immediately after the ICF is signed. All AEs occurring prior to first dose of study drug are considered medical history (MH). It is the responsibility of the Investigator to ensure that all serious and non-serious AEs are collected. For details on the assessment, reporting, recording and follow-up of adverse events, see Section 7. IBS-C is characterized primarily by abdominal pain and constipation; however, several additional symptoms are often associated with IBS-C including abdominal discomfort, abdominal bloating, incomplete evacuation and straining with bowel movements. Because IBS-C is the condition under study in this clinical trial these IBS-C related symptoms are expected over the course of a patients participation in the trial; therefore, when reported as related to IBS-C, these symptoms should not be recorded as adverse events.

4.4.2 Clinical Laboratory Variables

Clinical laboratory assessments will be performed by a central laboratory, as identified in the List of Study Personnel and Vendors. The Laboratory Manual provided to investigative sites includes detailed instructions regarding the collection, processing, and handling of laboratory samples, including those for immunogenicity testing.

6 to 12-hour fasting is recommended before laboratory assessments are performed. The laboratory variables presented in **Table 2** will be assessed in accordance with the Schedule of Assessments (**Table 3 or Table 4,** as applicable).

Approximately 2.0 mL of blood will be drawn for each hematology sample, 5.0 mL for each serum chemistry sample, and 3.5 mL for each immunogenicity sample. The total blood volume collected from each patient for laboratory tests, not including possible repeat tests, over the course of 53 weeks will be approximately 60 mL.

Table **2**: Clinical Laboratory Assessments

Hematology	Erythrocytes, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin, and hematocrit
Serum chemistry	Alanine aminotransferase, aspartate aminotransferase, creatinine, alkaline phosphatase, total bilirubin, direct bilirubin, blood urea nitrogen, total protein, albumin, uric acid, glucose and cholesterol *Electrolytes*: Sodium, potassium, chloride, magnesium, phosphorus, calcium
Urinalysis	Specific gravity, pH, protein, glucose, ketones, blood, and microscopic examination of sediment
Urine Pregnancy test	Pregnancy test via dipstick (performed at study site for women of childbearing potential)
Urine Drug Screen	Urine tests for methadone, morphine and oxycodone (performed at study site)
Immunogenicity	Serum collection for anti-plecanatide antibodies testing (samples will be stored until an assay is developed)

4.4.3 Vital Signs

Vital sign measurements will be performed after the patient has been seated for at least 5 minutes. The following vital signs will be performed in accordance with the Schedule of Assessments (**Table 3 or Table 4**, as applicable):

- Blood pressure (systolic and diastolic; mmHg)
- Heart rate (beats per minute)
- Body temperature (°C)
- Respiration rate (breaths per minute)

4.4.4 Electrocardiograms

Standard 12-lead ECGs will be performed in accordance with the Schedule of Assessments (**Table 3 or Table 4,** as applicable).

All ECGs will be performed in either the supine or semi-recumbent position.

4.4.5 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Assessments (**Table 3 or Table 4**, as applicable). The PE will be based on the following body systems: general appearance, head (ear, eyes, nose, and throat), cardiovascular, respiratory, abdomen, musculoskeletal, neurological, lymph nodes, and skin.

4.4.6 Concomitant Medications and Diet

Any new or changes to concomitant medications and dietary supplements will be documented at each study visit. Any clinically significant change in medications or dietary intake/supplements that could adversely affect the patient or study should be documented by the site and discussed with the Medical Monitor to determine whether the patient should continue in the study.

4.4.7 Rescue Medication

Bisacodyl (Dulcolax®) 5 mg tablets will be supplied as rescue medication (RM) for the study. Patients will be instructed to take the study-provided rescue medication ONLY if 72 hours have elapsed since their last bowel movement. Therefore, patients should not take RM on more than two days per week. See Sections 3.3.2 and 6.2 for instructions on RM use.

5 STUDY CONDUCT

5.1 Schedule of Assessments

Ideally, the roll-over patient's participation in this trial begins as soon as participation in the core study SP304203-04 or SP304203-05 has ended.

For Core Study Completers, Day 1 / Baseline Visit of this study will commence after completion of the core study (End-of-Study visit - Visit 6).

For Eligible Screen Failure patients, the first visit of this trial will also ideally occur on the same day as the core study's Visit 2.

For patients that withdrew early from the core study due to lack of efficacy, the first visit of this trial will ideally occur on the same day as the core study's EW Visit.

The Schedule of Assessments for Core Study Completers or Eligible Screen Failure patients or patients that withdrew early who are enrolling on the same day or within 4 weeks of the last study drug dose or within 4 weeks of core study participation (Short Interval Patients) is presented in **Table 3**.

For (a) plecanatide study-naive patients, (b) SP304-20212 patients, and (c) Core Study Completers or Eligible Screen Failure patients when (i) more than 4 weeks elapsed since the patient's participation in the study or (ii) more than 4 weeks since the last study drug dose (Long Interval Patients), the patient will have to undergo additional assessments, specifically study participation begins with the Screening Visit (presented in **Table 4**).

Table 3: Schedule of Assessments for Short Interval Patients

Study Visit	**Baseline Visit 1**	**Week 4 Visit 2**	**Week 12 Visit 3**	**Week 24 Visit 4**	**Week 36 Visit 5**	**Week 53 (EOT)* Visit 6**	**Early Withdrawal (EW)**
Visit Day ± Visit Window	**Day 1** [(a)]	**Day 28** ± 4 days	**Day 84** ± 7 days	**Day 168** ± 7 days	**Day 252** ± 7 days	**Day 371** + 7 days	Within 5 days of last study drug treatment
Informed Consent	X						
Rome IBS Modular Questionnaire [b] (Appendix 2)	X						
Inclusion/Exclusion Criteria	X						
Medical History (additional new information not recorded in the core study)	X						
Patient Questionnaires [c]		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Physical Examination [d]		X	X	X	X	X	X
Vital Signs [e]		X	X	X	X	X	X
Pregnancy Test (urine) [f]	X	X	X	X	X	X	X
Urine Drug Screen	X						
Hematology, Serum Chemistry, Urinalysis [g]		X	X	X	X	X	X
Immunogenicity Testing [h]			X	X	X	X	X
12-lead ECG [i]			X			X	X
Study Drug Dispensation [j]	X	X	X	X	X		
Study Drug Collection [k]		X	X	X	X	X	X
Rescue Medication (RM) Dispensation [l]	X	X	X	X	X		

* EOT visit is for patients that either complete week 53 or complete due to sponsor termination of the study

a. Ideally, Day 1 Visit will overlap with the end-of-study visit (Visit 6) of the core trial. The following most recent data collected at the core study: physical exam, vital signs, pregnancy test, ECG, labs (hematology, serum chemistry, urinalysis), immunogenicity testing, concomitant medications and adverse events will be used as baseline assessments in this study.
b. Required for Screen-Failures, who do not have confirmation of active IBS-C done by diary in the core study.
c. Selected questionnaires self-administered by patient, preferably prior to any other study assessments.
d. PE will be based on the following body systems: general appearance, head (ear, eyes, nose, and throat), cardiovascular, respiratory, abdomen, musculoskeletal, neurological, lymph nodes, and skin.
e. Seated blood pressure, heart rate, respiration, and temperature using the same calibrated instrument for each measurement.
f. Urine pregnancy test performed on-site for women of childbearing potential (site must confirm negative result prior to proceeding).
g. 6 to12 -hour fast is recommended before clinical laboratory assessments.
h. Serum samples for immunogenicity testing for antibodies to plecanatide will be collected and stored until analysis. See Laboratory Manual for processing and shipping instructions.
i. ECG is to be performed on the same calibrated machine during the study.
j. The study drug will be dispensed at each visit as follows: one study drug kit on Day 1, two study drug kits at Week 4, three study drug kits at Week 12 and Week 24, four study drug kits at Week 36. Patient will take the Day 1 medication at the clinical site on Day 1; it is recommended that for dosing at home, patient will take study drug once daily at approximately the same time in the morning of each day.
k. Patients will be instructed to return all unused study drug at the subsequent study visit. Site will perform study drug accountability at every visit.
l. Rescue medication - Dulcolax tablets will be supplied (in commercial packaging) at the first study visit and re-supplied as needed throughout the study

Table 4: Schedule of Assessments for Long Interval Patients

Study Visit	**Screening Visit 0**	**Baseline Visit 1**	**Week 4 Visit 2**	**Week 12 Visit 3**	**Week 24 Visit 4**	**Week 36 Visit 5**	**Week 53 (EOT)* Visit 6**	**Early Withdrawal (EW)**
Visit Day ± Visit Window	**Day -21 to -7****	**Day 1**	**Day 28** ± 4 days	**Day 84** ± 7 days	**Day 168** ± 7 days	**Day 252** ± 7 days	**Day 371** + 7 days	Within 5 days of last study drug treatment
Informed Consent	X							
Rome IBS Modular Questionnaire (Appendix2) [a]	X							
Inclusion/Exclusion Criteria	X	X						
Medical History (additional new information not recorded in the core study)	X							
Patient Questionnaires [b]			X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Physical Examination [c]	X		X	X	X	X	X	X
Vital Signs [d]	X		X	X	X	X	X	X
Pregnancy Test (urine) [e]	X	X	X	X	X	X	X	X
Urine Drug Screen	X	X						
Hematology, Serum Chemistry, Urinalysis [f]	X		X	X	X	X	X	X
Immunogenicity Testing [g]		X	X	X	X	X	X	
12-lead ECG [h]	X			X			X	X
Study Drug Dispensation[i]		X	X	X	X	X		
Study Drug Collection [j]			X	X	X	X	X	X
Rescue Medication (RM) Dispensation [k]	X	X	X	X	X	X		

* EOT visit is for patients that either complete week 53 or complete due to sponsor termination of the study
** Minimum of 7 days should be allowed for plecanatide study-naive and SP304-20212 patients between screening and baseline visits

a. Rome IBS Questionnaire is required for Screen-Failure Patients who do not have confirmation of active IBS-C done by diary in study SP304203-04 or SP304203-05.
b. Selected questionnaires self-administered by patient, preferably prior to any other study assessments.
c. PE will be based on the following body systems: general appearance, head (ear, eyes, nose and throat), cardiovascular, respiratory, abdomen, musculoskeletal, neurological, lymph nodes, and skin.
d. Seated blood pressure, heart rate, respiration, and temperature using the same calibrated instrument for each measurement.
e. Urine pregnancy test performed on-site for women of childbearing potential (site must confirm negative result prior to proceeding).
f. 6 to12 hours fast is recommended before clinical laboratory assessments.
g. Serum samples for immunogenicity testing for antibodies to plecanatide will be collected and stored until analysis. See Laboratory Manual for processing and shipping instructions.
h. ECG is to be performed on the same calibrated machine during the study.
i. The study drug will be dispensed at each visit as follows: one study drug kit on Day 1, two study drug kits at Week 4, three study drug kits at Week 12 and Week 24, four study drug kits at Week 36. . Patient will take the Day 1 medication at the clinical site on Day 1; it is recommended that for dosing at home, patient will take study drug once daily at approximately the same time in the morning of each day.
j. Patients will be instructed to return all unused study drug at the subsequent study visit. Site will perform study drug accountability at every visit.
k. Rescue medication - Dulcolax tablets will be supplied (in commercial packaging) at the first study visit and re-supplied as needed throughout the study.

5.2 Procedures by Visit

Prior to initiating any study-related procedures, written informed consent must be completed and documented. When a patient is found to be eligible to enter the study, the investigator or designee will document enrollment of the patient in the site enrollment log. The Patient ID number will be the same as the 6-digit Patient ID used in the previous plecanatide study, except in rare circumstances when an administrative change to the Patient ID, pre-approved by the Sponsor, is required. The Patient ID number is also reflected as same in the eCRF.

Plecanatide study-naive and SP304-20212 patient numbering: A unique 6-digit patient number will be assigned consecutively for each patient using the site enrollment log selection after he or she signs the ICF. Unique patient numbers will begin with the clinical site number, e.g., 001 followed by a 3-digit number such as 601. The unique patient numbers will be assigned sequentially by clinical site personnel. For example, for clinical site number 002, the unique patient numbers might be as follows: 002-601, 002-602, 002-603, etc. The patient will keep this unique patient number for the duration of the study.

Depending on the length of time elapsed since participation in the core study (SP304203-04 or SP304203-05) and whether patient is plecanatide study-naive or from SP304-20212 patients are divided into two subgroups which will follow distinct initial enrollment requirements:

1) Patients who either completed the core study, withdrew early, or screen failed ≤4 weeks earlier (Study Completers, Early Withdrawals, and Eligible Screen Failures), will be enrolled into this study at the Baseline Visit, with study procedures described in section 5.2.2.1 (Short Interval Patients)
2) Patients, for whom more than 4 weeks elapsed since the core study participation (Study Completers, Early Withdrawals, and Eligible Screen Failures and plecanatide study-naive patients and SP304-20212 patients), will be enrolled into this study at the Screening Visit, with study procedures described in section 5.2.1 (Long Interval Patients)

Procedures at Weeks 4, 12, 24, 36, 53 and Early Withdrawal will be the same for all patients.

5.2.1 Screening Visit for plecanatide study-naive patients, SP304-20212 patients, and core study patients with enrollment delay of more than 4 weeks

This visit is required for plecanatide study-naive Patients, SP304-20212 patients and core study completers, eligible early withdrawals and eligible screen failures whose participation in the core study ended more than 4 weeks prior to enrollment into this study and for any patient needing a colonoscopy as per the guidelines in Appendix 3. For plecanatide study-naive and SP304-20212 patients only – the interval between screening and baseline visit must be at least 7 days.

The following procedures will be performed at this visit:

- Informed consent
- Rome IBS Modular Questionnaire (confirmation of IBS-C diagnosis via ROME III modular questionnaire (see Appendix 2) is required for patients not randomized in study SP304203-04 or SP304203-05.
- Review of inclusion/exclusion criteria
- Review of recent medical history (for information not already recorded in the core study)
- Review and recording of concomitant medications
- Physical examination

- Vital signs measurement
- 12-lead ECG
- Clinical laboratory assessments: hematology, serum chemistry, immunogenicity, urinalysis (see section 4.4.2 for details)
- Urine pregnancy test, if applicable
- Urine drug screen for selected opioids (see section 4.4.2 for details)
- Dispensation of study-provided rescue medication (Dulcolax®)

Patients who fail to qualify for enrollment into this study will be considered Screen Failures and the reason for failure will be documented. Once a patient screen fails in this study, they cannot be re-screened.

5.2.2 Baseline / Day 1 Visit

Patients who are Study Completers, Eligible Early Withdrawals, or Eligible Screen Failures and enrolling into this study within 4 weeks of the core study completion or within 4 weeks of the last study drug dose will begin with the Baseline / Day 1 Visit. The Baseline Visit assessments are described in section 5.2.2.1. Any adverse event that commenced during the core studies and are still ongoing/stable will be recorded on the Medical History CRF in SP304203-06, with the medical term and start date identical to those in the core study.

Adverse events that occurred during the core studies and resolved or ongoing prior to enrollment in SP304203-06 will be reported in SP304203-06 in the patient's medical history, according to their medical relevance.

Results of laboratory tests performed in the core study and used as baseline at Visit 1 of this trial must be evaluated within 72 hours of the visit to confirm the patient's continual eligibility for this open-label study.

5.2.2.1 Baseline Visit for patients enrolling on the same day or within 4 weeks of core study completion or screen-failure

Ideally, Day 1 / Baseline Visit of this study will commence immediately after completion of core study's end-of-study visit (Visit 6) for patients completing the study. For eligible SP304203-04 or SP304203-05 screen-failure patients, the first visit of this trial will also ideally occur on the same day as the core study's Visit 2. For eligible SP304203-04 or SP304203-05 early withdrawal patients, the first visit of this trial will also ideally occur on the same day as the core study's EW visit.

The following procedures will be performed on Day 1:

- Informed consent
- Rome IBS Modular Questionnaire (confirmation of IBS-C diagnosis via ROME III modular questionnaire (see Appendix 2) is required for patients not randomized in study SP304203-04 or SP304203-05.
- Review inclusion/exclusion criteria
- Pregnancy Test (urine)
- Urine Drug Screen
- Review and recording of concomitant medications and procedures (only for new information that is not recorded in the core study)
- Medical History (new information that is not recorded in the core study must be captured in the source documents and eCRF)
- Dispensation of study drug

- Dispensation of study-provided rescue medication (RM)

If the SP304203-06 baseline visit is within 4 weeks of the end-of-study visit (Visit 6) of the core study, certain data collected at Visit 6 or Visit 5 or Visit 2 of the core study will also be used as the data for the SP304203-06 baseline visit, i.e., these assessments do not have to be performed again for entry into SP304203-06, for practical reasons. This is indicated in the Schedule of Assessments in **Table 3**.

The following last set of results collected at the core study (at Visit 5) will be used as baseline assessments in this study:

- Physical exam
- Vital signs
- Laboratory tests (hematology, serum chemistry, urinalysis)
- ECG
- Immunogenicity testing
- Medical History (new information that is not recorded in the core study must be captured in the source documents and eCRF)
- Review and recording of concomitant medications and procedures (new information that is not recorded in the core study must be captured in the source documents and eCRF)
- Review and recording of adverse events (new information that is not recorded in the core study must be captured in the source documents and eCRF)

5.2.2.2 Baseline Visit for plecanatide study-naive patients, SP304-20212 patients, and patients enrolling after more than 4 weeks of core study participation

For patients enrolling more than 4 weeks after the core study participation, plecanatide study-naive patients, and SP304-20212 patients and who completed the Screening Visit of this study, the following assessments will be performed at the Baseline Visit:

- Review inclusion/exclusion criteria
- Review and recording of concomitant medications
- Review of adverse events
- Pregnancy Test (urine)
- Urine Drug Screen
- Immunogenicity sample collection
- Dispensation of study drug
- Dispensation of study-provided rescue medication (RM)

5.2.3 Week 4, 12, 24 and 36 Visits (for all patients)

The following procedures will be performed:

- Patient self-administered questionnaires: Relief of Abdominal Symptoms and Treatment Satisfaction
- Documentation of concomitant medications
- Review of adverse events
- Physical examination

- Vital signs measurement
- Urine pregnancy test for women of childbearing potential
- Clinical laboratory assessments
- Immunogenicity sample collection
- 12-lead ECG (at Week 12 only)
- Unused study drug collection and accountability
- Dispensation of study drug as described in Section 6.4, and review dosing instructions with the patient
- Re-supply RM as needed
- Confirm the next visit and explain the importance of completing study visits within the allowable visit window. Remind the patient to return all study drug kits/folders at the next visit.

5.2.4 Week 53 Visit - End of Treatment

For patients that complete week 53 or complete due to sponsor termination of the study, the following procedures will be performed:

- Patient self-administered questionnaires: Relief of Abdominal Symptoms, Treatment Satisfaction, Treatment Continuation
- Documentation of concomitant medications
- Review of adverse events
- Physical examination
- Vital signs measurement
- Urine pregnancy test for women of childbearing potential
- Clinical laboratory assessments
- Immunogenicity sample collection
- 12-lead ECG
- Study drug collection and accountability

5.2.5 Early Withdrawal (EW) – visit performed ideally within 5 days of the last study drug intake

Patients are free to withdraw from participation in the study at any time. Investigators may choose to discontinue a patient's participation in the study if they believe it is in the patient's best interest clinically. Patients unwilling or unable to maintain compliance with study drug administration or protocol procedures may be discontinued from the study at the discretion of the Investigator.

The following qualify as adverse events (AEs) due to which study participation may be terminated:

- Changes in laboratory values, PE findings or other assessments considered by the Investigator to be clinically significant
- Clinically significant TEAEs including clinically significant laboratory test abnormalities or SAEs regardless of relatedness to study treatment that cause the patient, Investigator or Sponsor to feel it is not in the patient's best interest to continue.

A patient may also be withdrawn from study drug/study by the Sponsor, Regulatory Authorities, or the IRB/IEC. Since the study will end when its enrollment, regulatory and study drug exposure objectives have been met, patients may complete at the time of study termination even if they have not received 53 weeks of therapy. Patients will also be withdrawn if the entire study is terminated prematurely as described in Section 9.10.

For patients who discontinue early from the study, the following assessments for the Early Withdrawal (EW) visit should be performed, if possible, within 5 days of the last study drug dose:

- Patient self-administered questionnaires: Relief of Abdominal Symptoms, Treatment Satisfaction and Treatment Continuation
- Documentation of concomitant medications
- Review of adverse events
- Physical examination
- Vital signs measurement
- Urine pregnancy test for women of childbearing potential
- Clinical laboratory assessments
- Immunogenicity sample collection
- 12-lead ECG
- Study drug collection and accountability

In all cases, the reason(s) for withdrawal, and the primary reason, must be recorded on the eCRF and source records. If the primary reason for withdrawal is an adverse event, a single adverse event must be recorded as the primary reason. Patients who prematurely withdraw from study treatment will not be eligible to participate in this or any other plecanatide study in the future. Patients withdrawn after enrollment into the study will not be replaced.

For patients lost to follow-up, every attempt of contact (i.e. phone calls and registered letters) must be documented in the patient's source records.

6 STUDY DRUG

6.1 Identity

6.1.1 Plecanatide

The chemical name, molecular formula, molecular weight and amino acid sequence of plecanatide can be found in the Investigator Brochure. Plecanatide is a synthetic hexadecapeptide that is an analog of uroguanylin, a natural peptide that occurs in the GI tract.
The drug product is a tablet comprised of plecanatide, microcrystalline cellulose, and magnesium stearate. Plecanatide tablets are manufactured by UPM Pharmaceuticals (Bristol, TN) and packaged and supplied to the clinical study centers by Sharp Packaging Solutions (Allentown, PA) for Synergy.

6.2 Rescue Medication

The only RM allowed for use in this study is Dulcolax® 5 mg tablets supplied by the sponsor. Patients are instructed to take one to three 5 mg tablets in a single dose, when they have not had a bowel movement for 72 hours or more.

Rescue medication will be distributed to sites by Sharp Packaging Solutions (Allentown, PA). Sites may order additional bulk supplies of RM by submitting a Manual Shipment Request Form. RM will be dispensed to patients at Day 1 and re-supplied at study visits as needed. Supplies of Dulcolax® will not be reconciled at the completion of the study. Sites must track inventory of RM supplies for the purpose of ensuring adequate quantities for re-supplying patients as needed. The site's supply of RM will not be managed nor automatically re-supplied by IWRS.

6.3 Administration

If the patient is eligible and agrees to participate in this study, after signing the informed consent, the patient will be assigned to 6 mg plecanatide open-label treatment for the duration of their participation in the trial.

Study drug will be administered for up to 53 consecutive weeks. Except on Day 1, when patients will take the study drug at the clinical site, patients will be instructed to take the study drug once daily at home - one (1) tablet every morning (preferably at the same time each day) with approximately 240 mL (8 ounces) of liquid, with or without meals.

6.3.1 Dose Adjustments

Dose adjustments of study drug are not permitted in this study. Patients who interrupt study treatment for adverse events, intercurrent illness or study drug supply issues may continue in the study with the approval of the Principal Investigator and the Medical Monitor when the reason for interruption has been adequately reviewed.

6.3.2 Overdose

Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. Careful attention to fluid balance should be made. Standard treatment measures for the symptomatology being exhibited should be provided.

Single doses up to 48.6 mg have been administered without medically important consequence.

6.4 Packaging, Labeling and Storage

6.4.1 Packaging

The investigational drug kits will be supplied to the clinical sites by Sharp Packaging Solutions (Allentown, PA) for Synergy. Sites will manually order additional kits with the Manual Shipment Request form

The Investigator or qualified designee will dispense/administer the study drug only to patients eligible for participation and enrolled in this study, following the procedures described in this protocol.

Each investigational drug kit will contain a 4-week supply (28 tablets) in blister packaging with four extra tablets (total of 32 tablets) to allow for window extension for a study visit. Individually blister packaged tablets will be provided in four connected 1-week strips as a 4-panel key-pack that folds into a carton. The two bottom panels fold up into the two top panels, nesting blister cavities. Instructions for releasing a tablet from the blister dome are printed on the outside of the carton. At each dispensing visit, each patient will be given a numbered drug kit(s). The patient's unique number will be written in the designated area of the kit label; the tear-off portion of the label will be kept in the clinical site's source records.

Study drug will be dispensed to the patient as follows:

- Visit 1 (Day 1, Week 1): one (1) study drug kit for dosing from Day 1 to end of Week 4, inclusive.
- Visit 2 (End of Week 4): two (2) study drug kits for daily dosing from Week 5 to end of Week 12, inclusive.
- Visit 3 (End of Week 12): (3) study drug kits for daily dosing from Week 13 to end of Week 24, inclusive.

- Visit 4 (End of Week 24): (3) study drug kits for daily dosing from Week 25 to end of Week 36, inclusive.
- Visit 5 (End of Week 36): (4) study drug kits for daily dosing from Week 37 to end of Week 53, inclusive.

Four (4) drug kits will be dispensed at Visit 5 (End of Week 36). This supply will include 128 tablets (28 days plus 4 extra tablets per carton).

At Visit 6 (End of Week 53) or Early Withdrawal, document the patient's End of Treatment or Early Withdrawal visit date. The patient's reported last dose of study drug will be recorded in the eCRF.

6.4.2 Label

Each of the investigational drug kits will have a unique **yellow label** containing the following information: protocol number, drug kit number, contents, directions for use, storage conditions, identification of Synergy Pharmaceuticals Inc. as the Sponsor and the statements: "Caution: New Drug - Limited by Federal Law to Investigational use. Investigational Drug – To be used by Qualified Investigator Only. For Clinical Trial Use Only. Keep Out of Reach of Children."

The label will include the following fields to be completed by site personnel: Investigator name and phone number, subject identification number and treatment weeks. There will be a smaller label on the carton spine that identifies the study number and kit number. When dispensing a kit to a patient, complete the required information and retain the tear-off portion of the label in the source documents. At each monitoring visit, the source document records will be verified against the drug accountability logs.

6.4.3 Storage

The Investigator, or qualified designee, is responsible for the proper storage of the study medications according to the Sponsor's recommendations and all applicable Federal/State regulatory guidelines. At the clinical site, plecanatide must be stored at controlled room temperature 20 to 25°C (68 to 77°F) in a secure area with restricted access and with Min-Max temperature monitoring. Deviations from Sponsor's recommendations/guidelines should be reported, as directed in the Temperature Excursion Reporting Form.

Patients will be instructed to store their blister-packs at room temperature defined for this study as 20 to 25°C (68 to 77°F).

The Investigator must agree not to dispense or store investigational drug at any location other than that listed on the Form FDA 1572.

6.5 Drug Accountability

Distribution of all investigational drug kits and acknowledgement of receipt of drug shipments will be recorded in an IP shipment distribution tracker maintained by Sharp.

In addition, accurate records of study drug dispensed to patients will be kept by the Investigator, or qualified designee, specifying the kit number on the drug kit, the patient number assigned, the amount dispensed to each patient and the date dispensed, using the appropriate eCRF page for the patient.
At each visit after Baseline (Day 1), the patient is asked to return their previously dispensed drug kit and the number of remaining tablets is entered into the eCRF for drug accountability.
A drug accountability log must be available for inspection at each monitoring visit and at the completion of the study. At the completion of the study, the Investigator will provide copies of this accountability log to the Sponsor.

The Investigator is responsible for assuring the retrieval of all study supplies from patients. At the completion of the study, all unused investigational drug kits will be returned to a third party in accordance with the Sponsor's (or designee's) written instructions. The Investigator must verify that all unused or partially used study drug supplies have been returned by the patient and that no remaining supplies are in the Investigator's possession.

6.6 Compliance

Patients will be advised as to how to take their daily medication and will return all unused study drug to the clinical site at each visit during the Treatment Period. The number of remaining tablets will be counted and entered into the appropriate eCRF page for that patient. Patients unwilling or unable to maintain compliance with study drug administration or procedures may be discontinued from the study at the discretion of the investigator in conjunction with the medical monitor.

7 ASSESSMENT, REPORTING, RECORDING AND FOLLOW UP ADVERSE EVENTS

7.1 Definitions

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product or study procedure whether or not considered related to the product or procedure. All AEs, including intercurrent illnesses and regardless of the source of identification (e.g., PE, laboratory assessment, ECG, reported by patient), occurring during the study will be documented in the eCRF. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen (increase in intensity or frequency) during the treatment period.

Adverse events occurring from the time of ICF signing up to the intake of the first dose of study drug will be classified as pre-existing conditions for this study. Serious AEs (as defined below) occurring from the time of ICF signing up to the intake of the first dose of study medication will be collected and reported as such. A TEAE is defined as an AE that begins or that worsens in frequency and/or severity after at least one dose of study drug has been administered.

Minor fluctuations in laboratory values for standard monitoring (abnormal values) that the Investigator does not consider clinically significant or related to study drug will not be recorded as AEs. However, if the laboratory abnormality is associated with a diagnosis, then the AE term for that diagnosis will be reported (see Section 7.4 for recording of AEs).

7.2 Events of Special Interest - Diarrhea

An increase in the frequency of BMs and loosening of the stool consistency from baseline are expected pharmacodynamic effects of plecanatide. These same attributes (increased stool frequency and looser stool consistency) are often used to define "diarrhea'; however, in light of significant inter-patient variability in bowel habit "phenotype" and wide differences in the perception of a "normal" bowel habit there is no standard definition of "diarrhea" for this patient population. An increase in frequency or consistency for one person is a welcome event, while for another patient it might be bothersome "diarrhea".

One mechanism to introduce a level of consistency across patients, sites and the trial is to code an event as diarrhea only if it is characterized by a specific patient-reported and clinically relevant attribute such as "bothersomeness". Therefore, for this trial, for any event associated with a significant increase from baseline in BM frequency and/or loosening of BM consistency - that would otherwise be coded as

diarrhea - the site is instructed to record it as an AE only if the patient reports that it was bothersome (as defined by each patient).

7.3 Assessment of Adverse Events

The Investigator will assess each AE with regard to seriousness, intensity, and causality as described below.

7.3.1 Seriousness

An SAE is defined as any untoward medical occurrence that, at any dose, is one of the following:

- Results in death;
- Is life-threatening; (an adverse event or suspected adverse reaction is considered "life threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly or birth defect;
- Is a medically important event (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse)

The FDA has defined additional **"Medically Important Events"** that should also be reported as SAEs [13]. These include cases where:

- Aminotransferases (ALT or AST) are ≥ 3 times the upper limit of normal (ULN) with an associated elevation of Total Bilirubin ≥ 2 times ULN without evidence of hemolysis or with alkaline phosphatase < 2 times ULN or not available OR
- ALT or AST activity that is greater than 5 times the upper limit of normal.

All patients with the above abnormalities should return as soon as possible or within 48 hours to the study center for further evaluation of the abnormalities including repeat ALT and AST, total and direct bilirubin, alkaline phosphatase, and related laboratory assessments of albumin, PT and PTT, creatinine kinase, and GGTP or 5'nucleotidase. Hepatitis A, B, and C, hemolysis, and biliary obstruction should be ruled out. A detailed medical and drug use history should be taken to exclude all potential causes.

The Medical Monitor should be consulted prior to withdrawing a patient early due to elevated ALT or AST.

7.3.2 Intensity (Severity)

The Investigator will assess the intensity/severity of AEs according to the following general categorical descriptors:

Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Severe: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is a regulatory definition as per Section 7.3.1. An AE of severe intensity may not necessarily be considered serious (by definition) or a mild AE (e.g., mild stroke) may be considered as an SAE.

7.3.3 Causality

The Investigator will assess the causality/relationship between the study drug, or study procedure, and the AE and record that assessment in the eCRF.

The causal relationship of the AE to study drug will be described in terms of:

Reasonable Possibility: There is evidence to suggest a causal relationship between the drug and the AE (e.g., AE is uncommon and known to be strongly associated with drug exposure or is uncommon in the study population, but not commonly associated with drug exposure)

No Reasonable Possibility: There is no evidence to suggest a causal relationship between the drug and the AE.

The study conduct relatedness for AEs and SAEs will also be assessed and documented. The most likely cause of an AE or SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be recorded in the eCRF with details of the concomitant disease or medication or other cause.

7.4 Recording Adverse Events

Adverse event reporting will extend from signing of ICF up to 30 days after the administration of the last dose of the study medication. Adverse events occurring after the end of the study should be reported to the Sponsor by the Investigator only if the Investigator considers there to be a causal relationship to the study drug.

All AE reports should contain a brief description of the event, date of onset, date of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome of the adverse event, and whether the event is classified as serious.

All AEs experienced by patients who are assigned to treatment, regardless of the relationship to study drug, will be recorded in the eCRF.

7.5 Reporting Serious Adverse Events

All SAEs that occur during the study, as defined by the protocol, must be reported by the Investigator to the designated Safety Contact by faxing the SAE Form **within 24 hours** from the point in time when the Investigator becomes aware of the SAE. In addition, all SAEs including any deaths, which occur up to and

including 30 days after the administration of the last dose of the study medication, must be reported to the designated Safety Contact **within 24 hours.**

All SAEs and deaths (as SAE or as outcome of SAE) must be reported whether or not considered causally related to the study medication. Any SAE that occurs at any time after completion of the study (i.e., beyond 30 days after last study drug dose), which the Investigator considers to be related to study medication, must be reported to the designated safety contact. SAE forms will be provided to each clinical site. The information collected will include a minimum of the following: protocol number, Investigator information, patient number, event term, a narrative description of the event including its start date, and an assessment by the Investigator as to the intensity and possible relatedness to study medication. A sample of the SAE form can be found in the study manual. The Medical Monitor or Synergy may request follow up information regarding the SAE.

The Investigator will prepare or directly oversee preparation of each SAE report and the Medical Monitor will evaluate and confirm the seriousness and the causal relationship of the event to study treatment. In addition, the Investigator and Medical Monitor will evaluate the expectedness according to the reference document (Investigator Brochure). Based on the Medical Monitor's and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

All SAEs will be collected and reported from signing of ICF until the end of the study. Serious AEs occurring after the end of the study and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally related to the study drug.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS
ICON Clinical Research
Medical and Safety Services

SAE Hotline: [redacted]
SAE Fax Number: [redacted]
SAE e-mail: [redacted]

1. Telephone the Safety Center to inform them that you are faxing a SAE form. If you are calling after business hours (8:30 am to 5:00 pm Eastern time, Monday to Friday), leave a message in the voice mailbox.

2. Provide the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.

3. Fax the SAE form and any supporting documentation to the Safety Center within 24 hours of becoming aware of the event.

The CRO Safety Center telephone and fax numbers are available 24-hours a day. In case the CRO Safety Center cannot be contacted (e.g., out of normal working hours or on weekends), an automated reporting service is available. The required information should be faxed and a message should be left on the voicemail service. If you leave a message, provide the protocol number (**SP304203-06**), the study drug name (**plecanatide**), and Synergy Pharmaceuticals as the sponsoring company.

The minimum information required for an initial report is:

- Name of person sending the report (i.e., name and address of Investigator)
- Patient identification (randomization number, initials, NOT patient name)
- Protocol number
- Description of SAE
- Causality assessment, if possible

However, as far as possible all points on the SAE form should be covered in the initial report, or the completed SAE form itself must be faxed to the designated Safety Contact. In addition, the event must be documented in the eCRF.

After receipt of the initial report, the Safety Contact and safety center will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event.

All SAEs must be reported by the Investigator to their IRB/IEC in writing, as well as appropriate regulatory authorities as required by law. The CRO Safety Center will be responsible for all information processing and reporting according to local legal requirements.

7.6 Follow-up of Adverse Events

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until:

- the AE (including abnormal laboratory values) has resolved or have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor,
- there is a satisfactory explanation for the changes observed,
- the patient is lost to follow-up, or
- the patient has died.

7.7 Pregnancy

Every effort should be made to avoid pregnancy in this study. Female patients should be reminded at every visit to use appropriate birth control methods. However, if a female patient should become pregnant during the study (i.e., from the date the ICF was signed until the patient's last visit), the Investigator (or authorized delegate) should notify the designated Safety Contact on the initial Pregnancy Report Form **within 24 hours** of the Investigator (or authorized delegate) first becoming aware of the pregnancy.

The notification of pregnancy should be submitted using the initial Pregnancy Report Form. The initial Pregnancy Report Form should be completed with study patient's details (e.g., patient number, initials, date of birth, investigational product information, etc.). Whenever possible, the initial notification of pregnancy should include detailed information on the pregnancy, including last menstrual period and/or expected date of delivery. If pregnancy is to be terminated, the anticipated date of termination should be provided. If a maternal AE is reported during the initial notification of pregnancy, the details of the AE should also be described in the narrative field of the initial Pregnancy Report Form.

The Sponsor, Medical Monitor, or designated Safety Representative will request permission to follow the patient's progress with the doctor medically responsible for the pregnancy. If additional information on the progress of the pregnancy and/or any maternal AE is received by the clinical site, the Investigator (or designee) should also submit a pregnancy outcome report form to the designated Safety Contact within 24 hours of becoming aware of the information. If the outcome of the pregnancy is reported as premature birth, or as elective termination due to a medical reason or as spontaneous or accidental miscarriage, the details of the outcome should be described in the narrative section of the pregnancy outcome report form.

The pregnancy outcome will generally be reported as a follow-up report. Details of birth/delivery, including date of birth, weight and sex of the fetus/new born should also be described in the narrative field of the Pregnancy Report Form.

Pregnancy itself is not an AE, unless there is suspicion by the site that the investigational product may have interfered with the effectiveness of a contraceptive medication. Pregnancy reports, however, are tracked and reported in the safety (SAE) database. Pregnancy occurring in the patient between start of study drug until 30 days after last dose will fall under the expedited reporting procedure for serious adverse events. The pregnant patient will be immediately discontinued from the study but will be followed for the duration of the pregnancy. Details of the outcome of the pregnancy (e.g., full-term normal delivery, stillbirth, congenital anomalies, and miscarriage) will be collected and reported by the site.

All reports of congenital abnormalities/birth defects are SAEs. Complete a new SAE Report Form if the delivery outcome meets the criteria for a SAE (e.g., congenital anomaly/birth defect, still birth, some other sickness, etc.). The SAE Report Form should be completed with study patient's details (e.g., patient number, initials, date of birth, investigational product information, etc.) and the details of the fetal SAE should be described in the narrative field of the SAE Report Form. The initial SAE Report Form must be faxed by the Investigator to the designated Safety Contact within 24 hours of becoming aware of the event. Spontaneous miscarriages should also be reported and handled as SAEs. However, elective abortions without complications should not be handled as SAEs. All neonatal deaths occurring within 30 days of birth should be reported as SAEs, without regard to causality.

All outcomes of pregnancy, if known, must be reported by the Investigator to the Medical Monitor or the designated Safety Contact on the pregnancy outcome report form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion.

8 STATISTICAL METHODS

Evaluation of the safety of once daily (QD) plecanatide over up to 53 weeks of dosing will be based on the occurrence of TEAEs (treatment-emergent adverse events) and assessment of: vital signs, clinical laboratory tests, physical examinations and ECGs. Tolerability will be assessed by treatment interruptions due to diarrhea or other AEs, AE-free days, and continued participation in the trial.

A formal Statistical Analysis Plan (SAP) will be written and include details of all statistical methods to be used to analyze the long-term safety and tolerability of plecanatide. The SAP will supersede the protocol with respect to the analyses specified, although the general approach described in this section will remain unchanged.

8.1 Treatment Assignment

This is a long-term safety and tolerability study that will be conducted at approximately 250 clinical study centers. Approximately 1500 patients will be assigned to receive plecanatide (6 mg QD).

8.2 Sample Size and Power Considerations

Sample size and power calculations are not applicable. The sample size for this study is to ensure at least 300 to 600 patients complete 6 months of treatment with plecanatide and that 100 patients complete 12 months of treatment with plecanatide to satisfy ICH guidelines for drugs intended for chronic use. A sample size of approximately 1500 patients will also allow numerous patients who have completed a previous plecanatide study to have the opportunity for continued treatment.

8.3 Analysis Populations

The following populations will be assessed:

- **Safety:** All enrolled patients who have received at least one dose of the study drug. All safety analyses will be based upon the Safety Population.
- **Modified Intent-to-Treat (mITT):** All enrolled patients who have had at least one dose of study drug and who have at least one post-baseline PGA assessment. This will be the main population for assessment of patient-reported outcomes.

If considered necessary, further populations may be defined in the SAP.

8.4 General Considerations

Categorical variables will be summarized by the number and percent of patients in each level. Continuous variables will be summarized by number of observations, mean, standard deviation (SD), median, minimum, and maximum values. Where data are collected over time, both the observed data and change from baseline will be summarized at each time point. For all analyses, data will be summarized by open-label treatment.

8.5 Missing Data Conventions

In general, data will not be imputed. Details of the missing data methodology will be provided in the SAP.

8.6 Baseline Definition

Baseline values will be defined from the assessments collected at Visit 1 (Day 1; Baseline visit).

8.6.1 Baseline Characteristics

Demographic data and other baseline characteristics, medical history (ongoing AEs from previous trial), and concomitant medication will be summarized by means of descriptive statistics.

8.7 Patient-Reported Outcomes

8.7.1 Patient Questionnaires

Three patient self-reported questionnaires will be administered during study visits to assess the patient's overall IBS symptoms, treatment satisfaction and desire for treatment continuation. These patient questionnaires (see **Appendix 1**) will be administered preferably prior to any other study assessments.

- **Patient's Assessment of Relief of IBS symptoms,** collected at all visits, will be rated on a 5-point scale where 2=Significantly Relieved, 1=Moderately Relieved, 0=Unchanged, -1=Moderately worse, -2 =Significantly Worse.
- **Patient's Treatment Satisfaction Assessment**, collected at all visits except Visit 1, will be measured on a 5-point scale where 1=Not at all satisfied, 2=A little satisfied, 3=Moderately satisfied, 4=Quite satisfied, 5=Very satisfied.
- **Patient's Treatment Continuation Assessment**, collected at the last study visit (Visit 6 or Early Withdrawal), will be measured on a 5-point scale where 1=Not at all likely, 2=A little likely, 3=Moderately likely, 4=Quite likely, 5=Very likely

The change from baseline will be summarized for each post-baseline assessment.

All assessments will be summarized using descriptive statistics on observed data. Additional exploratory analyses such as linear mixed-effects models may be performed on the above assessments. Full details will be provided in the SAP.

8.8 Tolerability

Tolerability will be assessed by treatment interruptions due to diarrhea or other AEs, AE-free days, and continued participation in the trial. Full details will be provided in the SAP.

8.9 Safety Analyses

Evaluation of the safety of once daily (QD) plecanatide over 53 weeks of dosing will be based on the occurrence of TEAEs, vital signs, clinical laboratory assessments, physical examinations and ECGs as recorded in the clinical database. The safety analyses will use the Safety Population defined in Section 8.3.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) classifications with reference to system organ class and preferred terms. While all AEs will be listed, only TEAEs will be included in summary tables. Summaries of TEAEs will be presented by system organ class and preferred term. Tabular summaries will include frequency of TEAEs overall and by intensity and by relationship to study drug. Incidence rates by person-time will also be presented. TEAEs leading to treatment interruption, withdrawal from treatment, and SAEs will be presented separately.

Out of range laboratory tests, ECGs and vital signs of potential clinical importance will also be summarized. A listing of patients with at least 1 out of range value will be presented by visit for that test.

Hematology, serum chemistry, and urinalysis absolute values and, where applicable, changes from baseline for each of the laboratory assessments will be presented over time. An additional listing will be produced of clinically significant laboratory parameters. Shift tables will also be produced.

Changes in vital signs and ECG evaluations will be presented. Absolute values and changes from baseline for each parameter will be presented, where applicable.

Concomitant medications will be auto-encoded using the World Health Organization Drug Dictionary (WHODD) coding system with reference to Anatomical Therapeutic Chemical (ATC) Classification System text and preferred terms. Summaries of concomitant medication will be presented by ATC text and preferred terms. Prior and concomitant medications will be presented separately.

All physical examination findings will be presented in the data listing.

8.10 Interim Analyses

No interim analyses are planned.

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The Sponsor or Sponsor's designee will inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information

recorded on the eCRF for this study must be consistent with the patients' source documentation (i.e., medical records).

9.1.1 Database Management and Quality Control

All data generated by the clinical site personnel will be captured electronically at each clinical site using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

Computerized data check programs and manual checks will identify any clinical data discrepancies for resolution. If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the clinical site will answer queries sent to the site. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the data manager will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC will be provided to investigative sites in a manual e.g., eCRF Completion Guidelines. In addition, clinical site personnel will receive training on the EDC system, including the eCRF.

9.2 Electronic Case Report Forms and Source Documentation

All data obtained during this study should be entered into the EDC system promptly. All source documents from which eCRF entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments and ECG recordings.

Data that are entered directly into the EDC system (i.e., for which there is no prior written or electronic record of data) are considered to be source data.

All eCRF entries for each patient may be checked against source documents at the clinical site by the site monitor. Instances of missing or uninterpretable data will be discussed with the Investigator or designated site staff for resolution.

9.2.1 Data Collection

The Investigators (and appropriately authorized staff) will be given access to an online, web-based EDC system which is 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and rights to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. It is recommended that a patient's CRF is created in EDC as soon as the patient completes informed consent to reserve the patient's assigned Subject ID in the system. Then, all applicable eCRF pages are to be completed as soon as possible, i.e., during or immediately after the patient's visit or assessment. **The expectation is that sites will complete data entry within 48 hours of a patient visit**.

For patients who do not qualify for the study, only the following eCRF pages need to be completed in EDC: Informed Consent/Demographics, Inclusion/Exclusion Criteria and disposition page. All other forms are not required and should be marked as "Not Collected" in EDC, although sites are expected to have all source documentation supporting the patient's status available on site for review by the monitor.

The Investigator must attest that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable, or unknown, the Investigator (or designee) should indicate this in the eCRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the clinical site will be informed about new issues to be resolved on-line. All discrepancies will be solved online directly by the Investigator or by authorized staff. Data managers and clinical site monitors will be available to assist sites in resolving queries. Offline edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion of data entry and cleaning, the Investigator will be required to electronically sign off on the clinical data collected in the eCRF.

9.3 Access to Source Data

During the study, a site monitor will visit clinical sites to review protocol compliance, compare eCRF entries and individual patient medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be carried out giving due consideration to data protection and patient confidentiality.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities, IRBs, and/or the Sponsor's Quality Assurance Group (or designee) may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for all monitoring visits, inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator and authorized staff assure monitors, inspectors or auditors and the Sponsor of full access to study data and files and the necessary support of site personnel at all times.

9.4 Data Processing

All data will be entered by clinical site personnel into the EDC system/eCRF as detailed in Section 9.2.1.

The Data Management Plan for the study includes specifications for consistency and plausibility checks on data and also includes data-handling rules for obvious data errors. Unresolved queries will be shared with the study monitors for resolution with the Investigator or designated site personnel. The database will be updated on the basis of electronically-signed corrections.

Previous and concomitant medications will be coded using the WHODD, which employs the ATC classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

The versions of the coding dictionaries will be provided in the Statistical Analysis Plan (SAP) and the Clinical Study Report (CSR).

9.5 Archiving Study Records

According to International Conference on Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Ten years is the recommended storage duration to ensure compliance with ICH requirements. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of GCP as described in the CFR and ICH guidelines. The study also will be carried out in keeping with local legal and regulatory requirements and principles of the Declaration of Helsinki as currently endorsed by regional regulatory health authorities.

9.7 Informed Consent

Before each patient is admitted to the study, informed consent will be obtained from the patient (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. The informed consent form (ICF) must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the EDC system.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB, and signed by all patients subsequently enrolled into the study as well as those currently participating in the study.

9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient participates in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug (IND) application under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment but must be submitted to the applicable IRB/IEC. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.9 Duration of the Study

Once enrolled (on Day 1), the planned duration of the patient’s participation in the study is 53 weeks or 371 days (378 including the permitted window).

9.10 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to enrolled patients.
- Failure to enroll patients at an acceptable rate.
- A decision on the part of the Sponsor to suspend or discontinue development of the study drug.

Sponsor reserves the right to discontinue, terminate or suspend the study upon submission of the New Drug Application to the FDA. If discontinued, terminated or suspended Sponsor will inform (1) the Principal Investigator at each study site, (2) the FDA and (3) the IRB of the discontinuation, termination or suspension and the reason(s) therefore.

The Sponsor may also terminate the study when its enrollment, regulatory and study drug exposure objectives have been met. Consequently, not all enrolled patients will receive 53 weeks of treatment.

9.11 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to the Sponsor (or designee) by their patient number, initials, and/or birth date, not by name. Documents not to be submitted to Sponsor (or designee) that identify the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

9.12 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties: Regulatory Authorities, Investigators and IRBs.

A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent and the Investigator Brochure.

9.13 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to medical costs for physical injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for patients participating in this study to be insured against medical costs for physical injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

9.14 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance. Details are included in the Clinical Study Agreement completed for each investigational site.

10 REFERENCE LIST

1. Drossman DA, Morris CB, Hu Y, et al. A prospective assessment of bowel habits in irritable bowel syndrome in women: defining an alternator. Gastroenterol 2005; 128: 580–9.
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3. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterol. 2006;130:1480-1491.
4. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterol 2002; 123: 2108–31.
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6. Drossman DA, Dumitrascu DL. Rome III: New Standard for Functional Gastrointestinal Disorders. Gastrointestin Liver Dis 2006; 15: 237-241.
7. Sindic A and Schlatter E. Cellular Effects of Guanylin and Uroguanylin. J Am Soc Nephrol 2006; 17: 607–616.
8. Assessment of SP-304 in DSS and TNBS Murine IBD Models (Study No. 06-119)
9. Anti-Inflammatory Activity of SP-304 in an Animal Model of Experimental Colitis (Study No. SP-PH-005)
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11. Shailubhai K, Talluto, C, Comiskey S, Foss J, Joslyn A, Jacob G. A Ph IIa randomized. double-blind, placebo-controlled, 14 day repeat, oral, range finding study to assess the safety, pharmacokinetic and pharmacodynamic effects of Plecanatide (SP-304) in patients with CIC, American College of Gastroenterology (ACG) Annual Scientific Meeting, October 15-20, 2010 Poster no 762.
12. Synergy Pharmaceuticals Inc. A Randomized, 12-Week, Double-Blind, Placebo-Controlled, Repeat-Dose, Oral, Dose-Ranging Study to Assess the Safety and Efficacy of Plecanatide in Patients with Chronic Idiopathic Constipation. (Study SP304-20210) June 2013
13. Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, DHHS, FDA July 2009

11 APPENDICES

Appendix 1: PATIENT QUESTIONNAIRES: Global Relief of IBS Symptoms, Treatment Satisfaction and Treatment Continuation Assessment

The questionnaires will be used at the study site for collection of patients' assessments of: Global Relief of IBS Symptoms, Treatment Satisfaction and Treatment Continuation. The self-administered questionnaires will be conducted preferably prior to any other study assessments. The questionnaires take 1 to 5 minutes to be completed. The site must ensure to use the current, IRB-approved version of the questionnaires and in the appropriate language/translation for the study subject.

I. Patient Global Rating of Change – IBS Symptoms

For the questions below, please choose the response that applies best to you

RELIEF OF IBS SYMPTOMS
How would you rate your Irritable Bowel Syndrome (IBS) signs and symptoms overall over the past 7 days? **2 = Significantly Relieved** **1 = Moderately Relieved** **0 = Unchanged** **-1 = Moderately Worse** **-2 = Significantly Worse**

II. Patient Treatment Satisfaction Assessment

For the questions below, please choose the response that applies best to you

TREATMENT SATISFACTION ASSESSMENT
Overall, how satisfied are you with the study medication's ability to relieve your constipation symptoms? **1 = Not at all satisfied** **2 = A little satisfied** **3 = Moderately satisfied** **4 = Quite satisfied** **5 = Very satisfied**

III. Patient Treatment Continuation Assessment

For the questions below, please choose the response that applies best to you

TREATMENT CONTINUATION ASSESSMENT
If given the option, how likely is it that you would continue taking the study medication? **1 = Not at all likely** **2 = A little likely** **3 = Moderately likely** **4 = Quite likely** **5 = Very likely**

Appendix 2: Rome III Diagnostic Criteria for Irritable Bowel Syndrome with Constipation; Rome III Diagnostic Questionnaire – IBS Module

C1. Irritable Bowel Syndrome

Diagnostic Criteria*

Recurrent abdominal pain or discomfort** at least 3 days/month in last 3 months associated with two or more of criteria #1 - #3 below:

Pain or discomfort at least 2-3 days/month (question 1>2)

For women, does pain occur only during menstrual bleeding? (question 2=0 or 2)

1. Improvement with defecation

   Pain or discomfort gets better after BM at least sometimes (question 4>0)

2. Onset associated with a change in frequency of stool

   Onset of pain or discomfort associated with more stools at least sometimes (question 5>0), OR

   Onset of pain or discomfort associated with fewer stools at least sometimes (question 6>0)

3. Onset associated with a change in form (appearance) of stool

   Onset of pain or discomfort associated with looser stools at least sometimes (question 7>0), OR

   Onset of pain or discomfort associated with harder stools at least sometimes (question 8>0)

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 3=1)

**"*Discomfort" means an uncomfortable sensation not described as pain*.

In pathophysiology research and clinical trials, a pain/discomfort frequency of at least two days a week is recommended for subject eligibility.

Pain or discomfort more than one day per week (question 1>4)

Criteria for IBS-C

(question 9>0) and (question 10=0)

Rome III Diagnostic Questionnaire – IBS Module

For each question below, please choose the response (place "X" over the circled number) that applies best to you.

1. In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?	⓪ Never (→ *skip remaining questions*) ① Less than one day a month ② One day a month ③ Two to three days a month ④ One day a week ⑤ More than one day a week ⑥ Every day
2. For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?	⓪ No ① Yes ② Does not apply because I have had the change in life (menopause) or I am a male
3. Have you had this discomfort or pain 6 months or longer?	⓪ No ① Yes
4. How often did this discomfort or pain get better or stop after you had a bowel movement?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always
5. When this discomfort or pain started, did you have more frequent bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always
6. When this discomfort or pain started, did you have less frequent bowel movements?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always
7. When this discomfort or pain started, were your stools (bowel movements) looser?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always
8. When this discomfort or pain started, how often did you have harder stools?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always
9. In the last 3 months, how often did you have hard or lumpy stools?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always
10. In the last 3 months, how often did you have loose, mushy or watery stools?	⓪ Never or rarely ① Sometimes ② Often ③ Most of the time ④ Always

ROME III Modular Questionnaire Scoring for Study Eligibility

The following table should be utilized to confirm the diagnosis of IBS-C.

ROME Question Number	Score	Criterion Met Yes/No
1	3, 4, 5 or 6	
2	0 or 2	
3	1	
4*	1, 2, 3 or 4	
5 or 6*	1, 2, 3 or 4	
7 or 8*	1, 2, 3 or 4	
9	1, 2, 3 or 4	
10	0	

*Only two of these 3 criteria need to be met

The numbers listed in Column 1 reflect the specific questions of the **Rome III Diagnostic Questionnaire – IBS Module**.

Column 2 lists the range of required answers for each question; the patient must supply individual answers to Questions 1, 2, 3, 4, 9 &10. Questions 5 through 8 are treated differently as follows:

- Questions 5 and 6, ***either but not both*** questions (5 or 6) would need to be answered as required
- Questions 7 and 8, ***either but not both*** questions (7 or 8) would need to be answered as required

*Note that for questions 4, 5/6 and 7/8, only two out of the three need to be met.

Mark YES in Column 3 if the required answer was met or mark NO if a required answer is not met.

The diagnosis of IBS-C is confirmed only if Column 3 contains a YES for Questions 1, 2, 3, 9 & 10 AND at least two of Question 4, Questions 5/6 or Questions 7/8.

Appendix 3: Summary of American Gastroenterological Association (AGA) Guidelines for Colon Cancer Screening1 and Surveillance2

The American Gastroenterological Association (AGA) colon cancer screening and surveillance guidelines recommendations as they apply to the study protocol:

Patients of average risk aged 50 years and older must have had a colonoscopy with negative findings during the 10 years before the Screening Visit.

Patients who have had polyps identified (and removed) on a previous screening colonoscopy should undergo surveillance at an accelerated interval (i.e., <10 years) depending on the number, size and histology of the identified polyps. For example, a patient who had >3 and <10 tubular adenomas identified should undergo a follow-up colonoscopy 3 years from the initial colonoscopy during which the polyps were identified (See AGA publication for further details).

Patients who have a first-degree relative with colorectal cancer or adenomatous polyps diagnosed **before age 60** or two **first-degree** relatives with colorectal cancer diagnosed at any age must have had a colonoscopy with negative findings during the **5 years** before the Screening Visit. This applies to patients who are ≥ 40 years old and to patients < 40 years old who are ≤ 10 years from the age when their youngest relative was found to have one of the conditions described above.

Patients who have a first-degree relative with colorectal cancer or adenomatous polyps diagnosed at **age 60 or older** or two **second-degree** relatives with colorectal cancer diagnosed at any age must have had a colonoscopy with negative findings during the 1**0 years** before the Screening Visit. This applies to patients who are ≥ 40 years old and to patients < 40 years old who are ≤ 10 years from the age when their youngest relative was found to have one of the conditions described above.

Patients of any age who have alarm symptoms must have had a colonoscopy with negative findings after the onset of the alarm symptoms and during the five years before the Screening Visit. Alarm symptoms include lower GI bleeding (rectal bleeding or heme-positive stool), iron-deficiency anemia, unexplained clinically-significant weight loss, and systemic signs of infection or colitis.

Appendix 3: References

1. Levin B, Lieberman DA, McFarland B, Andrews K, et al Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline From the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008; 1434: 1570–1595

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