A PILOT STUDY TO EVALUATE SAFETY AND EFFECTIVENESS OF LANREOTIDE IN THE TREATMENT OF PATIENTS WITH SMALL BOWEL MOTILITY DISORDERS (SBMD): A PROSPECTIVE, NON-RANDOMIZED, SINGLE CENTER STUDY OF 20 PARTICIPANTS.

NCT NUMBER: - NCT03012594

DATE: - OCTOBER 28TH, 2016

STUDY PRODUCT: SOMATULINE DEPOT (LANREOTIDE)

CONFIDENTIAL

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
b.i.d.	twice a day
CRF	Case Report/Record Form
CRD	Clinical Research and Development
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
FDA	Food and Drug Administration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
i.v.	intravenous(ly)
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
o.d.	once a day
PAGI-SYM	Patient Assessment of upper GastroIntestinal disorders-symptom severity index
p.o.	oral(ly)
REB	Research Ethics Board
SAE	serious adverse event
SBMD	Small Bowel Motility Disorder
WMC	Wireless Motility Capsule

1 Previous Study History

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

☒ No ☐ Yes – if yes, please explain:

2 Brief Summary of Research

This is a human research study looking at the effectiveness of Lanreotide (study medication) in treating small bowel motility disorders. It is similar to a natural hormone somatostatin that is produced in the body in the stomach, duodenum, pancreas and brain. Somatostatin is a growth hormone-inhibiting hormone. Lanreotide is a man made hormone and is a long acting medication that is given once a month. It is marketed with a trade name "Somatuline Depot". It is given deep subcutaneously (deep within the layers of the skin) in the superior external quadrant of the buttock. Injection site will be alternated on subsequent injections.

We hypothesize that in patients with small bowel motility disorders, Lanreotide helps in alleviating the symptoms. Lanreotide is an FDA approved medication for management of acromegaly and neuroendocrine tumors, but has never been used for treating small bowel motility disorders. However Octreotide which is similar to lanreotide but is a short acting synthetic somatostatin has been used in few research studies.

If a patient is interested and qualifies for the study then he/she will be explained about the study and signature will be collected on the consent form. Health and social history will be collected. Blood work, urine analysis, pregnancy test (in women of reproductive age group and have the capability of getting pregnant)) will be performed to make sure that patient qualifies for the study and for follow-up during the treatment. Physical examination, ECG, wireless motility capsule testing and hydrogen breath testing will be performed. Patients will be required to complete a questionnaire regarding their health.

The total study duration from the first administration of study drug is 12 weeks. The study medication will be given once a month for 3 months and there is a 1 month follow-up after the last study medication. There will be a screening visit approximately 1 month before the first study drug administration.

3 Introduction

This document is a clinical research protocol. This study is to be conducted according to US and

international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

3.1 Background

Small bowel motility disorder (SBMD) is characterized by signs and symptoms of a mechanical obstruction in the flow of intestinal contents, without any presence of an anatomic lesion. It may be acute or chronic, and imaging shows dilation of the bowel on imaging. It is postulated to be due to an underlying neuropathic disorder, a myopathic disorder, or abnormality in the interstitial cell of Cajal. Approximately a half of the cases are secondary to neurologic, paraneoplastic, autoimmune, metabolic/endocrine, and infectious diseases.(4)

This condition is considered rare and reports estimating the incidence and prevalence mostly originate from tertiary referral centers. For example, a nation-wide survey in Japan has estimated the prevalence as 0.80 to 1.00 per 100,000 with an incidence of 0.21 to 0.24 per 100,000. The mean age at diagnosis was 63.1 years for males and 59.2 for females.(5) The prognosis is very poor in children, with majority of them requiring parenteral nutrition with mortality rate ranging from 10 to 25 percent.(6) In adults, the majority of patients suffer nutritional compromise, and about a third requiring long-term parenteral nutrition.(7) Complications secondary to parenteral nutrition are seen in 45-80 percent and mortality rate approaches 10 percent.(8)

Patients with SBMD may require supplemental nutrition. Prokinetics are used for acute and chronic therapy, antibiotics are recommended when small bowel bacterial overgrowth is suspected, and immunomodulator therapy is typically reserved for an established underlying inflammatory neuropathy. Surgery is only performed if needed to provide access for venting/feeding, and resection or bypass of localized disease of the small bowel is avoided. Intestinal transplantation may be indicated when long-term parenteral nutrition cannot be initiated or continued safely.(9)

As a prokinetic, short-acting somatostatin analogue octreotide has been one of the few options in treating SBMD. Long-acting Lanreotide Depot (Autogel), with its 4-weekly dosing regimen, may improve the efficacy of treatment by enhancing patient compliance.(10)

Lanreotide (1, 11, 12) is a somatostatin analogue, like octreotide, but with known long acting small bowel prokinetic property, and can be very effective in treating small bowel motility disorders. Lanreotide has been approved by FDA(See attachment 1) for the treatment of well differentiated neuroendocrine tumors of low and intermediate grade. According to Lexicomp, its safety profile has been established and most adverse reactions such as bradycardia and cholelithiasis can be easily monitored.

3.2 Investigational Agent

----------INDICATIONS AND USAGE----------

SOMATULINE DEPOT (lanreotide) Injection is a somatostatin analog indicated for:

- The long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
- The treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

----------DOSAGE AND ADMINISTRATION----------

- Injected in the superior external quadrant of the buttock. Injection site should be alternated.

Acromegaly

- Dose range is 60 mg to 120 mg every 4 weeks. Recommended starting dose is 90 mg every 4 weeks for 3 months. Adjust thereafter based on GH and/or IGF-1 levels.
- Moderate and Severe Renal and Hepatic Impairment: Initial dose is 60 mg every 4 weeks for 3 months. Adjust thereafter based on GH and/or IGF-1 levels.

GEP-NET

- Recommended dose is 120 mg every 4 weeks.

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 60 mg/0.2 mL, 90 mg/0.3 mL, and 120 mg/0.5 mL single-use prefilled syringes

----------CONTRAINDICATIONS----------

- Hypersensitivity to lanreotide

----------WARNINGS AND PRECAUTIONS----------

- Gallbladder: Gallstones may occur; consider periodic monitoring
- Glucose Metabolism: Hypo- and/or hyperglycemia may occur. Glucose monitoring is

recommended and antidiabetic treatment adjusted accordingly

- Cardiac Function: Decrease in heart rate may occur. Use with caution in at-risk patients

----------ADVERSE REACTIONS----------

- Acromegaly: Most common adverse reactions are diarrhea, cholelithiasis, abdominal pain, nausea and injection site reactions
- GEP-NET: Most common adverse reactions (>10%) are abdominal
- pain, musculoskeletal pain, vomiting, headache, injection site reaction, hyperglycemia, hypertension, cholelithiasis

----------DRUG INTERACTIONS----------

- Hypoglycemia agents: Hypo- and/or hyperglycemia may occur. Glucose monitoring is recommended and antidiabetic treatment adjusted accordingly
- Cyclosporine: Somatuline may decrease the bioavailability of cyclosporine. Cyclosporine dose may need to be adjusted
- Drugs affecting heart rate: Somatuline may decrease heart rate. Dose adjustment of coadministered drugs may be necessary

----------USE IN SPECIFIC POPULATIONS----------

- Renal Impairment: Start dose is 60 mg for patients with acromegaly and moderate and severe renal impairment
- Hepatic Impairment: Start dose is 60 mg for patients with acromegaly and moderate and severe hepatic impairment

3.3 Preclinical Data

Essential nonclinical pharmacology, toxicology and PK were initially performed to support the MPF formulation. Subsequent studies have assessed the nonclinical safety and PK profile of the Autogel formulation. Toxicology data have been assessed based on serum lanreotide concentrations in animals compared with humans after administration of lanreotide Autogel 120 mg (1.7 mg/kg based on body weight of 70 kg). Based upon the pharmacology, PK and

toxicology studies (including cardiovascular tolerance), lanreotide Autogel is considered to be safe for chronic use in humans.
Additional PK and local tolerance studies of lanreotide PRF have been performed to support this new development formulation. Furthermore, because limited information is available on the excipient glycofurol that is used in this formulation a dedicated program to evaluate its toxicity has been initiated.

Please see additional information in the Lanreotide Investigators Brochure. (Attachment 2)

3.4 Clinical Data to Date

14.1 Acromegaly

The effect of SOMATULINE DEPOT on reducing GH and IGF-levels and control of symptoms in patients with acromegaly was studied in two long-term, multiple-dose, randomized, multicenter studies.

Study 1

This one-year study included a 4-week, double-blind, placebo-controlled phase; a 16-week single-blind, fixed-dose phase; and a 32-week, open-label, dose-titration phase. Patients with active acromegaly, based on biochemical tests and medical history, entered a 12-week washout period if there was previous treatment with a somatostatin analog or a dopaminergic agonist.

Upon entry, patients were randomly allocated to receive a single, deep subcutaneous injection of SOMATULINE DEPOT 60 mg, 90 mg, or 120 mg or placebo. Four weeks later, patients entered a fixed-dose phase where they received 4 injections of SOMATULINE DEPOT followed by a dose-titration phase of 8 injections for a total of 13 injections over 52 weeks (including the placebo phase). Injections were given at 4-week intervals. During the dose-titration phase of the study, the dose was titrated twice (every fourth injection), as needed, according to individual GH and IGF-1 levels.

A total of 108 patients (51 males, 57 females) were enrolled in the initial placebo-controlled phase of the study. Half (54/108) of the patients had never been treated with a somatostatin analog or dopamine agonist, or had stopped treatment for at least 3 months prior to their participation in the study and were required to have a mean GH level > 5 ng/mL at their first visit. The other half of the patients had received prior treatment with a somatostatin analog or a dopamine agonist before study entry and at study entry were required to have a mean GH concentration >3 ng/mL and at least a 100% increase in mean GH concentration after washout of medication.

One hundred and seven (107) patients completed the placebo-controlled phase, 105 patients completed the fixed-dose phase, and 99 patients completed the dose-titration phase. Patients not completing withdrew due to adverse events (5) or lack of efficacy (4).

In the double-blind phase of study 1, a total of 52 (63%) of the 83 lanreotide-treated patients had

a > 50% decrease in mean GH from baseline to Week 4, including 52%, 44%, and 90% of patients in the 60 mg, 90 mg, and 120 mg groups, respectively, compared to placebo (0%, 0/25). In the fixed-dose phase at Week 16, 72% of all 107 lanreotide-treated patients had a decrease from baseline in mean GH of > 50%, including 68% (23/34), 64% (23/36), and 84% (31/37) of patients in the 60 mg, 90 mg, and 120 mg lanreotide treatment groups, respectively. Efficacy achieved in the first 16 weeks was maintained for the duration of the study (see Table 4).

Table 4: Overall Efficacy Results Based on GH and IGF-1 Levels by Treatment Phase in Study 1

		Baseline **N=107**	**Before Titration 1 (16 weeks)** **N=107**	**Before Titration 2 (32 weeks)** **N=105**	**Last Value** **N=**
GH					
≤5.0 ng/mL	Number of Responders (%)	20 (19%)	72 (67%)	76 (72%)	7 (69
≤2.5 ng/mL	Number of Responders (%)	0 (0%)	52 (49%)	59 (56%)	5 (51
≤1.0 ng/mL	Number of Responders (%)	0 (0%)	15 (14%)	18 (17%)	1 (16
Median GH	ng/mL	10.27	2.53	2.20	2.
GH Reduction	Median % Reduction	--	75.5	78.2	75
IGF-1					
Normal[3]	Number of Responders (%)	9 (8%)	58 (54%)	57 (54%)	6 (58
Median IGF-1	ng/mL	775.0	332.0[1]	316.5[2]	32
IGF-1 Reduction	Median % Reduction	--	52.3[1]	54.5[2]	55
IGF-1 Normal[3] + GH ≤2.5 ng/mL	Number of Responders (%)	0 (0%)	41 (38%)	46 (44%)	4 (41

[1]n=105, [2]n=102, [3]Age-adjusted, *Last Observation Carried Forward

Study 2

This was a 48-week, open-label, uncontrolled, multicenter study that enrolled patients who had an IGF-1 concentration ≥ 1.3 times the upper limit of the normal age-adjusted range. Patients receiving treatment with a somatostatin analog (other than SOMATULINE DEPOT) or a dopaminergic agonist had to attain this IGF-1 concentration after a washout period of up to 3 months.

Patients were initially enrolled in a 4-month, fixed-dose phase where they received 4 deep subcutaneous injections of SOMATULINE DEPOT 90 mg, at 4-week intervals. Patients then entered a dose-titration phase where the dose of SOMATULINE DEPOT was adjusted based on GH and IGF-1 levels at the beginning of the dose-titration phase and, if necessary, again after another 4 injections. Patients titrated up to the maximum dose (120 mg) were not allowed to titrate down again.

A total of 63 patients (38 males, 25 females) entered the fixed-dose phase of the trial and 57 patients completed 48 weeks of treatment. Six patients withdrew due to adverse reactions (3), other reasons (2), or lack of efficacy (1).

After 48 weeks of treatment with SOMATULINE DEPOT at 4-week intervals, 43% (27/63) of the acromegalic patients in this study achieved normal age-adjusted IGF-1 concentrations. Mean IGF-1 concentrations after treatment completion were 1.3 ± 0.7 times the upper limit of normal compared to 2.5 ± 1.1 times the upper limit of normal at baseline.

The reduction in IGF-1 concentrations over time correlated with a corresponding marked decrease in mean GH concentrations. The proportion of patients with mean GH concentrations < 2.5 ng/mL increased significantly from 35% to 77% after the fixed-dose phase and 85% at the end of the study. At the end of treatment, 24/63 (38%) of patients had both normal IGF-1 concentrations and a GH concentration of ≤ 2.5 ng/mL (see Table 5) and 17/63 patients (27%) had both normal IGF-1 concentrations and a GH concentration of <1 ng/mL.

Table 5: Overall Efficacy Results Based on GH and IGF-1 Levels by Treatment Phase in Study 2

		Baseline **N=63**	**Before Titration 1 (12 wks) N=63**	**Before Titration 2 (28 wks) N=59**	**Last Value Ava** **N=63**
IGF-1					
Normal[1]	Number of Responders (%)	0 (0%)	17 (27%)	22 (37%)	27 (43%)
Median IGF-1	ng/mL	689.0	382.0	334.0	317.0
IGF-1 Reduction	Median % Reduction	--	41.0	51.0	50.3
GH					
≤5.0 ng/mL	Number of Responders (%)	40 (64%)	59 (94%)	57 (97%)	62 (98%)
≤2.5 ng/mL	Number of Responders (%)	21 (33%)	47 (75%)	47 (80%)	54 (86 %)
≤1.0 ng/mL	Number of Responders (%)	8 (13%)	19 (30%)	18 (31%)	28 (44%)
Median GH	ng/mL	3.71	1.65	1.48	1.13
GH Reduction	Median % Reduction	--	63.2	66.7	78.6[2]
IGF-1 normal[1] + GH ≤2.5 ng/mL	Number of Responders (%)	0 (0%)	14 (22%)	20 (34%)	24 (38%)

[1]Age-adjusted, [2]N= 62, *Last Observation Carried Forward

Examination of age and gender subgroups did not identify differences in response to SOMATULINE DEPOT among these subgroups. The limited number of patients in the different racial subgroups did not raise any concerns regarding efficacy of SOMATULINE DEPOT in these subgroups.

14.2 Gastroenteropancreatic Neuroendocrine Tumors

The efficacy of SOMATULINE DEPOT was established in a multicenter, randomized, double-blind, placebo-controlled trial of 204 patients with unresectable, well or moderately differentiated, metastatic or locally advanced, gastroenteropancreatic neuroendocrine tumors.

Patients were required to have non-functioning tumors without hormone-related symptoms. Patients were randomized 1:1 to receive SOMATULINE DEPOT 120 mg (n=101) or placebo (n=103) every 4 weeks until disease progression, unacceptable toxicity or a maximum of 96 weeks of treatment. Randomization was stratified by the presence or absence of prior therapy and by the presence or absence of disease progression within 6 months of enrollment. The major efficacy outcome measure was progression-free survival (PFS), defined as time to disease progression as assessed by central independent radiological review using the Response Evaluation Criteria in Solid Tumors (RECIST 1.0), or death.

The median patient age was 63 years (range 30-92 years) and 95% were Caucasian. Disease progression was present in nine of 204 patients (4.4%) in the 6 months prior to enrollment and twenty-nine patients (14%) received prior chemotherapy. Ninety-one patients (45%) had primary sites of disease in the pancreas, with the remainder originating in the midgut (35%), hindgut (7%), or unknown primary location (13%). The majority (69%) of the study population had grade 1 tumors. Baseline prognostic characteristics were similar between arms with one exception; there were 39% of patients in the SOMATULINE DEPOT arm and 27% of patients in the placebo arm who had hepatic involvement by tumor of > 25%.

Patients on the SOMATULINE DEPOT arm had a statistically significant improvement in progression-free survival compared to patients receiving placebo (see Table 6 and Figure 1).

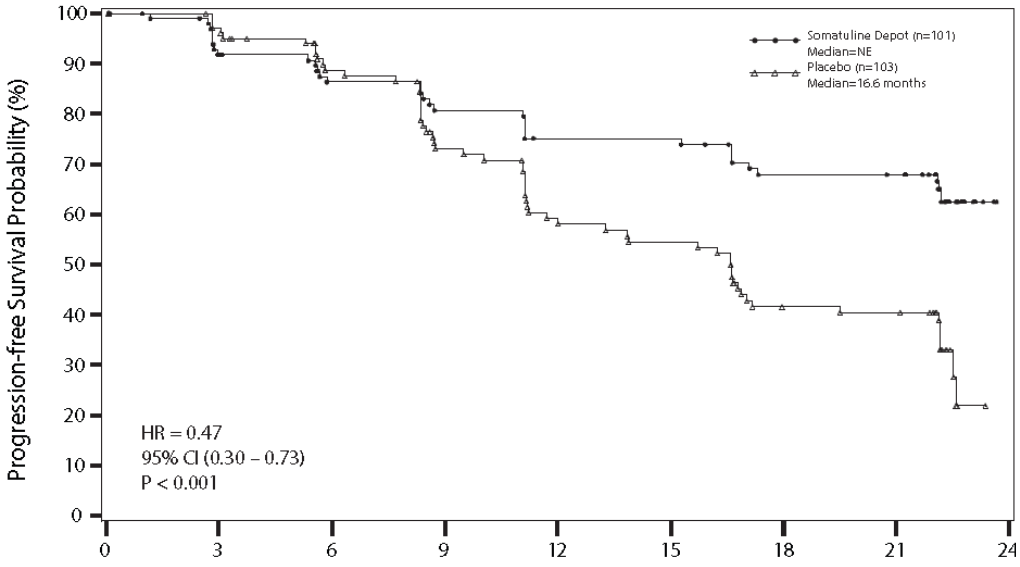
Table 6: Efficacy Results in Study 3

	SOMATULINE DEPOT	Placebo
	n = 101	n = 103
Number of Events (%)	32 (31.7%)	60 (58.3%)
Median PFS (months)(95% CI)	NE[1] (NE, NE)	16.6 (11.2, 22.1)
HR (95% CI)	0.47 (0.30, 0.73)[2]	
Log-rank p-value	< 0.001	

1: NE = not reached at 22 months

2: Hazard Ratio is derived from a Cox stratified proportional hazards model

Figure 1: Kaplan-Meier Curves of Progression-Free Survival



Number of subjects still at risk									
Somatuline Depot	101	87	78	72	64	64	56	55	0
Placebo	103	97	81	64	50	47	34	33	0

Please see additional information in the Lanreotide Investigators Brochure. (Attachment 2)

3.5 Dose Rationale and Risk/Benefits

There has not been an effective treatment for SBMD, especially in patients with delayed small bowel transit time accompanied by abdominal bloating.

Somatostatin is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones. It is widely distributed in the central nervous system, gastrointestinal tract, and endocrine cells. It modulates many physiological processes, such as pro-absorption, anti-secretion, anti-proliferation, immunological modulation, neuronal excitability, and vascular smooth muscle contractility. In the intestine, somatostatin is known to affect intestinal motility, to reduce secretion, and to stimulate water and sodium absorption(1, 10, 13).

While octreotide, is a short-acting somatostatin and has been used with moderate success, it suffers from the short serum bioavailability requiring frequent administrations (half life of 100

minutes).

As an analogue to somatostatin, lanreotide is known for its prokinetic properties, and it is also long-acting, making it a desired alternative to the current treatment regime using short-acting octreotide. This study will investigate the usefulness of lanreotide in the treatment of SBMD, as measured by small bowel transit time in wireless motility capsule testing. This is a pilot, non-randomized, unblinded study and there is no placebo in the study.

The results from both single dose administration and four dose administrations suggested a dose-response relationship between lanreotide treatment and GH concentration control. At higher doses of lanreotide Autogel, greater proportions of patients had at least a 50% reduction from baseline in mean serum GH concentration. Additionally, a greater proportion of patients (regardless of the treatment group) had at least a 50% reduction in GH concentration after receiving four dose administrations than after receiving a single dose. The long-term open-label dose titration periods of two studies (14) provide pivotal data about the optimal control of patients with lanreotide Autogel following titration of the monthly dose for more than 6 months. The combined analysis of the dose titration periods of Studies shows that patients with acromegaly achieved long-term optimal hormonal control as defined by GH and IGF-1 concentrations.

1. This study is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug.
2. This study is not intended to support a significant change in the advertising for the product.
3. This study does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug.
4. This study is conducted in compliance with the requirements for Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and informed consent.
5. This study is conducted in compliance with the requirements concerning the promotion and sale of drugs.
6. This study does not intend to invoke 21 CFR 50.24 (exception from informed consent for emergency research)."

This study satisfies all the above criteria and hence it is not required to submit an IND to FDA.

Please see additional information in the Lanreotide Investigators Brochure. (Attachment 2)

4 Study Objectives

Primary objective/s

The primary objective is to identify if lanreotide will help in alleviating the effects of small bowel motility disorders. Effect of lanreotide on small bowel motility disorder will be assessed in 20 patients by looking at small bowel transit time using wireless motility capsule (SmartPill) testing. Achieving small bowel transit time of less than 6 hrs will be considered as a positive response.

Secondary objective/s

1. Improvement in symptoms as assessed by symptom questionnaire (Eg: - improvement in nausea, vomiting, abdominal pain, bloating), improvement in upper gastrointestinal disorders-symptom severity index (PAGI-SYM) scores.

2. Resolution of small intestinal bacterial overgrowth as assessed by hydrogen breath testing.

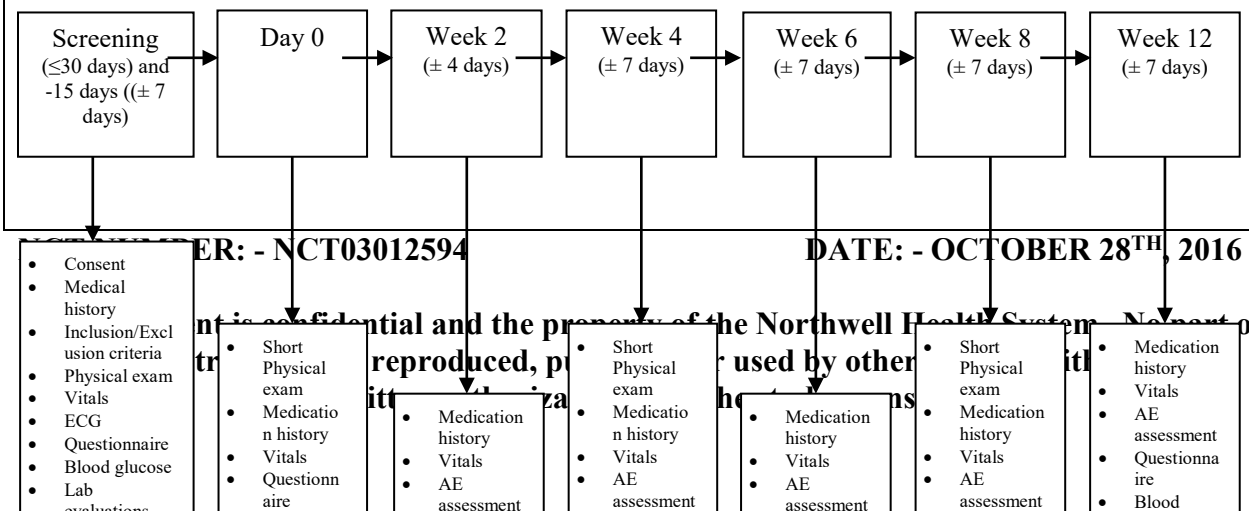
5 Resources Available to Conduct the Human Research

All the three hospitals included as sites in the study are tertiary care centers with well known gastroenterology departments. Thousands of patients are treated each year in these hospitals with various gastroenterological conditions. These hospitals are also one of the leading referral centers for gastroenterological conditions in Manhattan and in Long island. Even though the condition being addressed in this study is rare, we anticipate no problem in recruiting due to the large patient population and referral base.
The gastroenterology department has the capability, facilities and personnel to perform all the procedures that are described in this research study.
All research personnel involved in the study are required to complete the essential requirements for participation in the study (e.g.: CITI trainings (Human research section, Conflict of interest)). All study personnel will be required to complete the delegation log describing their roles in the project.

6 Study Design

6.1 General Design

This is a pilot, single center, single arm, open-label, non-randomized, prospective study of consecutive patients with small bowel motility disorder.



Study set-up will take approximately 2-3 months, enrollment period for 6 months, treatment duration for 8-12 weeks, follow up for 1 month post treatment, and manuscript preparation/submission for 2 months.

[1] Performed only if the tests are not performed in the last 2 months as standard of care.

6.2 Primary Study Endpoints

- Effect of lanreotide on small bowel motility disorders, as assessed by small bowel transit time using wireless motility capsule (SmartPill) testing. If the small bowel transit time, as measured by wireless capsule endoscopy, is decreased to < 6hrs, then patient would be considered a responder and that lanreotide is efficacious. % of responder would be reported as endpoint. We expect >50% patients to be responders.

6.3 Secondary Study Endpoints

- Improvement in symptoms as assessed by improvement in upper gastrointestinal disorders-symptom severity index (PAGI-SYM) scores. PAGI-SYM is a brief (20-items with 6 sub scales) symptom severity questionnaire that captures information on common upper gastrointestinal symptoms, including heartburn, regurgitation, fullness, early satiety, bloating, nausea and vomiting, and upper abdominal pain. If the PAGI-Sym scores were decreased by at least 0.7 points compared to pre treatment, then it will be considered that lanreotide has significantly improved the symptom severity. (15-17)

- Resolution of small intestinal bacterial overgrowth as assessed by hydrogen breath testing. If the hydrogen breath test is positive (>20 ppm from the baseline) before treatment and it decreases (changes to <20 from the baseline) after treatment, it will be considered that lanreotide is efficacious in decreasing the small intestinal bacterial overgrowth.

6.4 Primary Safety Endpoints

- Cardiac Function (Bradycardia (Decreased heart rate) and hypertension) - If the subjects heart rate decreases by more than 20%, and either systolic or diastolic pressures increase by more than 20% during any of the visits when compared to that of the screening visit.
- Cholelithiasis (Gallstones)- Symptoms include severe right upper quadrant abdominal pain , nausea and vomiting, abdominal tenderness, clay colored stools, Jaundice (yellowing of skin and whites of the eye).
- Glucose Metabolism - (Hyperglycemia or hypoglycemia) – Blood glucose will be monitored during every visit. If there is a variation of more than 20% then it is considered as a safety end point.
- Acute anaphylactic reactions – If the subjects develops anaphylactic reaction then he/she will be removed from the study and will be monitored and treated as per standard of care.
- Pancreatitis – It is characterized by Upper abdominal pain that radiates into the back; it may be aggravated by eating, especially foods high in fat, Swollen and tender abdomen, Nausea and vomiting, Fever and Increased heart rate. Signs of pancreatitis will be checked for during every visit.
- Hepatitis – Signs of hepatitis include Loss of appetite, Nausea and vomiting, Diarrhea, Dark-colored urine and pale bowel movements, Stomach pain and Jaundice (yellowing of skin and eyes). Signs of hepatitis will be checked for during every visit.
- Thyroid Function Abnormalities - If there is a variation of more than 20% from the screening visit values of T3, T4, TSH and if the subject is on any other thyroid medication that might have caused this, then the subject will be referred to her endocrinologist for dose adjustment. If the change occurred without any concomitant medication then the subject will be removed from the study and will be monitored and treated as per standard of care.

7 Subject Selection and Withdrawal

7.1 Inclusion Criteria

1. Consecutive patients with evidence of small bowel motility disorders, referred to (or) are patients of the Gastroenterology and Motility Center at Northwell health system.
2. Aged between 18 and 70 years.

3. Subjects should be capable of understanding the study and be able to give informed consent.
4. Patient having small bowel motility disorder as evidenced by delayed small bowel transit by wireless motility capsule (WMC) testing to > 6 hours.
5. To participate in the study you will have to stop taking Octreotide (because it has the same mechanism of action as the study medication) if you are currently taking it, it should be stopped for at least 4 weeks before taking the first dose of this study medication.

7.2 Exclusion Criteria

General Exclusion Criteria

- Age <18 or age >70
- Pregnancy as assessed by urine pregnancy test.

Exclusion Criteria for performing wireless motility capsule testing

1. History of gastric bezoar
2. History of Disorders of swallowing
3. Known or suspected small bowel diverticula, diverticulitis, strictures, fistulas, Crohn's disease, or any other relevant medical comorbidity (e.g. chronic alcohol abuse)
4. Prior intestinal surgery, including IC valve resection or gastrointestinal surgeries that create a blind loop (e.g. Bilroth II or Roux-en-Y)
5. History of Severe dysphagia to food or pills
6. A participant who uses an implanted or portable electro-mechanical medical device such as a cardiac pacemaker or infusion pump
7. Inability to be off intestinal transit altering medication for at least one week (e.g. opiates, laxatives, etc.)
8. Any person unable or unwilling to undergo abdominal surgery.
9. BMI > 40.

Exclusion Criteria due to Lanreotide

1. Current use or recent (within last 7 days) use of acid suppressive therapy, prokinetic agents, laxatives, and opiates, or other agents known to affect gastrointestinal motility.
2. Disorders associated with presumed small intestinal motility disorders including: scleroderma, intestinal pseudo-obstruction, and autonomic visceral neuropathy (e.g. longstanding diabetes of more than 20 years and/or poorly controlled diabetes (glucose > 250, glycosylated hemoglobin (HbA1c) > 8.5%)
3. Current use of cyclosporine (Gengraf, Neoral, or Sandimmune), a medicine called bromocriptine (Parlodel, Cycloset), or medicines that lower your heart rate, such as beta blockers.
4. Cardiac arrhythmia based on health history (palpitations, feeling a pause between heartbeats, lightheadedness, passing out, shortness of breath, or chest pain.

   Bradycardia and Tachycardia are monitored during every visit to the clinic, using pulse

rate.

ECG will be performed during screening visit and during 8th week of the study. The following are accessed with the ECG.

- Bradycardia <60 beats/min.
- Tachycardia >100 beats/min.
- Atrial Fibrillation - Rapid irregular atrial signal with no real P-waves and irregular ventricular rate.
- Ventricular Fibrillation - Irregular ventricular waveforms.
- Sinus Arrhythmia - Normal beats, but triggered at an irregular interval from 60 to 100 BPM, causing varying R-R interval.
- Missed beats.

5. Chronic kidney disease(moderate and severe renal impairment as calculated by creatinine clearance of <50 mL/min)
6. Hepatic Impairment – Subjects with Child-Pugh Class B and Class C.
   As assessed by

Factor	1 point	2 points	3 points
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Child-Pugh classification	Class A	Class B	Class C
Total points	5-6	7-9	10-15

7. Significant electrolyte abnormalities: Anything outside of the normal range by +/- 20 % will be considered as abnormal.
8. Cholilithiasis (Total bilirubin >2x of normal)
9. Pancreatitis
10. Hepatitis (AST, ALT or Alk Ph, greater than upper limit of normal(ULN), Serum albumin <3.0 g/dL unless prothrombin time is within the normal range)
11. Present cholecystitis
12. Uncontrolled congestive heart failure
13. Known hypersensitivity to the study drug

7.3 Vulnerable Populations

Vulnerable populations will not be targeted for the purpose of the study. However some of the patients that we might see may belong to one or more of the above vulnerable population groups.

7.4 Subject Recruitment and Screening

The subjects will be recruited from the gastroenterology clinical practices at Northshore university hospital, Long island Jewish medical center and Lenox hill hospital. Patients referred to these hospitals will also be approached for recruitment. Potential subjects will be identified from their medical history. If a subject shows interest in participation, then the study will be explained in a private room and medical history collected after the subject signs the consent form.

The following information will be collected.

- Age and gender
- Race and ethnicity
- Height and weight

- Review of symptoms
- Medical history
- Medication history
- Past blood test history and results
- Past gastroenterological tests/ procedures history and findings
- Past surgical history
- Family history
- Social history
- Vitals
- Questionnaire

If the subject qualifies based on the above history and vitals then the following tests will be performed to look at eligibility.

- Blood Glucose
- ECG
- Urine pregnancy test [Only in reproductive age group women with ability to conceive(no Hysterectomy, tubal ligation etc)]

If the subject qualifies based on all the above then the following tests will be performed to look at eligibility.

- Wireless motility capsule
- Hydrogen breath test

If the subject qualifies based on all the above then the subject will be enrolled to get the study medication.

Subjects will be numbered chronologically based on the order they sign the consent form.

7.5 Consent Process

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol).

The process of obtaining informed consent should be documented in the patient source documents.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

- One of the study team members approved by the IRB will be obtaining the consent from the potential subjects.
- Consent will be obtained in a private room(Eg;- Clinic room)
- After explaining the study the subject will be given some time to think about the study and participation and once they are ready will be asked to sign the consent form. If they request more time, they will be sent home with a copy of the consent form to go over and will be approached later for completing the consent process if they are interested.
- All subjects will be questioned about some of the critical points in the study and their understanding of the study will be accessed based on their responses. A questionnaire will be used to assess their understanding of the study.
- An IRB approved consent form will be used in the study.

We might have non English speaking subjects in the study. Phone translational services of the hospital will be used while explaining the study to these patients. The consent forms will not be translated in to any other language.

7.6 Early Withdrawal of Subjects

7.6.1 When and How to Withdraw Subjects

- If the PI feels that continuing the subject in the study is going to be detrimental to the subject's health then the subject will be informed and withdrawn from the study.
- If the subject fails to adhere to the protocol requirements then they will be notified and even after informing if the subject fails to comply with the protocol requirements then the subject will be withdrawn from the study.
- Other safety conditions for subject withdrawal based on safety end points.

- Cardiac Function (Bradycardia (Decreased heart rate) and hypertension) - If the subjects heart rate decreases by more than 20%, and either systolic or diastolic pressures increase by more than 20% during any of the visits when compared to that of the screening visit,

and if the subject is on any other cardiac medication that might have caused this, then the subject will be referred to cardiologist for consultation and dose adjustment. If the change occurred without any concomitant medication then the subject will be removed from the study and will be monitored and treated as per standard of care.

- Cholilithiasis (Gallstones)- Symptoms include severe right upper quadrant abdominal pain , nausea and vomiting, abdominal tenderness, clay colored stools, Jaundice (yellowing of skin and whites of the eye). If this occurs and has been confirmed (with Gallbladder echography), then the subjects will be removed from the study and will be monitored and treated as per standard of care.

- Glucose Metabolism - (Hyperglycemia or hypoglycemia) – Blood glucose will be monitored during every visit. If there is a variation of more than 20% and if the subject is on any other diabetic medication that might have caused this, then the subject will be referred to her endocrinologist for dose adjustment. If the change occurred without any concomitant medication and life style changes then the subject will be removed from the study and will be monitored and treated as per standard of care.

- Acute anaphylactic reactions – If the subjects develops anaphylactic reaction then he/she will be removed from the study and will be monitored and treated as per standard of care.

- Pancreatitis – It is characterized by Upper abdominal pain that radiates into the back; it may be aggravated by eating, especially foods high in fat, Swollen and tender abdomen, Nausea and vomiting, Fever and Increased heart rate. Signs of pancreatitis will be checked for during every visit. If pancreatitis is confirmed then the subjects will be removed from the study and will be monitored and treated as per standard of care.

- Hepatitis – Signs of hepatitis include Loss of appetite, Nausea and vomiting, Diarrhea, Dark-colored urine and pale bowel movements, Stomach pain and Jaundice (yellowing of skin and eyes). Signs of hepatitis will be checked for during every visit. If hepatitis is confirmed then the subjects will be removed from the study and will be monitored and treated as per standard of care.

- Thyroid Function Abnormalities - If there is a variation of more than 20% from the screening visit values of T3, T4, TSH and if the subject is on any other thyroid medication that might have caused this, then the subject will be referred to her endocrinologist for dose adjustment. If the change occurred without any concomitant medication then the subject will be removed from the study and will be monitored and treated as per standard of care.

7.6.2 Data Collection and Follow-up for Withdrawn Subjects

- After withdrawal from the study, effort will be made to collect at least survival data from the subjects for the rest of the duration of the study. At least two modes of communication (email, phone etc) will be used to try to contact subjects who are lost to follow-up to get the survival data.

8 Study Drug/Device

8.1 Description

SOMATULINE® DEPOT (lanreotide) INJECTION
Initial U.S. Approval: 2007

- It comes as a single use pre filled syringe.

8.2 Treatment Regimen

- Recommended dose is 120mg.
- Subcutaneous injection.
- Location of injection - Superior external quadrant of the buttock. Injection site should be alternated with subsequent injections.
- The total duration of the study is 12 weeks from the first drug administration.
- The last drug administration is on week 8 from the first drug administration.(Total of 3 administrations 4 weeks apart)
- All participants will be taken off of the study medication at the study completion.

8.3 Method for Assigning Subjects to Treatment Groups

Not applicable as everyone who qualifies and willing to participate will be given treatment.

8.4 Preparation and Administration of Study Drug/Implantation of Study Device

There is no preparation required for the drug. The medication comes in pre-filled syringes.

After consenting and if the subject qualifies, study drug will be administered subcutaneously in the superior external quadrant of the buttock. This will be performed in a private room under the guidance of the research staff (eg: Clinic room). The injections will be administered by the licensed qualified staff.

8.5 Subject Compliance Monitoring

The medication is a subcutaneous injectable and will be performed in the clinic under the guidance of the research staff. The subjects will be sent a reminder before each of their appointments. The injections will be performed by the licensed qualified staff.

8.6 Prior and Concomitant Therapy

All prior and current medications history will be collected.

The limited published data available indicate that somatostatin analogues may decrease the metabolic clearance of compounds known to be metabolised by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that lanreotide may have this effect, other drugs mainly metabolised by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution.

Cyclosporine bioavailability may be reduced.

Drug interactions observed for octreotide, such as increased bromocriptine bioavailability, should be considered as possible drug interactions for lanreotide.

In clinical studies of acromegalic patients with diabetes, lanreotide treatment generally resulted in improved glucose tolerance. However, blood glucose levels should be monitored at the start of lanreotide treatment or when the dose is altered, and anti-diabetic treatment should be adjusted accordingly.

Due to a potential additive effect of bradycardia inducing drugs, such as beta-blockers with lanreotide, care should be taken when initiating lanreotide treatment.

Prohibited concomitant medications for the entire duration of the study

- Quinidine,
- Terfenadine
- Cyclosporine bioavailability may be reduced (Gengraf, Neoral, or Sandimmune)

Prohibited concomitant medications for at least 1 week prior to Motility testing with wireless motility capsule, or Hydrogen breath testing.

- Prokinetic agents
    - Bethanechol
    - Cisapride
    - Metaclopromide(Reglan®, Maxeran®)
    - Selective serotonin re-uptake inhibitors (SSRI's) (Paroxetine, Fluoxetine)

- Laxatives
- Opiates

Prohibited concomitant medications for at least 3 weeks prior to Hydrogen breath testing.

- Oral Antibiotics

Concomitant medications that may need dose adjustment due to possible effect on concomitant drug metabolism

- Codeine (Codiene clearance decreased, hence dose should be decreased)
- Bromocriptine (Parlodel, Cycloset) (Increases bioavailablity of Bromocrioptine)
- Non Selective Beta Blockers
    - Propranolol
    - Bucindolol
    - Carteolol
    - Carvedilol
    - Labetalol
    - Nadolol
    - Oxprenolol
    - Pindolol
    - Sotalol
    - Timolol
    - Eucommia bark

- Acid suppressive therapy
    - H2 Receptor blockers Cimetidine (Tagamet), Famotidine (Pepcid), Nizatidine (Axid) and Ranitidine (Zantac))
    - Proton Pump Inhibitors ((Nexium), Lansoprazole (Prevacid), Omeprazole (Prilosec, Zegerid), Pantoprazole (Protonix), Rabeprazole (Aciphex) and Dexlansoprazole (Dexilant)
- Antibiotics

Concomitant medications that can be taken any time during the study.

- Probiotics

8.7 Packaging

Lanreotide Autogel and lanreotide PRF are contained in a polypropylene syringe fitted with a stainless steel needle covered by a sheath. Each filled syringe is then inserted into a laminated pouch which is heat sealed.
The lanreotide Autogel syringe includes, in addition, an automatic sharp needle protection system.

The drug will be shipped in boxes of 6 syringes.

8.8 Blinding of Study Drug/Device

Not Applicable.

8.9 Receiving, Storage, Dispensing and Return

8.9.1 Receipt of Drug Supplies/Device

The drug will be shipped from the sponsor to the Lenox Hill pharmacy, NSUH Research pharmacy and LIJ Pharmacy.

Procurement

- Supplier -Ipsen Pharmaceuticals
- Staff responsible for ordering drug(s) – Research Coordinator
- Drug ordering method and form – Through email to the sponsor.

Accountability

Upon receipt of the of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. The designated study staff at Lenox hills, NSUH research pharmacy or LIJ Pharmacy counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator will notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

Treatment Schedule

- Treatment arms and assigned doses including dose calculation - This is unblinded study and every qualifying subject will receive the medication. There is no dose calculation; the medication comes in prefilled 120mg syringes.

- Dose schedules (e.g., loading, maintenance and tapering doses) - Each qualified subject will receive the medication 3 times (once per month).

- Criteria for any dose modifications (i.e., dose escalation and/or reduction) – There is no dose modification

Dose Preparation

- Time frame for a drug request – The drug will be requested by a prescription from the physician emailed to the pharmacist at least 1 day before the actual treatment date.

- The medication comes in prefilled 120mg syringes.

8.9.2 Storage

Study drug will be stored at research facility or research pharmacy at Lenox Hill pharmacy, NSUH Research pharmacy and LIJ Pharmacy in a secured area, under recommended temperature monitored storage conditions (between +2°C and +8°C).

8.9.3 Dispensing of Study Drug/Device

This is non-Randomized study and every subject who signs the consent form and qualifies will get the study medication. Regular study drug/device reconciliation will be performed to document drug assigned; drug consumed, and drug remaining. This reconciliation will be logged on the drug/ reconciliation form, and signed and dated by Lenox Hill pharmacy, NSUH Research pharmacy and LIJ Pharmacy.

Pick-up or Delivery

The drug will be picked up from pharmacy by study coordinators and delivered to locations. The drug will be picked up and kept on ice/cold pack in an ice box and then taken to the location of the drug administration. The drug will be administered either at LIJMC, Lenox hill, 600 northern blvd drive or NSUH (drug collected from NSUH Pharmacy). We expect majority of the drug to be administered at Lenox hill or LIJMC, the other sites are for back up, just in case if patients does not want to or cannot travel for the medication. While transporting the medication from NSUH to 600 Northern blvd, the study staff will collect the medication from the NSUH pharmacy, place it in a Ziploc bag, seal it and place the bag on ice/cold pack in an ice box and deliver it to 600 northern blvd. The usual expected travel time from NSUH to 600 Northern blvd is 5-10 minutes. Upon reaching the destination the medication and the ice/cold pack will be checked to see if everything is in place, that the ice has not melted completely/cold pack has not reached the room temperature and that there is no damage to the medication (change in color, turbidity, and breakage). If any of the above occurs then that medication will not be used and a new medication will be brought from NSUH.

Administration

- Location of injection – Sub-cutaneously in superior external quadrant of the buttock. Injection site should be alternated with subsequent injections.
- The injections will be administered by the licensed qualified staff.

Drug Retrieval

- All the drugs are administered at the site by the qualified personnel. Drug is not given to the patient to take home for self administration.

8.9.4 Return or Destruction of Study Drug/Device

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

9 Study Procedures

LIST OF STUDY PROCEDURES

Consent

Medical and Medication History

Inclusion Exclusion Criteria

Height and weight

Physical exam

Vitals - Heart rate, Blood Pressure, Respiratory rate and SPO2

ECG - ECG will be used to screen patients for cardiac arrhythmia, especially any QT prolongation that might be present.

Questionnaire - PAGI-SYM: This questionnaire is a validated symptom scale, which asks about

the severity of symptoms related to gastrointestinal problem.

Pregnancy test (In Women of reproductive age group**)**

Wireless capsule testing (*During Screening performed if it is not performed as a standard of care in the last 2 months. During Week 12 they are being performed as part of the study*) - The SmartPill wireless motility device will be used to gather data. SmartPill is an ingestible capsule utilizing sensor technology to evaluate GI motility. It can senses and record pH, pressure and temperature data from within the entire GI tract, which are transmitted wirelessly to the SmartPill data recorder. It is superior to existing diagnostic tests for elimination of radiation exposure, minimized patient downtime, and comfort and easiness of the procedure. This device is already FDA approved and has been in use for the evaluation of suspected gastroparesis and chronic constipation since 2007.

Hydrogen breath testing *(*During Screening performed if it is not performed as a standard of care in the last 2 months. During Week 6 and Week 12 they are being performed as part of the study*) - The hydrogen breath test is a test that uses the measurement of hydrogen in the breath to diagnose several conditions that cause gastrointestinal symptoms. In humans, only bacteria - specifically, anaerobic bacteria in the colon - are capable of producing hydrogen. The bacteria produce hydrogen when they are exposed to unabsorbed food, particularly sugars and carbohydrates, but not proteins or fats. Although limited hydrogen is produced from the small amounts of unabsorbed food that normally reach the colon, large amounts of hydrogen may be produced when there is a problem with the digestion or absorption of food in the small intestine, that allows more unabsorbed food to reach the colon.
Large amounts of hydrogen also may be produced when the colon bacteria move back into the small intestine, a condition called bacterial overgrowth of the small bowel. In this latter instance, the bacteria are exposed to unabsorbed food that has not yet had a chance to completely traverse the small intestine to be fully digested and absorbed. Some of the hydrogen produced by the bacteria, whether in the small intestine or the colon, is absorbed into the blood flowing through the wall of the small intestine and colon. The hydrogen-containing blood travels to the lungs where the hydrogen is released and exhaled in the breath where it can be measured.

STUDY LAB TESTS

1. Blood Glucose
2. CBC + HbA1c
3. Cardiac Panel
4. Hepatic function panel
5. Renal Function Panel
6. Thyroid Function Tests
7. Urinalysis (dipstick)

9.1 Visit 1 (Screening)

The following tests/procedures will be performed during this visit

- Consent
- Medical and Medication History
- Inclusion and Exclusion Criteria
- Vitals
- Complete Physical examination
- ECG
- Questionnaire
- Blood Glucose
- Lab evaluations (CBC + HbA1c, Cardiac Panel, Hepatic function panel, Renal Function Panel, and Thyroid Function Tests)
- Urine Pregnancy test

9.2 Visit 2 (-15 Days (±7 days))

- Wireless motility capsule testing - Performed only if the subject did not have a clinically indicated testing within the last 2 months as standard of care
- Hydrogen breath test - Performed only if the subject did not have a clinically indicated testing within the last 2 months as standard of care

If both of these tests are already performed within the last 2 months as per standard of care and the subject can provide the report then they will not be repeated during this visit, and this visit is not required.

9.3 Visit 3 (Day0 (±7 days))

- Short Physical exam
- Medication History
- Vitals
- Questionnaire
- Blood Glucose
- Pregnancy test

& Study drug administration and patient monitoring for at least 30 minutes after drug administration

9.4 Visit 4 (Week 2 (±7 days))

- Medication History
- Vitals
- Blood Glucose
- Adverse event assessment

- Questionnaire

9.5 Visit 5 (Week 4 (±7 days))

- Short Physical exam
- Medication History
- Vitals
- Questionnaire
- Blood Glucose
- Lab evaluations(CBC + HbA1c, Cardiac Panel, Hepatic function panel, Renal Function Panel, and Thyroid Function Tests)
- Pregnancy test

& Study drug administration and patient monitoring for at least 30 minutes after drug administration

9.6 Visit 6 (Week 6 (±7 days))

- Medication History
- Vitals
- Blood Glucose
- Adverse event assessment
- Questionnaire
- Hydrogen breath test

9.7 Visit 7 (Week 8 (±7 days))

- Short Physical exam
- Medication History
- Blood Glucose
- ECG
- Vitals
- Adverse event assessment
- Questionnaire
- Pregnancy test

& Study drug administration and patient monitoring for at least 30 minutes after drug administration

9.8 Visit 8 (Week 12 (±7 days))

- Medication History
- Vitals

- Adverse event assessment
- Questionnaire
- Urine analysis
- Lab evaluations (CBC + HbA1c, Cardiac Panel, Hepatic function panel, Renal Function Panel, and Thyroid Function Tests)
- Hydrogen Breath testing
- Wireless motility capsule testing

Risks to Subjects

Known side effects of lanreotide.

mild to moderate pain, itching or lump at the injection

Very Common (more than 10% of patients)

Diarrhea,

Abdominal pain,

Nausea,

Dizziness

Fairly common

Bradycardia (Mean heart rate decreased by 4 beats per minute in 7.1% of acromegalic patients)

Cholilithiasis (With double the suggested dose, gall stones were observed in 12.5% of normal control patients)

Known side effects of Octreotide.

Most frequent adverse effects (more than 10% of patients)

Headache,

Hypothyroidism,

Cardiac conduction changes,

Gastrointestinal reactions (including cramps, nausea/vomiting and diarrhoea or constipation),

Gallstones,

Reduction of insulin release,

Hyperglycemia

Symptoms include Increased thirst, Headaches, Trouble concentrating, Blurred

vision, Frequent peeing, Fatigue (weak, tired feeling), Weight loss.

Hypoglycemia

Symptoms include Shakiness, Nervousness or anxiety, Sweating, chills and clamminess, Irritability or impatience, Confusion, including delirium, Rapid/fast heartbeat, Lightheadedness or dizziness, Hunger and nausea, Sleepiness, Blurred/impaired vision, Tingling or numbness in the lips or tongue, Headaches, Weakness or fatigue, Anger, stubbornness, or sadness, Lack of coordination, Nightmares or crying out during sleep and Seizures. Subjects will be advised to carry with them at all times hard candies, jellybeans, or gumdrops and consume them if any of the above symptoms occur.

Transient injection site reactions

Adverse effects (more than 1%)

Slow heart rate,

Skin reactions such as pruritus,

Hyperbilirubinemia,

Dizziness and

Dyspnoea

Rare side effects include

Acute anaphylactic reactions,

Pancreatitis and

Hepatitis.

One study reported a possible association with rheumatoid arthritis, some studies reported alopecia, Rats which were treated by octreotide experienced erectile dysfunction.

During every visit after the initiation of the treatment the subjects will be assessed for any of these side effects.

10 Potential Benefit to Subjects

The potential benefit for the subject is the decreased frequency of administration, compared to the current treatment and hence increased compliance and better control of the disease.

11 Research Related Harm/Injury

All the three hospitals participating in this study are tertiary care centers with the ability to

diagnose and treat various medical conditions. If a complication arises, then subjects will be withdrawn from the study and appropriate care will be given as per standard of care.

The expenses of the research related harm/injury will be covered either by the research participant or their insurance company.

12 Provisions to Protect Privacy Interests of Subjects

Potential subjects will be identified from their medical records and the investigators practice by the investigators or the study team. Other physicians in the department will be notified about the study and refer their patients if they fell that the patient might benefit from participating in the study. All the discussions with the patient will be performed in a private room by the research staff. All email communication with the subjects will be through secure Northwell health system email server.

13 Statistical Plan

13.1 Sample Size Determination

This is a pilot study and there is no preliminary data available to calculate the sample size for this study.

13.2 Statistical Methods

Summary statistics (mean, SD, frequencies, and percentages) will be presented for demographic variables.

Wireless motility capsule parameters such as Small bowel transit time, gastric transit time, colonic transit time, whole gut transit time, contractions/minute, amplitude, and motility index will be compared pre and post intervention using paired Student's t-test. When the variables are extremely skewed (i.e. when the required assumption of normality of the paired differences is violated), the appropriate nonparametric test, Wilcoxon signed rank test, will be used instead, and medians will be reported.

Hydrogen breath test parameters such as hydrogen concentration (ppm) and Methane concentration (ppm) in the breath will be compared for pre and post intervention using repeated measures ANOVA to determine if there is any change in the bacterial overgrowth after intervention. If the standard model assumptions are not met then data transformations will be explored.

PAGI-SYM Questionnaire – This questionnaire uses a 6-point Likert scale, ranging from 0

(none/absent) to 5 (very severe) for various gastrointestinal symptoms. 20 items and 6 subscales covering heartburn/regurgitation (7 items), nausea/vomiting (3 items), post-prandial fullness/early satiety (4 items), bloating (2 items), upper abdominal pain (2 items), and lower abdominal pain (2 items). Mean of the items in each subscale will be compared pre and post intervention using repeated measures ANOVA. If the standard model assumptions are not met then data transformations will be explored. The half-scale rule will be applied for missing data (i.e., the subscale score is calculated using the mean of non-missing items; when more than 50% of items are missing, the score will be set to missing). The total score is calculated by taking the mean of the subscales. If a subscale score is missing, the PAGI-SYM total score will be set to missing.

Based on the limited sample size, instead of performing regression analysis, sub-group analysis will be applied by age, gender or any confounding variables.

13.3 Subject Population(s) for Analysis

Not Applicable

14 Safety and Adverse Events

14.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity

- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

14.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

14.3 Reporting of Serious Adverse Events

14.3.1 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB according to their policies. Copies of each report and

documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator's binder.

14.3.2 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

14.4 Unblinding Procedures

Not applicable as this is not a blinded study.

14.5 Stopping Rules

Study drug must be discontinued and the patient withdrawn from the trial if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances **require** study drug discontinuation: **Please look at early withdrawal of subjects section.**

14.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 17 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

14.7 Data and Safety Monitoring

14.7.1 Data and Safety Monitoring Plan

The Dr. Miller is responsible for evaluating and monitoring the data. Data will be assessed after

every 10 patients that receive the investigational medication.

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The data that is being captured under the monitoring plan includes – Heart rate, Cholilithiasis, Blood glucose, Anaphylactic reactions, Pancreatitis, Hepatitis and thyroid function abnormalities. Serious adverse events will be reported within 24 hours to the data and safety monitor. Non-serious adverse events and non-serious unanticipated problems will be reported after every 10 patients.

Please refer to the stopping rules in the section 7.6.1 titled when and how to withdraw subjects.

15 Data Handling and Record Keeping

15.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

15.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete,

microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

15.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

15.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

ClinicalTrials.gov Registration
A description of this clinical trial will be available on http://www.Clinical Trials.gov , as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

16 Study Monitoring, Auditing, and Inspecting

16.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

16.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups

of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

17 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment ___ for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

18 Study Finances

18.1 Funding Source

This study is financed through a grant from Ipsen Biopharmaceuticals. There are no additional foreseeable costs to the subject due to his/her participation in the study, other than their normal standard of care costs.

18.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-

sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All North Shore-LIJ Health System investigators will follow the University conflict of interest policy.

18.3 Subject Stipends or Payments

Subjects will be paid $50 during each of their visits of Day 0, Weeks 2, 4, 6, 8, and 12 for total of $300.

19 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

The results of the study might be published in scientific journals, abstracts and or conferences. However no personal information will be disclosed in these publications.

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