Efficacy of liraglutide therapy in patients with an ileal -pouch anal anastomosis (IPAA) and chronic high bowel frequency

Investigator-sponsored Study

Universal Trial Number (UTN): U1111-1252-6589

NCT 04763564

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BACKGROUND

Ulcerative colitis (UC) is a chronic inflammatory gastrointestinal disorder, which is limited to the colon and characterized by the involvement of the mucosa only (in contrast to the transmural inflammation seen in CD). UC affects approximately 500.000 Americans, most of them being primarily young adults (20 - 40 years) but the disease may present at a very early age (5-10 years) or later in life (>60 years).[1-3] The inflammatory process in UC is primarily localized to the rectum (proctitis) or can extend proximally in a contiguous manner involving the mucosa up to the splenic flexure (left sided colitis) or involving the entire colon (extensive colitis). The key clinical feature is bloody diarrhea. Approximately 20-35% of patients with UC eventually undergo colectomy, which is most frequently performed in conjunction with ileal pouch-anal anastomosis (IPAA, Figure 1) due to a refractory course of UC or histological proven dysplasia.[4-6] The ileal pouch serves as a reservoir for the stool and improves functional outcomes following IPAA. While colectomy is often depicted as a curative surgery for UC,[7] multiple short- and long-term complications can occur, including pouchitis, which occurs in 40% of patients within the first year after IPAA creation.[8] Up to 80% of patients will report pouchitis symptoms at some point after IPAA,[9] with 19% of patients developing a recurrent form of pouchitis.[10] Despite a preoperative diagnosis of UC or indeterminate colitis (IC), an estimated 10% of patients will be diagnosed with a Crohn's-like disease (CLD) of the pouch after IPAA.[11] Epidemiologic studies to better define the pouch population are currently underway (headed by Edward Barnes at the University of North Carolina). It is estimated that approximately 50.000 – 100.000 patients live with a pouch in the US and 100.000-150.000 in Europe. Thus, the pouch and its associated medical problems, according to the FDA, can be defined as an orphan disease.

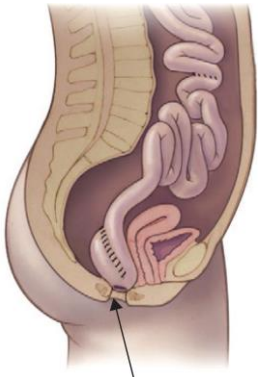

Figure 1:
Ileal pouch-anal anastomosis

POUCH PATIENTS AND THE PROBLEM OF BOWEL FREQUENCY

Increased bowel frequency interfering with daily activities presents a significant clinical problem for many pouch patients. Patients with a pouch typically have 4-8 bowel movements over 24 hours.[12, 13] However, a group of patients have a higher baseline bowel frequency in the range of 8-14 or higher bowel movements in a 24 hour period including increased nightly bowel frequency, incontinence and leakage, which significantly impacts their work and social life due to impaired sleep and need to alter the mealtimes.[14, 15] The reasons for a higher bowel frequency in patients with an otherwise not significantly inflamed pouch are thought to be due to hypermotility or pouch dysmotility. Thus far, no unique pathomechanism has been identified. Many patients report bowel movements which occur shortly after even small meals or especially after meals with a higher fat content. Currently, there are very limited medical options such as loperamide or anticholinergic drugs (dicyclomine) to control frequent bowel movements.

However, many patients do not respond to even extremely high doses of these medications or experience intolerable side effects (such as dry mouth or heart palpitations) while being on anticholinergic medications.

EFFECTS OF GUCAGON -LIKE PEPTIDES (GLP'S) ON GASTROINTESTINAL TRANSIT TIME AND BOWEL FREQUENCY

GLP-1 and GLP-2 belong to the group of incretins and are pleiotropic hormones that not only affect glucose metabolism (GLP-1) but also play a role in the regulation of gastrointestinal motility (GLP-1, GLP-2) and intestinal regeneration (GLP-2).[16, 17] Other effects on intestinal biology such as impact on bile acid metabolism, anti-inflammatory properties or effects on the intestinal microbiome are currently debated.[18-20] GLP-1 prolongs gastric duodenal emptying and decreases gastrointestinal motility, whereas GLP-2 exerts a potential effect in intestinal weight gain, mucosal development, and intestinal integrity.[18, 21] GLP- 1 and GLP-2 are simultaneously produced via posttranslational processing of proglucagon and are secreted by intestinal enteroendocrine L-cells after contact with ingested nutrients. Additionally, GLP-1 secretion occurs by α cells in the pancreas. L-cells are predominantly located in the distal ileum and colon. Absence or a decrease of these enteroendocrine cells leads to lower GLP-1 levels as well as lower levels of other incretins such as GLP-2 as shown in patients, who underwent colectomy and had a pouch or an ileo- or jeunostomys.[22-24] GLP-1 plasma levels increase especially after high fat meals in healthy volunteers, but only partially increase in patients with ileostomy with less than 5 cm of terminal ileum resected (see Figure 2 from paper by Robertson et al. Journal of Endocrinology 1999)[23].

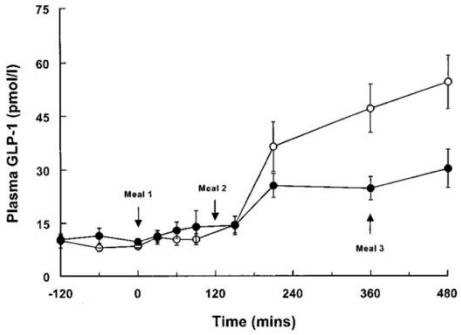

Figure 2: Plasma GLP-1 following a starch-rich test meal and two subsequent high fat carbohydrate-free meals in control (○) and ileostomist (●) subjects. Values are means ± S.E.M., n=6 for both groups.

CLINICAL DATA

So far no threshold for sufficient postprandial GLP-1 levels have been described, but low levels of GLP-1 are associated with rapid small bowel transit in patients with a jejunostomy suggesting a defective neuro-endocrine "ileo-colonic brake" after removal of parts of ileum and/or colon.[25] Application of GLP-1 or GLP-2 restores the transit time and decreases diarrhea and fecal excretions.[25] Whereas the therapeutic efficacy of GLP-2 receptor agonist therapy e.g. with teduglutide for patients with short bowel syndrome is well established, two small studies in patients with ileostomies or short gut syndrome also suggest a clinical beneficial effect of a GLP-1 receptor agonist therapy.[17, 26, 27] The GLP-1 receptor agonist liraglutide significantly reduced ileostomy output in a small group of 8 patients with high ileostomy output.[27] In this study liraglutide reduced ostomy wet weight output by 474 ± 563 g/d from 3249 ± 1352 to 2775 ± 1187

g/d. Interestingly the effects were immediately evident in 3 patients after the start of therapy, whereas 2 patients were even after prolonged therapy non-responders explaining the high standard variation. Exenatide, a short acting GLP-1 receptor agonist, successfully reduced bowel frequency in 5 patients and even enabled 3 patients to discontinue total parenteral nutrition.[26] Again similar to liraglutide the authors of this study report theta the beneficial effects of the exenatide occurred immediately after start of therapy (Table 1 adapted from Kunkel et al. Neurogastroenterol Motil 2011).[26] In addition, a recently published translational study demonstrated the beneficial effects of liraglutide therapy in 2 patients with bile acid malabsorption syndrome.[19] Due to decreased small bowel motility and increased bile acid absorption the bowel frequency normalized to 1-2 bowel movements daily in both patients.

Before exenatide	Immediately after exenatide
Bowel movement within 10 min of eating	Bowel movement 3–6 h after eating
TPN in three patients	No TPN
Malnutrition without TPN in three patients	No malnutrition despite not having TPN
Urine frequency one to two times per day	Urine frequency four to six times per day plus increased volume
Repetitive gastric contractions in three patients	Reduced

TPN, total parenteral nutrition.

Table 1: Effects of exenatide in patients with SBS

Taken together, the data strongly suggest that patients with either increased small intestinal motility due to low GLP-1 levels after removal of the colon or patients with impaired small intestinal absorption of bile acids can be successfully treated by GLP-1 receptor agonists.

RATIONAL FOR STUDY POPULATION

UNMET NEEDS IN POUCH PATIENTS AND RATIONALE FOR A GLP-1 RECEPTOR AGONIST STUDY

Treatment of diarrhea in patients with inflammatory bowel diseases including pouch patients is one of the top 10 research questions for patients and clinicians.[28] The average daily bowel frequency for a pouch patient is around 6 and 1-2 bowel movements during the night.[13] However, frequently patients have > 8 bowel movements in 24 hours in the absence of significant pouch inflammation. This high bowel frequency in many pouch patients may be due to low GLP-1 and GLP-2 levels leading to postprandial accelerated gastric emptying and increased small bowel motility as shown in ileostomy patients.[22-24, 29] The fact that most patients report that they experience urgency and need for immediate evacuation of the pouch 10-20 min after meals point towards the absence of the in the literature described neuroendocrine ileocolonic brake mediated by GLP-1. As outlined above, patients with ileostomies or a pouch have low GLP-1 and GLP-2 levels and GLP-1 as well as GLP-2 receptor agonist therapy can decrease gastric and small intestinal motility as well as stool wet weight output by increasing intestinal absorption.[21, 25-27] The only available GLP-2 receptor agonist teduglutide is exclusively approved for patients with short gut syndrome depending on parenteral support.[30] Currently a therapy with teduglutide outside of this indication would be cost prohibitive due to a price tag > $300.000/year. Given the

overall accepted safety profile and affordability of a GLP-1 receptor agonist, this therapy has the potential to re-establish the neuro-endocrine "brake mechanism", which was abolished due to colectomy. By slowing down the stomach-pouch transit time, increasing wet weight absorption of intestinal contents and decreasing irritant effects of bile acids in the pouch GLP-1 receptor agonist therapy would lead to a higher quality of life for pouch patients with high bowel frequency.

STUDY HYPOTHESIS

Liraglutide is a safe and effective therapy to decrease the number of daily bowel movements in pouch patient with higher than usual bowel frequency.

STUDY AIMS

1. To evaluate the effects of liraglutide on bowel frequency in patients with an ileo-anal pouch anastomosis (IPAA) and abnormal high bowel frequency and no signs of endoscopically moderate-severe inflammation (pouchitis). Increased bowel frequency is defined as an increased average > 8 bowel daily over a 7-day time period.
2. To study safety, tolerability and quality of life in the trial period of liraglutide vs placebo application
3. To collect first data about the efficacy of a liraglutide therapy in patients with an ileo-anal pouch anastomosis (IPAA) and abnormal high bowel frequency in the absence of inflammation for planning a larger phase 3 study in this orphan status patient population

STUDY DESIGN

Randomized, double-blind, 2-period, placebo- controlled, crossover proof of concept study. Ten patients with increased bowel frequency is defined as > 8 bowel daily/week without significant pouchitis* will be randomized to either liraglutide or placebo treatment for 6 weeks (Period 1). Subjects will be randomized 1:1 to 1 of 2 treatment sequences, liraglutide–placebo or placebo–liraglutide, and receive either liraglutide or volume-matched placebo. After a wash-out period of at least 5 days (the half-life of liraglutide is 11-12 hours, thus the minimal washout period of 5 days is equal to 10 half-life's) patients will be crossed over to the other treatment arm (Period 2). Since high bowel frequency can result in significant malaise and dehydration, patients not responding to the respective therapies in period 1 may be crossed over after 4 weeks of therapy or in period 2 can be terminated early at week 4. The rationale behind the early termination is based on 2 open label cohorts reporting the efficacy of liraglutide or exenatide in patients with high output ileostomies (the patient group the most comparable to the pouch patient population). GLP-1 receptor agonist therapy even at the lowest dose showed an almost immediate effect reducing the ostomy output after 1-3 days in most patients.[26, 27] Thus, patients not responding to a 4-week therapy with a GLP-1receptor agonist are highly unlikely to respond if the therapy would be continued.

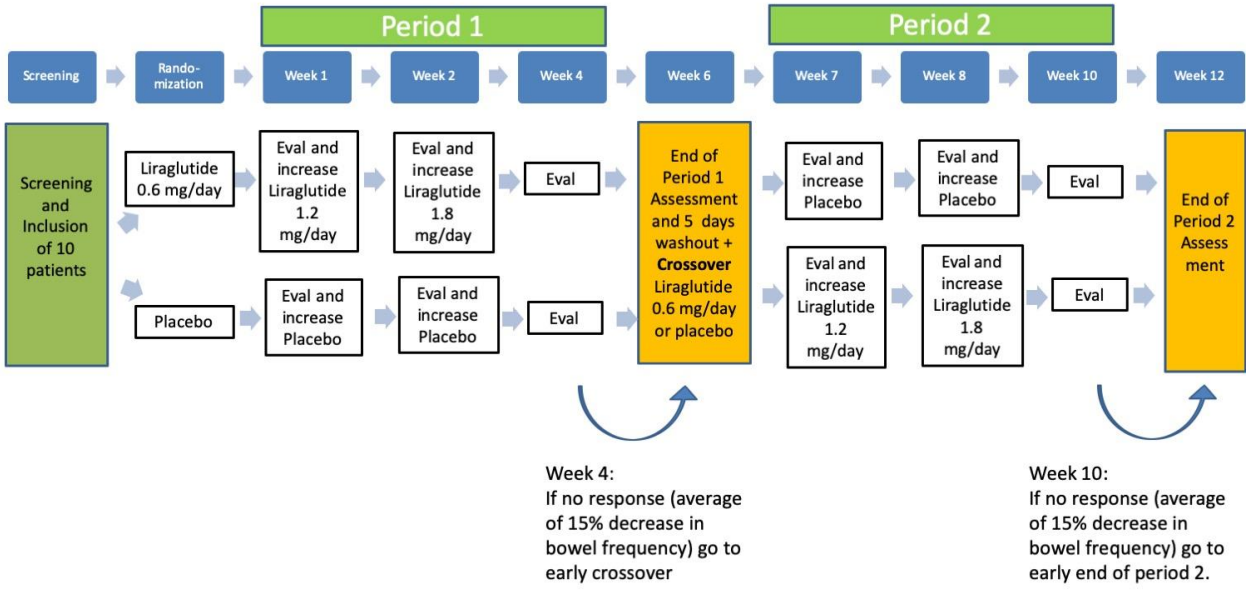

Figure 3: Study design

Randomization: Subjects will be randomized 1:1 to 1 of 2 treatment sequences, liraglutide–placebo or placebo–liraglutide, and receive either liraglutide or volume-matched placebo.

* While there is an ongoing debate about potential anti-inflammatory effects of GLP-1 receptor agonists (reviewed in [18]), we prefer to have a well-defined patient population with endoscopically low inflammatory load (endoscopic pouch disease activity index < 4 in pre-pouch and pouch, only mild cuffitis). However, we will monitor intestinal inflammation using calprotectin levels. We anticipate that some patients will have higher calprotectin levels but still low endoscopic inflammation and potential effects of GLP-1 receptor agonist therapy on inflammation will be captured with this biomarker.

STUDY DRUG, SUPPLY OF STUDY DRUG AND RECRUITMENT PLAN

Hvistendahl et al. described a significant decrease of fecal wet weight in ileostomy patients treated with liraglutide.[27] Based on this study and the fact that a longer acting GLP-1 receptor agonist such as semaglutide would also have a longer washout period in the setting of a crossover study, we have chosen the short acting liraglutide (Victoza®). A washout period between the two-treatment periods is required in crossover trials and a prolonged crossover period without any treatment intervention makes such a study design in a patient population with a significant clinical burden (high bowel frequency, incontinence) not feasible. Liraglutide has half-life of 11-12 hours compared to e.g. semaglutide with a half-life of 165 hours. With a washout period of at least 5 days between treatments, we do not expect any carry over effects.

Liraglutide (Victoza®) or placebo will be supplied by Novo Nordisk A/S and dispensed by the UNC investigational pharmacy. The liraglutide or placebo solution for subcutaneous injection will be delivered as blinded pre-filled, multi-dose pens that deliver doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL cartridge). In order to blind the product, a clinic variant of the marketed product is supplied. The clinic variant of the 3 ml cartridge is produced with an army green closure cap compared to a light blue closure cap in the marketed Victoza® product. The push button and cartridge holder are light brown, while the marketed pen-injector has a light blue push button and cartridge holder. Neither closure cap nor the pen is in contact with the product and the differences in colors have no impact on the stability of the product. The investigator will ensure the availability of proper storage conditions, and record and evaluate the temperature. The dose escalation and administration of liraglutide therapy will be performed according to the current FDA approved prescribing information to improve glycemic control in adults with type 2 diabetes. A Directions for Use (DFU) for the device will be provided by Novo Nordisk A/S. It will be handed out to subject at first dispensing visit and the subject must be trained according to DFU. Liraglutide will be administered once daily independently of meal. The patient will choose the optimal administration time (morning, midday, evening) and will continue with this timing throughout the study. Liraglutide will be injected subcutaneously in the abdomen, thigh or upper arm according to the DFU. The patient will be instructed by the investigator how to use the pen using the DFU provided by Novo Nordisk A/S. Treatment will be initiated at 0.6 mg per day for one week. The patient will be instructed to increase the dose to 1.2/day and 1.8 mg /day in week 2 and in week 3, respectively. From week 3 after start of drug until week 6 (or week 8-12 in period 2 depending on randomization) the patient will apply 1.8 mg/day liraglutide. In case of intolerance (e.g. occurrence of refractory nausea) at a higher dose (e.g. 1.8 mg daily, the highest dose in this trial) liraglutide can be reduced to the previous level.

LIRAGLUTIDE AND TACHYPHYLAXIS

So far extent of tachyphylaxis of the effects of liraglutide on gastric emptying are inconclusive or not well defined. Liraglutide (1·2 mg, 1·8 mg, or 3·0 mg daily) delays 1-h gastric emptying, as measured by the plasma acetaminophen method (which reflects predominantly the gastric emptying of liquids, not solids) compared with placebo.[31-34] However, tachyphylaxis of the delay of gastric emptying seems to occur over time but the extent is not clear. For liraglutide 3.0 mg daily one study reports complete tachyphylaxis for delay in gastric emptying based on the plasma acetaminophen method after 5 weeks whereas another study, using a scintigraphy method for gastric emptying which includes the emptying of solid food describes partial tachyphylaxis but still significant efficacy compared to placebo after 16 weeks of therapy.[32, 34] All studies so far have been performed in patients with an intact GI-tract. The question remains if tachyphylaxis occur in patients with low GLP-1 levels and potentially upregulated GLP-1 receptors in the absence of

a colon. In the only available 2 studies analyzing the effects of liraglutide or exenatide on jejunostomy output no tachyphylaxis was reported after 8 weeks(liraglutide) or 1 year (exenatide) of therapy.[26, 27]

RECRUITMENT PLAN

We estimate to screen 20 - 25 pouch patients/month and randomize 1 patient/month. We expect that all patients will complete the study after randomization. Under the direction of Dr. Hans Herfarth, the University of North Carolina has a Multidisciplinary Pouch Clinic that involves gastroenterology and surgery care for pouch-related disorders. We follow approximately 450 patients from throughout the southeast region of the United States that are treated regularly in our clinic.

STUDY MILESTONES

Months	1-4	4-16	16-22
Activities	Start-up of trial IRB IND/FDA	Recruitment	Follow-up last patients Analysis of clinical data

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

- Informed consent will be obtained before any trial-related procedures
- Age > 18 years
- Patients with IPAA and bowel frequency > 8 bowel movements in 24 hours on at least 4 of 7 days/week and presence of high bowel frequency > 4 weeks despite adequate therapy for acute pouchitis or Crohn's like disease of the pouch

EXCLUSION CRITERIA

- Significant pouch inflammation defined as an endoscopic pouch disease activity index (PDAI) ≥ 4
- Known clinically significant obstructive stricture of the ileo-anal anastomosis or afferent limb
- New onset of high bowel frequency in the setting of acute pouchitis
- IPAA since < 6 months
- Known Clostridium difficile pouchitis
- Known clinically significant chronic nausea and/or vomiting in the past

- Known type 1 or type 2 diabetes
- History of or active neoplasia
- Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2
- Renal impairment defined as glomerular filtration rate (GFR < 30))
- Clinically significant decompensated liver disease defined as elevation of AST, ALT or bilirubin > 2-fold the upper limit of normal (Primary Sclerosing Cholangitis with LFT's <1.5 upper limit of normal can be included)
- New York Heart Association class 3 or greater heart failure or recent (within 6 months) cardiovascular event
- Prior history of pancreatitis
- Prior treatment with a GLP-1RA
- Known hypersensitivity to liraglutide or any product components
- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method. *NOTE: this includes two forms of barrier contraception (e.g. condoms and foam; e.g. condoms and diaphragm); long-acting reversible contraception (e.g. subdermal contraceptive implant, intrauterine device, contraceptive injections), and oral contraceptive pills*
  NOTE: Non-childbearing potential is defined as postmenopausal for at least 1 year or surgically sterile, meaning your ovaries and/or uterus have been removed (bilateral oophorectomy and/or hysterectomy)
- Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening.
- Any disorder, which in the investigator's opinion might jeopardize patient's safety or compliance with the protocol.

ALLOWED CONCOMITANT MEDICATIONS

- Biologics to treat Crohn's disease like disease of the pouch
- Antibiotics to treat antibiotic dependent pouchitis (Antibiotics should be stable 2 weeks before start of study medication and kept stable or can be stopped and if needed be restarted at the same dose or lower during the study)
- Anti-diarrheal medication (e.g. loperamide) should be kept stable. Changes in the dosage will be documented in patient's diary.

Following drug groups are **not** permitted as concomitant medication:

- New start of biologics, antibiotics, steroids, anti-motility therapies (e.g. hyoscyamine, loperamide, atropine)

- Non - steroidal anti-inflammatories (NSAIDs) as long-term treatment, defined as use for at least 4 days a week each month

STUDY OUTCOMES

PRIMARY OUTCOME

- Reduction of the mean of the 7-daily bowel frequency by 30% in week 4 and week 10.

SECONDARY OUTCOME

- Safety and Tolerability of GLP-1
    - Number of study patients, who discontinued therapy
    - Adverse events grouped by body system
    - Changes in laboratory values
    - Changes in nausea, appetite, abdominal pain and well being
- Change in bowel frequency during day (patient is awake from morning until bedtime) and during night (patient is asleep and has to get up because he has a bowel movement) comparing screening period to week 1, week 2, week 3 and week 4 during active treatment with liraglutide or placebo in period 1 or in period 2 (week 7, 8, 9 and 10).
- Change in clinical PDAI week 0 and week 4 and week 10

EXPLORATORY OUTCOMES

- Change in stool calprotectin from baseline
- Change in SF-36
- Change in PROMIS measures
- Change in PROBE score
- Change in body weight and experience of nausea, decreased appetite or increased abdominal pain
- Change in PDAI at week 6 or week 12 in patients responding to liraglutide therapy
- Change in bowel frequency during day (patient is awake from morning until bedtime) and during night (patient is asleep and has to get up because he has a bowel movement) comparing screening period to week 5 and 6 in period 1 or 11 or week 11 and 12 in period 2.

ASSESSMENTS/INDICES

In regard to when the assessments are performed please also refer to study visits and table study visits and assessments.

- Patient diary (performed daily): Bowel frequency during the day (6 am-6 pm) and night (6 pm -6 am) and recording of bowel movement consistency (liquid, pasty or formed)[14]
- Patient diary (performed daily): Timing of bowel movement in relation to meals (within 15 min, 30 min or >30 min)
- Modified pouch disease activity index (mPDAI)[35]

  The Pouchitis Disease Activity Index (PDAI) was developed by Sandborn et al for diagnosing active pouchitis and quantifying the severity of pouchitis [36]. Shen et al. later on modified the index (mPDAI) and showed that similar outcomes can be measured after omitting the evaluation of histology, thus omitting the biopsy and histology costs.[35] The PDAI or the modified PDAI has been used in a number of clinical studies where it appears quite useful in discriminating between subjects with and without pouchitis and in quantifying the severity of pouchitis [37-45] The mPDAI will be evaluated based at screening, week0,2,4,6,7,8,10,12.

- Stool calprotectin (assessment of pouch inflammation over time)

  Calprotectin, a member of the S100 family of calcium-binding proteins is abundant in the stool and its level correlates with the endoscopic degree of intestinal inflammation in patients with ulcerative colitis and pouchitis. [46, 47] Calprotectin can be quantified in feces using enzyme-linked immunosorbent assay (ELISA) or an immunoassay. We will collect stool samples for the measurement of calprotectin at the screening visit and on weeks 2,4,6,8,10,12.
- 36-Item Short Form Health Survey (SF-36)

  The SF-36 will be evaluated at screening, week 2,4,6,8,10 and 12.
- PROMIS measures for incontinence[48]

  The GI-PROMIS scales belong to the PROMIS system, which was created by the National Institutes of Health (NIH) to allow efficient, online measurements of patient reported outcomes and correlate with other established quality of life measures.[48, 49] The PROMIS scale for incontinence will be evaluated at screening, week 2,4,6,8,10 and 12.
- PROBE score[50]

  PROBE assesses the psychosocial burden of IBD and has been recently validated.[50] PROBE will be evaluated at screening, week 2,4,6,8,10 and 12.
- Body weight and visual analogue scales for nausea, appetite, abdominal pain and well being[25] Body weight will be evaluated at screening and on weeks 4,6,10,12.

OVERVIEW OF TRIAL SEQUENCE

Screening visit (site visit): The trial will begin with the **screening visit (days -14 to -10).** The investigator will ask patients who are interested in participating in the study after a careful explanation, to sign an informed consent form prior to study specific examinations. The study patient will receive a copy of the consent form, which outlines the sequence of events in brief and summarizes the advantages and disadvantages of participation in the study.

After the patient has given his/her written consent, the screening examination will be performed to evaluate whether the patient is probably eligible for the study.

The coordinator and PI will take a complete history will be taken including concomitant medication and demographic data will be collected. If subject is a woman of child-bearing potential, a reliably and highly effective contraceptive method will be confirmed. A physical examination will be performed, and vital signs will be documented. Blood samples (max. 20 ml) will be taken from the study patient (all study patients: Haematology, serum chemistry, creatinine, CRP (female study patients: urine samples for pregnancy test). Also the study patient will be provided with a stool collection kit to provide a stool sample, which should be collected at this visit or before the week 0 visit. This stool kit will also contain a sample kit for C. difficile toxin. The study patient will also be provided with an access password to a web based a diary, which he/she will be asked to complete the diary every day in the evening during the trial. The study patient will also undergo a pouchoscopy as standard of care for evaluation of the pouch inflammation as the reason for the high bowel frequency and to rule out complications in the pouch structure (e.g. strictures, isolated cuffitis, which would lead to exclusion of the trial).

After the screening visit the patient will also start a daily electronic diary to assess the average weekly bowel frequency. Before week 0 at least 7 days of bowel frequency data need to be available to assess baseline bowel frequency.

Visit week 0 (site visit): The study patient will have a physical exam and a urine pregnancy test. If subject is a woman of child-bearing potential, a reliably and highly effective contraceptive method will be confirmed. The patient's AE and symptom diary will be reviewed and the clinically modified PDAI calculated. The patient's concomitant medications will be reviewed. If the study patient fulfils all inclusion criteria and does not have an exclusion criterion the study patient will be randomized to either the placebo or the liraglutide group and a unique study ID number will be assigned, which will appear on all medication packs, which will be containing treatment until week 6 period 1. A glucometer, supplies, and instructions for use will be provided as well as a review of signs and symptoms of hypoglycemia, plus a review of hypoglycemic protocol and reporting form.

Visits week 1 and 2 (phone visits): The coordinator will ask the study patient if adverse events occurred and will review the adverse event diary with the study patient. The coordinator will also evaluate the web registered clinical components of the mPDAI of the last 3 days before the phone call (stool frequency, rectal bleeding, fecal urgency/ abdominal cramping, fever) as well as the concomitant medications. At visit week 1 and 2 the patient will be asked to collect/send in a stool sample for the next (in person or as mail in collected days -2 - +2 around the visit date). There will also be a review of glucose diary and hypoglycemic protocol and reporting form. If subject is a woman of child-bearing potential, a reliably and highly effective contraceptive method will be confirmed.

Visit week 4 (site visit): The coordinator will review the adverse events, which occurred since the previous visit. A physical exam and blood tests will be performed and the mPDAI will be calculated. The concomitant medications will be assessed. If subject is a woman of child-bearing potential, a reliably and highly effective contraceptive method will be confirmed. A stool sample will be collected from the patient either at visit or days -2 - +2 around the study visit or as mail in. Instructions to either mail in or provide in person stool sample at visit week 6 period 1. In case of early crossover female patients will provide urine samples for pregnancy test at week 4. There will also be a review of glucose diary and hypoglycemic protocol and reporting form.

If at visit week 4 the bowel frequency of the patient did not respond to treatment (at least a 15% decrease compared to baseline the patient can proceed to early crossover. The patient will be given study drug (either the placebo or the liraglutide group) in medication packs with his unique study ID medication packs, which will be containing treatment until week 12 and be instructed to bring back the study medication from study period 1 at the final visit of period 2 (week 12). He will be instructed to start injections on day 6 after 5 days of washout. The day he starts will be defined as week 6 period 2.

Visit week 6 period 1 (site visit): If the patient did not qualify for early crossover, he will come to visit week 6 period 1 the coordinator will review the adverse events, which occurred since the previous visit. A physical exam and blood tests will be performed and the mPDAI will be calculated. The concomitant medications will be assessed. If subject is a woman of child-bearing potential, a reliably and highly effective contraceptive method will be confirmed. A stool sample will be collected from the patient either at visit or days -2 - +2 around the study visit as mail in. Female patients will provide urine samples for pregnancy test at week 6 period 1. The patient will be given either the placebo or the liraglutide group with his unique study ID for period 2 and will be instructed to start injections on day 6 after 5 days of washout. The day he starts will be defined as week 6 period 2. The patients will be also be instructed to bring back the study medication from study period 1 at the final visit of period 2 (week 12). There will also be a review of glucose diary and hypoglycemic protocol and reporting form.

Visits week 7 and 8 (phone visits): The coordinator will ask the study patient if adverse events occurred and will review the adverse event diary with the study patient. The coordinator will also evaluate the web registered clinical components of the mPDAI of the last 3 days before the phone call (stool frequency, rectal bleeding, fecal urgency/ abdominal cramping, fever) as well as the concomitant medications. At visit week 7 and 8 the patient will be asked to send in a stool sample for visit week the next visit (in person or as mail in collected days -2 - +2 around the visit date). There will also be a review of glucose diary and hypoglycemic protocol and reporting form. If subject is a woman of child-bearing potential, a reliably and highly effective contraceptive method will be confirmed.

Visit week 10 (site visit): The coordinator will review the adverse events, which occurred since the previous visit. A physical exam and blood tests will be performed and the mPDAI will be

calculated. The concomitant medications will be assessed. If subject is a woman of child-bearing potential, a reliable and highly effective contraceptive method will be confirmed and they will provide urine samples for pregnancy test at week 10. A stool sample will be collected from the patient either at visit or days -2 - +2 around the study visit or as mail in. Instructions to either mail in or provide in person stool sample at visit week 12. There will also be a review of glucose diary and hypoglycemic protocol and reporting form.

If at visit week 10 the bowel frequency of the patient did not respond to treatment (at least a 15% decrease compared to baseline this visit will be classified as end of treatment (week 12). If the patient meets the criteria of non-response, he/she will be instructed to bring back all medication of study period 1 and 2 to a follow-up visit at week 12. The patients who were responders at week 10 and finished the trial at week 12 will be informed about follow-up visit 2 weeks later (week 14).

Visit week 12 (site visit): the coordinator will review the adverse events, which occurred since the previous visit. A physical exam and blood tests will be performed and the mPDAI will be calculated. The concomitant medications will be assessed. If subject is a woman of child-bearing potential, a reliable and highly effective contraceptive method will be confirmed and they will provide urine samples for pregnancy test at Week 12. A stool sample will be collected from the patient either at visit or days -2 - +2 around the study visit or as mail in. All study medications from period 1 will be collected to assess compliance. All patients who completed visit week 12 and the full treatment period 2 patient will be informed about follow- up visit 2 weeks later (week 14). There will also be a review of glucose diary and hypoglycemic protocol and reporting form.

For all non-responders at week 10, week 12 will be the final follow-up visit in person to collect all study medications from period 1 and 2 to assess compliance.

Week 14 (phone visit): The coordinator will call the patients, who finished the trial at week 12 (responders week 10) and will assess changes in concomitant medication and occurrence of new adverse events since last week.

STUDY VISITS

SCREENING VISIT

Data to be recorded:

- General parameters:
- Initials
- Date of birth
- Sex
- Smoker (yes/no/ex-smoker)
- Race (NIH categories)
- Ethnicity (NIH categories)

Case history

- Date of confirmation of the diagnosis
- Classification of UC before IPAA (proctitis, left sided colitis, pancolitis)
- Type of extraintestinal symptoms
- Specific therapies for pouchitis within the last year
- Type of medication
- Specific therapies for pouchitis within the last 4 weeks
- Type of medication

Examinations

- Vital signs: blood pressure (mm Hg), heart rate (min^{-1}), weight (kg), calculation of BMI, temperature
- Height (cm)
- Physical examination:

- Head (including ENT and eyes)
- Lymphatic system
- Endocrine system
- Lungs and respiratory tract
- Peripheral vascular system
- Cardiovascular system
- Gastrointestinal tract, liver, spleen
- Urogenital system
- Nervous system
- Muscular and skeletal system
- Skin and connective tissue
- Other

each: actual status: Present finding / normal condition / not examined

Blood sampling and measurement of laboratory parameters

- Labs
- Urine pregnancy test (female)
- Stool sample for C. difficile toxin
- Pouchoscopy (standard of care): Evaluation of endoscopic PDAI.

Formal aspects:

- Informed consent procedure
- Verification of inclusion / exclusion criteria (eligibility check)
- Confirm reliable and highly effective contraceptive method if subject is a woman of child-bearing potential
- Dispense stool collection kit for stool sample period 1
- Explain and distribute stool diary to study patient (at least 7 days of daily bowel frequency are necessary to calculate baseline weekly bowel frequency)

VISIT WEEK 0

Examinations

- Vital signs: blood pressure (mm Hg), heart rate (min-1), weight (kg), temperature
- Physical examination:

- Head (including ENT and eyes)
- Lymphatic system
- Endocrine system
- Lungs and respiratory tract
- Gastrointestinal tract, liver, spleen
- Urogenital system
- Nervous system
- Muscular and skeletal system

- Peripheral vascular system
- Cardiovascular system
- Skin and connective tissue
- Other

each: actual status: Present finding / normal condition / not examined

Blood sampling and measurement of laboratory parameters

- Urine pregnancy test (female patients)
- If no GLP-1 baseline yet at screening, if possible fasting GLP-1 baseline blood draw
- Dispense stool collection kits for stool samples

Formal Aspects:

- Review diary data and calculation of the mPDAI

- Confirm reliable and highly effective contraceptive method if subject is a woman of child-bearing potential

- Verification of inclusion / exclusion criteria (eligibility check)
- Randomization
- Dispensation of glucometer including auxiliary supplies as well as instructions for use, review of glucose diary, review of signs and symptoms of hypoglycemia, review of hypoglycemic protocol and reporting form

VISITS PERIOD 1 WEEK 1 AND 2 (PHONE VISIT; +/- 1 DAY)

Blood sampling and measurement of laboratory parameters

- Check if stool sample was received (Period 1 week 2)

Formal aspects:

- Adverse events (review adverse events diary)
- Review of glucose diary and hypoglycemic protocol and reporting form
- Concomitant medication
- Calculation of clinical mPDAI
- Remind of stool sample collection at Period 1 week 1 for Period 1 week 2 and Period 1 week 2 for Period 1 week 4.
- Confirm reliable and highly effective contraceptive method if subject is a woman of child-bearing potential

VISIT PERIOD 1 WEEK 4: (SITE VISIT; =/- 3 DAYS)

Examinations

- Vital signs: blood pressure (mm Hg), heart rate (min-1), weight (kg), temperature
- Physical examination:
- Head (including ENT and eyes)
- Lymphatic system
- Gastrointestinal tract, liver, spleen
- Urogenital system

- Endocrine system
- Lungs and respiratory tract
- Peripheral vascular system
- Cardiovascular system
- Nervous system
- Muscular and skeletal system
- Skin and connective tissue
- Other

each: actual status: Present finding / normal condition / not examined

Blood sampling and measurement of laboratory parameters

- Labs
- Check if stool sample was received
- In case of early crossover:
    - Urine pregnancy test (female)
    - Dispense stool collection kits for stool samples Period 2

Formal aspects:

- Adverse events (review adverse events diary)
- Confirm reliable and highly effective contraceptive method if subject is a woman of child-bearing potential
- Review of glucose diary and hypoglycemic protocol and reporting form
- Concomitant medication
- Calculation of clinical mPDAI and assess if patient is responder or not (early crossover)
- If patient continues reminder stool Period 1 week 6.
- Early crossover: Dispense study medication for Period 2. Instruct patient to restart study medication on day 6. Instruct to keep study medication from Period 1 and bring back at last visit of Period 2 (week 12) or Period 2 week 10.

VISIT PERIOD 1 WEEK 6: (SITE VISIT; =/- 3 DAYS)

Examinations

- Vital signs: blood pressure (mm Hg), heart rate (min-1), weight (kg), temperature
- Physical examination:
    - Head (including ENT and eyes)
    - Lymphatic system
    - Endocrine system
    - Lungs and respiratory tract
    - Peripheral vascular system
    - Cardiovascular system
    - Gastrointestinal tract, liver, spleen
    - Urogenital system
    - Nervous system
    - Muscular and skeletal system
    - Skin and connective tissue
    - Other

each: actual status: Present finding / normal condition / not examined

Blood sampling and measurement of laboratory parameters

- Labs

- Check if stool sample was received
- Urine pregnancy test (female)

Formal aspects:

- Adverse events (review adverse events diary)
- Confirm reliable and highly effective contraceptive method if subject is a woman of child-bearing potential
- Review of glucose diary and hypoglycemic protocol and reporting form
- Concomitant medication
- Calculation of clinical mPDAI
- Crossover: collect all study medication and dispense study medication for period 2. Instruct patient to restart study medication on day 6.

VISITS PERIOD 2: WEEK 7 AND 8 (PHONE VISIT; +/- 1 DAY)

Blood sampling and measurement of laboratory parameters

- Check if stool sample was received (week 8)

Formal aspects:

- Adverse events (review adverse events diary)
- Review of glucose diary and hypoglycemic protocol and reporting form
- Concomitant medication
- Calculation of clinical mPDAI
- Remind of stool sample collection at Period 2 week 7 for Period 2 week 8 and at Period 2 week 8 for Period 2 week 10
- Confirm reliable and highly effective contraceptive method if subject is a woman of child-bearing potential

VISIT PERIOD 2 WEEK 10: (SITE VISIT; =/- 3 DAYS)

Examinations

- Vital signs: blood pressure (mm Hg), heart rate (min-1), weight (kg), temperature
- Physical examination:

- Head (including ENT and eyes)
- Lymphatic system
- Endocrine system
- Lungs and respiratory tract
- Peripheral vascular system
- Cardiovascular system
- Gastrointestinal tract, liver, spleen
- Urogenital system
- Nervous system
- Muscular and skeletal system
- Skin and connective tissue
- Other

each: actual status: Present finding / normal condition / not examined

Blood sampling and measurement of laboratory parameters

- Labs
- Urine pregnancy test (female)
- Check if stool sample was received

Formal aspects:

- Adverse events (review adverse events diary)
- Confirm reliable and highly effective contraceptive method if subject is a woman of child-bearing potential
- Review of glucose diary and hypoglycemic protocol and reporting form
- Concomitant medication
- Calculation of clinical mPDAI and assess if patient is responder or not (early termination in case of non-responder). If non-responder, patient should stop medication and will be considered early termination
- If patient continues reminder stool week 12.
- Early termination: Remind patient to come to final visit at Period 2 week 12 and bring all study medication of (if not done already from Period 1 and complete from Period 2). For this patient group at visit Period 2 week 12 only adverse events (review adverse events diary) and concomitant medication will be assessed. An alternative approach is a phone visit Period 2 week 12 and patient returns all study medication 2 before Period 2 week 12.

VISIT PERIOD 2 WEEK 12: (SITE VISIT; =/- 3 DAYS)

Examinations

Vital signs: blood pressure (mm Hg), heart rate (min-1), weight (kg), temperature

Physical examination:

- Head (including ENT and eyes)
- Lymphatic system
- Endocrine system
- Lungs and respiratory tract
- Peripheral vascular system
- Cardiovascular system
- Gastrointestinal tract, liver, spleen
- Urogenital system
- Nervous system
- Muscular and skeletal system
- Skin and connective tissue
- Other

each: actual status: Present finding / normal condition / not examined

Blood sampling and measurement of laboratory parameters

- Labs
- Urine pregnancy test (female)
- Check if stool sample was received

Formal aspects:

- Adverse events (review adverse events diary)

- Review of glucose diary and hypoglycemic protocol and reporting form
- Concomitant medication
- Calculation of clinical mPDAI .
- Collect all study medication (Period 1 and 2).
- Confirm reliable and highly effective contraceptive method if subject is a woman of child-bearing potential

For non-responders at Period 2 Week 10 use assessment as outline in Period 2 Week 14, since patient is off study drug for 2 weeks now (only assessment of adverse event and concomitant medication assessment as well as collect all study). Also collect all study medication (period 1 and 2).

VISITS PERIOD 2 WEEK 14 (PHONE VISIT; +/- 3 DAYS)

Formal aspects:

- Adverse events (review adverse events diary)
- Concomitant medication
- Confirm reliable and highly effective contraceptive method if subject is a woman of child-bearing potential

MEASUREMENT OF COMPLIANCE

Compliance will be assessed at the end of period 1 and period 2 by checking the study medication (pens) returned at the follow-up visits and the final visit by the investigator. During the Induction and Maintenance Period all returned pens will be counted by the investigator and the number will be documented in the electronic CRF.

LABORATORY PARAMETERS AND POUCHOSCOPY

All laboratory analyses will be carried out in a central laboratory.

Acute phase reactants (nonspecific inflammatory markers)

- C-reactive protein (CRP)

Hematology:

- Blood count (erythrocytes, hemoglobin, hematocrit, leukocytes, platelets and differential WBC)

Serum chemistry:

- Kidney function: serum urea and creatinine
- Liver function (alanine aminotransferase {ALT}, aspartate aminotransferase {AST}, alkaline phosphatase, bilirubin), albumin
- Other serum parameters (total protein, Na+, K+)

Stool sample for C. diff .toxin

POUCHOSCOPY (SCREENING)

Pouchoscopy will be performed to evaluate the pouch, prepouch ileal segment and the cuff. The pouch and prepouch inflammation will be graded according mPDAI (see attachment). If a pouchoscopy describing prepouch pouch and cuff is available and this pouchoscopy was performed in 6 months previous to screening and a PDAI can be calculated based on the report, no additional pouchoscopy is necessary.

ETHICS

IRB approval for the study will be obtained after the study is funded. The study protocol will be submitted to the UNC IRB and the office of Human research ethics (https://research.unc.edu/human-research-ethics). The study will be conducted in accordance with the Declaration of Helsinki, the ICH GCP guidelines. This study will comply with all applicable regulatory and legal requirements, ICH GCP guidelines and the Declaration of Helsinki in obtaining and documenting the informed consent.

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

DEFINITIONS

ADVERSE EVENT

An adverse reaction is an adverse event for which the causal relationship between the product and the adverse event is suspected i.e. e.g.:

- any new diagnosis
- any symptom that requires medical clarification or leads to in-patient admission (surgery or accident)
- any suspected adverse drug reaction (ADR)
- any symptom that appears on the patient's medical records
- any event related in time with the application of the study medication and affecting the health of the patient (including laboratory value changes)

Adverse events (AEs) will be recorded at each regular scheduled study visit or study phone contact in the patient record (source document) as well as on a specific AE form on the electronic CRF.

SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death

- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an Serious Adverse Event when, based upon appropriate medical judgement, they may jeopardize the patient or subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Suspicion of transmission of infectious agents must always be considered an SAE.

Non-serious adverse events are all AEs that do not fall into any of the above categories.

SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

A suspected unexpected serious adverse reaction (SUSAR) is an SAE which is unexpected and regarded as possibly or probably related to the trial/study product by the investigator

UNEXPECTED ADVERSE DRUG REACTIONS

An unexpected adverse drug reaction (ADR) is an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

EXPECTED ADVERSE DRUG REACTIONS

Liraglutide (Victoza®)is a FDA approved drug for treatment of diabetes and obesity. The protocol uses the current version of US/FDA approved Prescribing Information or any updates hereof for assessment of expectedness. Diarrhea, nausea or vomiting, the more frequent ADR have not been reported to be severe in the available studies in patients treated with a GLP-1 receptor agonist for diarrhea or high ileostomy output. This may be due to pre-existing low GLP-1 levels in this patient population or in case of diarrhea the lack of the colon (ileostomy patients).[19, 26, 27]

Common ADRs caused by liraglutide include the following:

- nausea
- diarrhea
- constipation
- vomiting
- headache
- dyspepsia
- fatigue
- dizziness
- abdominal pain

- abdominal distension/flatulence
- GERD
- gastroenteritis
- eructation
- UTI
- cholelithiasis
- lipase increase
- injection site reaction
- insomnia
- xerostomia
- asthenia
- anxiety
- tachycardia

HYPOGLYCEMIA MONITORING, HYPOGLYCEMIC PROTOCOL AND REPORTING FORM

Hypoglycemia can occur in patients without concomitant treatment with a sulfonylurea drug or other drugs used to treat diabetes. There is currently no requirement to measure glucose levels in non-diabetic patients while being treated with liraglutide therapy for weight loss. Previous single center series in patients with ileostomy have not revealed an increased risk of hypoglycemia while treated with drugs like liraglutide. However, since this type of drug has not yet been evaluated in patients with an ileo- pouch anal anastomosis, patients will measure daily glucose levels before breakfast.

All study patients will be provided with a blood glucose (BG) meter including auxiliary supplies as well as instructions for use. The subjects will be instructed in to measure blood glucose fasting before breakfast daily, how to use the device and how to fill out the daily glucose protocol. The glucose diary will be reviewed at every study visit.

HYPOGLYCEMIC PROTOCOL AND REPORTING FORM

At randomization, all study patients will be instructed in symptom recognition and handling of hypoglycemia. Symptoms of hypoglycemia will be explained which may be hunger, shakiness, nervousness, sweating, dizziness or light-headedness, sleepiness, confusion, difficulty speaking, anxiety, weakness.

If one of these symptoms occur study patients will be instructed to measure plasma glucose level and record these in the hypoglycemic protocol and reporting form. Study patients will report all plasma glucose values:
≤ 3.9 mmol/L (70 mg/dL)
or
> 3.9 mmol/L (70 mg/dL) occurring in conjunction with hypoglycemic symptoms.

Upon onset of a hypoglycemic episode with a plasma glucose of ≤ 3.9 mmol (70 mg/dl) the subject is recommended to measure plasma glucose every 15 minutes until the self-measured plasma glucose value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines. Repeated self-measured plasma glucose measurements and/or symptoms, occurring within a period of 60 min after onset on a hypoglycemic episode, will by default be considered as one hypoglycemic episode until a succeeding self-measured plasma glucose value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported on one hypoglycemic episode form. Self-measured plasma glucose measurements ≤ 3.9 mmol/L (70 mg/dL) or hypoglycemic symptoms after the 60 min period shall trigger the reporting of a new hypoglycemia episode and prompt the subject to fill out a new hypoglycemic episode form until a succeeding measurement is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved.

Hypoglycemic protocol and reporting form will advise the patient how to treat the hypoglycemia with either one of the following:
• 1/2 cup, or 4 ounces, of any fruit juice
• 1/2 cup, or 4 ounces, of a regular— not diet—soft drink
• 1 cup, or 8 ounces, of milk
• 5 or 6 pieces of hard candy
• 1 tablespoon of sugar or honey

The lowest value measured during the hypoglycemic episode will be reported as the plasma glucose value for the episode. The patient will also report symptoms, the time of the last meal and the activity preceding the episode.

If the question "Was the hypoglycemic episode so severe that you could not care for yourself and needed help from others?' which suggests that the hypoglycemic episode is associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?" is answered "YES"; the following information will be recorded:

- Who assisted in the treatment of the hypoglycemic episode (i.e., medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other.
- Type of treatment provided by other person (i.e., oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?

If the hypoglycemic episode fulfils the criteria for an SAE then an AE form and a safety

information form will be completed.

DOCUMENTATION AND REPORTING OF ADVERSE EVENTS

The patients will be instructed to contact the investigator, if any serious or unexpected AE occurs, so that appropriate action can be taken.
Moreover, the investigator must ask at each follow-up visit a generally worded question without searching for any special symptoms, e.g. “Has your state of health worsened since we last met?” If the answer to this question is “no”, no further questions will be asked. If the answer to the question is "yes”, the investigator will document the nature, time, severity, seriousness and duration as well as the causality of the AE. For each AE a specific AE documentation form will be provided to the investigators. In case of an AE, this should be completed by the physician as an initial report. The report must contain a detailed description of the symptoms observed and the concomitant treatment administered. Furthermore, the investigator must comment on a possible causative relationship between the AE and the trial medication. Each AE must be followed until it is resolved or can be explained satisfactory.

The following has to be documented for each AE:

- Nature of the event
- Time of onset: date, time
- Concomitant treatment: product (generic name), indication, dosage, dosage interval, presentation, mode of administration, administration regimen
- Duration of the AE
- Severity
- Seriousness
- Causality
- Outcome

SEVERITY

The severity is evaluated as follows:
1. Mild: - event/symptom does not interfere with normal daily activities
2. Moderate: - event/symptom interferes with normal daily activities
3. Severe: - event/symptom prevents normal daily activities

Causality
The relationship between an AE and the study medication is classified according to the WHO classification:

Certain

A clinical event, including laboratory test abnormality, is occurring in a plausible time relationship to drug administration, and which concurrent disease or other drugs or chemicals cannot explain. The response of the patient to withdrawal of the drug should be clinically plausible. The event must be definite pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely
A clinical event, including laboratory test abnormality, with a reasonable time sequence to the administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de challenge). Rechallenge information is not required to fulfil this definition.

Possible
A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely
A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/Unclassified
A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.

Not assessable / Unclassifiable
A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

As an alternative to the above-mentioned WHO assessments, the following assessment can be made:

Not related
There is sufficient information available to show that the etiology is unrelated to the study medication.

MEASURES AT THE ONSET OF ADVERSE EVENTS
Measures at the onset of adverse events are classified and described as follows:
1) None, i.e. the study medication was not changed
2) The dose of the study medication was reduced
3) The study medication was withdrawn and/or
4) Other measures (clear text)

The **course and outcome** of the adverse event will be commented on as follows:

1) Recovered without sequelae
2) Not yet recovered
3) Recovered with sequelae
4) Fatal

DOCUMENTATION AND REPORTING OF SERIOUS ADVERSE EVENTS

On enrolment in the study, the patients will be instructed to contact the investigator if a serious or unexpected AE occurs, so that appropriate measures can be taken.

Any SAE (including death, irrespective of the cause) occurring during or for up to 14 days after the end of the study will be reported without delay, i.e. within 24 hours, irrespective of its relationship with the administration of the study medication (minimum information required: investigator's name/study center, patient number, patient initials, date of first dose, date of last dose, date of event, description of event, causality assessment, and countermeasures).

A specific AE documentation form will be available. In case of an SAE, this will be completed by the PI (sponsor-investigator) as an initial report. The report must contain a detailed description of the symptoms observed and the concomitant treatment administered. Furthermore, the investigator must comment on a possible causative relationship between the AE and the trial medication. Each SAE must be followed until it is resolved or can be explained satisfactorily.

The general procedure for the observation, collection and analysis of drug risks (regulatory affairs) in conformity with the appropriate national Drug Law shall apply without qualification.

In accordance with drug safety and national requirements, the PI of the study (sponsor investigator) will inform the Data and IRB of the study and will make sure that the involved persons will obtain adequate information.

The PI of the study (sponsor-investigator) will report to Novo Nordisk all SAEs, SUSARs, and SADRs at the same time such events are reported to regulatory authorities or within 15 days from the sponsor-investigator becoming aware of such adverse events, whichever comes first.

The sponsor-investigator will collect the following information at minimum for each of these events:

1. Study name
2. Patient identification (e.g. initials, sex, age)
3. Event (preferably a diagnosis)
4. Drug
5. Reporter identification (e.g. Name, or initials)
6. Causality
7. Outcome might be reported, but this is not mandatory.

ABNORMAL LABORATORY RESULTS

All laboratory values outside of the normal range will be repeated if judged appropriate by the investigator to ensure the validity of the abnormal result. The investigator will document all

laboratory values on the relevant page of the electronic CRF and will assess the etiology of the clinically relevant abnormal laboratory values.
Clinically relevant abnormal laboratory values are only documented on the AE form of the electronic CRF, if the patient is discontinued, hospitalized, or, in the investigator's opinion, it should be considered as an AE.
Abnormal laboratory results caused by ulcerative colitis should not be reported on the AE form.

Pregnancy

Pregnancy tests will be performed at the screening visit, week 0, week 4 (in case of early cross over), week 6, week 10, and week 12 of the study. Women of child bearing potential will be asked about contraception compliance at each study contact. If there is concern for pregnancy during the study, the subject will be asked to immediately come to the site for a pregnancy test. The PI (sponsor-investigator) will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by sponsor-investigator should occur within the same timelines described above for reporting of serious adverse events.

WITHDRAWAL OR STOP OF STUDY DRUG CRITERIA

CRITERIA IN INDIVIDUAL CASES

Any patient can withdraw from the study at any time without personal disadvantages and without having to give a reason. The time of withdrawal, the results available up to that time, and, if known, the reason for withdrawal must be documented in the CRF. The investigator can also discontinue the study after considering the risk-to-benefit ratio, if he/she no longer considers the further participation of the patient justifiable. The date of and the primary reason for the withdrawal as well as the observations available at the time of withdrawal are to be documented on the electronic CRF.
Reasons leading to the **withdrawal** of a patient can include the following (primary reason must be determined):

- inclusion criterion not fulfilled, or exclusion criterion fulfilled; coming to knowledge after recruitment
- patient's request
- technical/logistical reasons (e.g. a change in place of residence, not referred by family physician, etc.)
- withdrawals due to adverse events (including non-serious adverse events leading to withdrawal)
- withdrawal to known adverse drug reaction (ADR as listed above), which is defined as severe according to the listed severity criteria (event/symptom prevents normal daily activities).
- Acute gallstone disease confirmed by
  - Signs and symptoms of acute gallstone disease
  - Specific laboratory test supporting a diagnosis of gallstone disease

- Imaging performed and consistency with gallstone disease

- New onset of Pancreatitis confirmed if a minimum 2 of 3 criteria ae met:
  - Severe acute abdominal pain
  - Blood amylase and/or lipase >3x upper limit of normal (ULN)
  - Characteristic findings on relevant imaging (e.g., computerized axial tomography/magnetic resonance imaging/ultrasound)

- Any medical condition or clinically significant abnormal finding(s) (physical, laboratory, vital sign) that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or sponsor's opinion; this may include the development of persistent events such as:
  - ALT or AST > 3x ULN and either total bilirubin > 2x ULN or INR > 1.5
  - ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
  - Creatinine elevation > 2x above upper limit of normal

- Recurrent hypoglycemia defined as a blood glucose of ≤ 3.9 mmol/L (70 mg/dL)

- other reasons (noting reason)

Reasons leading to the **stop of study drug but follow-up according protocol** can include the following (primary reason must be determined):

- lack of efficacy of the study medication, e.g.
  - need for a prohibited concomitant medication (e.g. need for steroids)
- lack of patient's cooperation, e.g.
  - patient's request
  - lack of compliance (fails to attend the follow-up visits as agreed)
  - existing pregnancy or intended pregnancy* (females), lactation (females)

In all patients who finish the study prematurely, a withdrawal examination should be carried out within 2 weeks after the last application of the study medication. The withdrawal examination must be conducted as a final examination and documented in the CRF.

REPLACEMENT OF WITHDRAWN PATIENTS

Replacement lists will not be provided since it is not planned to replace subjects if they withdraw or become ineligible after the first dose of study drug has been given.

CRITERIA FOR THE TERMINATION OF THE WHOLE STUDY

If safety concerns arise, the PI can terminate or interrupt the study by agreement with Novo-Nordisk. If new information on the risk-to-benefit ratio of the drug or on the treatment methods

used in the study is obtained in the meantime, the PI reserves the right to interrupt or terminate the project by agreement with Novo-Nordisk. Premature termination is also possible if patient recruitment is insufficient and cannot be expedited by appropriate measures.

LIABILITY AND SUBJECT INSURANCE

The PI (sponsor-investigator) and his/her institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. Sponsor-investigator should state that this medical care for study subjects will be provided regardless of their insurance status.

The PI (sponsor-investigator) will be responsible for the conduct of the study. The PI (sponsor-investigator) agrees to defend, indemnify, and hold harmless Novo Nordisk, any of its parent companies, affiliates, or subsidiaries, and their respective officers, directors, employees, agents, representatives, distributors, salespersons, customers, licensees, and end-users from and against any claim, suit, demand, loss, damage, expense or liability imposed by any third party arising from or related to: (a) any breach of PI's (sponsor-investigator's) obligations or representations; or (b) PI (sponsor-investigator's) negligent or grossly negligent use or willful misuse of the study drug, the results, or services derived therefrom. This indemnification shall not apply in the event and to the extent that a court of competent jurisdiction or a duly appointed arbiter determines that such losses or liability arose as a result of Novo Nordisk's gross negligence, intentional misconduct, or material breach of its responsibilities.

RANDOMIZATION, DATA MANAGEMENT AND DATA MONITORING

The randomization sequence of the patients and the processing and analysis of the data will be carried out by the Biostatistics core of the Center for Gastrointestinal Biology and Disease at UNC Chapel Hill. The randomization sequence will be established by the CGIBD Biostatistics core and communicated with the investigational drug services of UNC.

Study data for this study will be collected and stored using electronic records. Data captured will be entered in real time *using web forms developed to replicate paper case report forms*. All data will be created, modified, maintained, archived, retrieved and distributed by a computer system**.** The use of electronic records will increase the speed of data collection and exchange and facilitates daily reporting of patient reported outcomes. This will reduce the manpower necessary to perform double-data entry from paper forms and transcription error. In addition, electronic records permit economical storage of study data and ease of accessibility and analysis. Data management and data quality systems will be built into the system.

Data quality using electronic records will ensure that data are attributable, legible, contemporaneous and original.

The Data Management Center (DMC) at the CGIBD at the University of North Carolina will track the data collection, provide data security, control for confidentiality of study data, maintain

computer backups to protect data until study closure and archive study data according to FDA requirements (21 CFR 11). Electronic signatures will be linked to each entry.
All computer systems and programs will be password protected, and all electronic communications of study and other confidential information will be encrypted. Personnel at the CGIBD have extensive training and experience using electronic data systems. Good computer security practice (restricting physical access to machines, prohibition of password sharing, and logging off computers after work hours or when away from the machine) will be required of all study personnel.
Standard Operating Procedures exist for users of the DMC. Only authorized persons are authorized for data entry and access. Data security systems require password protected identification codes for data entry and provide protection against data manipulation. The database is located on a server protected by firewalls. Access to the database server will not be allowed by users on computers outside of the firewall-protected zone. Virus protection software is installed on each study machine. System access to computer systems will be audited. Redundant backups and off-site backup storage will allow for quick restoration of data in the unlikely event that a hardware failure, disaster, or security breach should occur. Servers and backups will be located in a secured location with access limited to authorized personnel.

Data cleaning will include range and edit checks, cross form edit checks, query generating and tracking and periodic data status reports. Any data errors or inconsistencies detected after data entry will be automatically tracked, communicated and resolved using a web-based application. An audit trail of all data changes over the life of the study will be maintained. All study raw data, forms, documents, software programs, software applications and computer data files will be indexed and archived routinely. Strict version control of documents and software applications will be instituted. Retention of study documentation after study completion will conform to FDA and NIH requirements.
Standardized study management reports will be generated monthly during the recruitment phase of the study. These reports will be used to track study progress including patient enrollment, randomization, compliance, patient status changes, and study events.

DATA ANALYSIS

Efficacy analyses will primarily be based on a modified intent-to-treat {mITT} analysis set, which includes all randomized patients, who took at least one dose of the investigational product.
Statistical tests will be 2-sided and performed at the 0.05 level of significance. Missing data will be imputed for the mITT population using the last observation carried forward (LOCF) method. Baseline observations will not be carried forward if all subsequent measurements are missing.

Primary analyses

The primary outcome is the reduction of the mean 7-day bowel frequency of 30% compared to baseline (baseline is defined as the mean 7-day bowel frequency in a 7-day period during the screening period before week 0). A crossover trial will be performed. Subjects with a history of averaging > 8 bowel movements per day over a 7-day span will be entered into the study and the

order in which they receive treatments (liraglutide or placebo) will be randomized. At the end of each week, the average number of bowel movements the subject had during that week will be computed. A repeated measure mixed model will be fit to the data with treatment (liraglutide or placebo), period and treatment sequence as fixed effects and the repeated measures within subject as a random effect. After the model is run, any non-significant effects for period or treatment sequence will be removed from the model. The treatment effect will remain in the model and is the outcome of interest. P-value less than 0.05 will be considered statistically significant. In a sensitivity analysis the same model will be run without removing any effects. P-value less than 0.05 will be considered statistically significant.

Secondary analyses

Continuous secondary outcomes (stool frequency, clinical PDAI) will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) of the values at each assessment and the change from baseline to each assessment. A repeated measure mixed model will be fit to the data with treatment (liraglutide or placebo), period and treatment sequence as fixed effects and the repeated measures within subject as a random effect. After the model is run, any non-significant effects for period or treatment sequence will be removed from the model. The treatment effect will remain in the model and is the outcome of interest. P-value less than 0.05 will be considered statistically significant.

Safety analyses

The safety analyses will comprise all included patients, who got at least one dose of the investigational product.

– Number of study patients, who discontinued therapy
– Adverse events grouped by body system
– Changes in laboratory values

Exploratory analyses

We will perform exploratory analyses using descriptive statistics (mean, median, standard deviation, minimum, and maximum) and bivariate analyses of the values at each assessment and the change from baseline to each assessment. In the evaluation of the PROMIS measure for incontinence, PROMIS measures utilize a T-score metric where a score of 50 is the mean of a relevant reference population and 10 is the standard deviation. Additionally, a clinically minimally important difference is reflected by a change of 2.

Missing data

Due to short and intensive period of follow-up for the primary outcome, we do not anticipate significant missing data.

SAMPLE SIZE CALCULATION

The analysis will be based on the within-subject difference between two one-week averages of the number of bowel movements per day (BMPD). A one-sample t-test will be used to test the

null hypothesis that the mean difference is zero. With a sample size of 10 subjects and Type-I 0.05 (2-sided), the power is 0.80 against a difference of 1 standard deviation (SD) of the difference (not SD of the individual outcomes). The first average within each patient, by design, will be greater than 8 BMPD, and the range is most likely to be 8-11. The standard deviation (SD) of such an outcome can't (mathematically) exceed 1.5, and this will be used in the sample size calculations as the SD of each weekly average (control and treatment). Additionally, the SD of the difference depends on the correlation between the two weekly averages. Taking that into account, the power is 0.80 against a difference of 2.1 BMPD if the correlation is 0, 1.8 BMPD if the correlation is 0.25, 1.5 BMPD if the correlation is 0.50, 1.1 BMPD if the correlation is 0.75. Assuming a baseline average of 10 BMPD, the design has good power against relative changes of 21% or higher if the within-subject correlation is zero. The power increases with increasing positive correlation and, naturally, is higher against larger effects. If patients drop out during the study the power will decrease, however patents will be carefully selected and thus dropouts are unlikely to occur.

FUTURE PERSPECTIVE

If this proof-of-concept study does not reveal any safety concerns and suggests efficacy of a GLP-1 receptor agonist therapy, we propose to conduct a multicenter phase 2, double blind, parallel group, randomized, placebo-controlled trial. Financial support for such a trial could be obtained by the investigators in the setting of a NIH funded collaborative trial. Given the orphan disease status of the pouch population, such a trial could be also conducted in advisory collaboration with the FDA. The applicants of this project have profound experience in successfully conducting NIH funded multi-center studies in the US. [51-53] Eight academic US centers collaborate already in the setting of the Crohn's and Colitis Foundation supported multicenter registry (THE PROP-RD Study: A Prospective Registry for the Study of Outcomes and Predictors in Pouchitis and Pouch-Related Disorders). Additional centers can be easily recruited through the Clinical Research Alliance (CRA) of the Crohn's and Colitis Foundation (Millie Long is currently chair of the CRA, which comprises 72 centers, Hans Herfarth was chair of the CRA between 2010 and 2018).

PUBLICATION PLAN

The trial will be registered at ClinicalTrials.gov. The applicants will present and discuss all clinical trial data with the sponsor. All relevant trial data will be posted on ClinicalTrals.gov following the discussion of the results. The applicants plan to submit a final paper of the results of this trial to a peer-reviewed gastroenterology journal.

TABLE STUDY VISITS AND ASSESSMENTS

Study periods			**Period 1**				**Period 2**				
	Screening & randomization					Cross over[f]					Follow-up
Visits	Screen 10-14 days before week 0	Week 0	Week 1[d] ± 1 day	Week 2[d] ± 1 day	Week 4 ± 3 days	Week 6 ± 3 days	Week 7[d] ± 1 day	Week 8[d] ± 1 day	Week 10 ± 3 days	Week 12[k] ± 3 days	Week 14[k] ± 3 days
Medical History	X										
PDAI score[a]	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X
Physical Exam (including body weight)	X	X			X	X			X	X	
Blood Tests[b]	X				X	X			X	X	
C. diff stool test	X										
Pregnancy Test	X	X			X[g]	X			X	X	
Confirm contraceptive method if applicable	X	X	X	X	X	X	X	X	X	X	X
Stool calprotectin	X	X		X[d]	X	X		X[d]	X	X	
Pouchoscopy with endoscopic PDAI (standard of care)	X										
Pouch biopsies (standard of care)	X										
Review Subject Diary[c]	X	X	X	X	X	X	X	X	X	X	
Review of glucose diary and hypoglycemic protocol and reporting form			X	X	X	X	X	X	X	X	
Assessment of response[h]					X				X		
PROMIS questionnaires, SF36, PROBE	X			X	X	X		X	X	X	
Study drug dispensation		X			X[i]	X					
Study drug collection										X[j]	

[a] Clinical PDAI excluding pouchoscopy
[b] CBC, AST, ALT, AP, Bilirubin, Creatinine, CRP. Serum samples for GLP-1 baseline fasting if possible (Screening or week 0).
[c] Subject diary will be maintained electronically and completed daily reporting stool frequency, rectal bleeding, fecal urgency or abdominal cramps, and/or fever. The patient will complete this diary each day, beginning with the screening visit and ending at the visit. The average 7-day bowel frequency will be calculated for each 7-day period. For the clinical PDAI scores the last three days of diary entries before each visit will be used to calculate stool frequency and fecal urgency/abdominal pain scores.
[d] Phone visit only with review of diaries and dose increase of study drug if tolerated. Patient will mail stool sample calprotectin or bring in person.
[f] Crossover occurs after at least 5 days of washout after the last study dose
[g] Pregnancy test at week 4 in case of early crossover
[h] Assessment of response: If average weekly bowel frequency of patient did not decrease by at least 15% compared to baseline the patient can proceed to early crossover (Period 1 week 4) or early termination (Period 2 week 10).
[i] Non-responder at Period 1 week 4 receive study drug for period 2 to start 5 days after the last study dose of period 1
[j] Collection of study drug from non-responders in Period 2 week4 and all patients who were responding at Period 2 week 10 and completed study at Period 2 week 12.
[k] For non-responders at Period 2 week 10 the safety outcomes below will be assessed at Period 2 week 12. For this patient group at Period 2 week 12 only adverse events (review adverse events diary) and concomitant medication will be assessed at Period 2 week 12. An alternative approach is a phone visit at Period 2 week 12 (similar to the final visit at Period 2 week 14) and patient returns all study medication from period 1 and 2 before Period 2 week 12.

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APPENDICES

APPENDIX A: MODIFIED POUCHITIS DISEASE ACTIVITY INDEX (MPDAI)

According to Shen et al.; 2003 [35]

Clinical Criteria	Score
Stool Frequency	
Usual post-op stool frequency	0
1-2 stools/day > post-op usual	1
3 or more stools/day > post-op usual	2
Rectal Bleeding	
None or rare	0
Present daily	1
Fecal Urgency / Abdominal Cramps	
None	0
Occasional	1
Usual	2
Fever (temperature> 100^{o}F)	
Absent	0
Present	1
Endoscopic Criteria	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucus exudate	1
Ulceration	1

APPENDIX B: SF-36

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

---

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

---

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

---

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1 - All of the time
- 2 - Most of the time
- 3 - Some of the time
- 4 - A little of the time
- 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

APPENDIX C: PROMIS MEASURE INCONTINENCE

According to Kochar et al.[48]
In the past 7 days...

	1 = No days	2 = 1 day	3 = 2-3 days	4 = 4-5 days	5 = 6-7 days
31611 - How often did you have bowel incontinence—that is, have an accident because you could not make it to the bathroom in time?					
31621 - How often did you soil or dirty your underwear before getting to a bathroom?					
31631 - How often did you leak stool or soil your underwear?					

	1 = Never	2 = Rarely	3 = Sometimes	4 = Often	5 = Always
31641 - How often did you think you were going to pass gas, but stool or liquid came out instead?					

APPENDIX D: PROBE SCORE

PROBE, a 6-question measure of quality of life among patients with inflammatory bowel disease[50]

In the past 7 days…

I found it hard to focus on anything other than my anxiety
- (5) Never
- (4) Rarely
- (3) Sometimes
- (2) Often
- (1) Always

I felt hopeless
- (5) Never
- (4) Rarely
- (3) Sometimes
- (2) Often
- (1) Always

How fatigued were you on average
- (5) Not at all
- (4) A little bit
- (3) Somewhat
- (2) Quite a bit
- (1) Very much

I am satisfied with my ability to meet the needs of my friends
- (1) Not at all
- (2) A little bit
- (3) Somewhat
- (4) Quite a bit
- (5) Very much

How much did pain interfere with work around the home?
- (5) Not at all
- (4) A little bit
- (3) Somewhat
- (2) Quite a bit
- (1) Very much

How would you rate your IBD activity?
- (5) Remission
- (4) Minimal symptoms
- (3) Mildly active
- (2) Moderately active
- (1) Severely active

Note: Scores for each response to an individual question are listed in parentheses

	APPENDIX E: SUBJECT DIARY FOR POUCHITIS **Instructions:** Begin recording in your diary each night. You should record before going to bed and the answers should describe the preceding 24 hours.						
Date	During the past 24 hours how many bowel movements did you have? (Please provide number)		During the past 24 hours how many of your bowel movements contained blood? (Please provide number)	How many of these bowel movements were liquid (BL; number), pasty (BP; number) or formed (BF number)	During the past 24 hours how many of your bowel movements were preceeded by abdominal cramps or an urgent need to go to the bathroom? (Please provide number)	During the past 24 hours did you experience fever higher than 37.8°C (100.0°F)? (Please mark "yes" or "No")	
	Day 8 am-22 pm	Night 22pm-8 am				Yes	No
						Yes	No
						Yes	No
						Yes	No
						Yes	No
						Yes	No
						Yes	No

APPENDIX F: ADVERSE EVENT DIARY

Front pages of diary

Efficacy of GLP-1 receptor agonist therapy in patients with an ileal -pouch anal anastomosis (IPAA) and chronic high bowel frequency

Record of Side Effects

This diary is one way researchers will get information from you regarding any possible problems or side effects in this study.

- **What you are going to do is simple.** Just keep a record of any unpleasant thing that happens to you while you are in the study, before, during, and after we started the study therapy. We even want you to record things that do not seem to be part of the study therapy, at all.
- **When do you start? When do you end?** You will complete one entry per day starting with the first day of study treatment time as well as daily until the last phone visit of the trial is completed.
- **What do you look for? What do you report?** Any symptom or problem whether or not it may be from the medicine, stool therapy. This could include: fever, abdominal pain, a big belly, lots of gas, diarrhea, nosebleeds, and anything else you know is not quite right.
- **What will you do?** Starting with the first day of the study medication, you will report some of the specific things that have bothered you by checking the boxes in the diary (see below). You can also write any other problems that you may have had during that time.

How will you record it? Like this…

EVENT	DATE OF ONSET	INTENSITY	ACTION TAKEN	MEDICATION	DATE RESOLVED
Fever	3/1/12	3	Missed 2 days of school	Tylenol-200mg	3/3/12
Sore throat	3/5/12	1	None	None	3/6/12

OTHER SYMPTOMS

Record each symptom at its ***worst*** level for each day.

For example, a sore throat that starts at ‘Grade 1” but increases to ‘Grade 2’ should be recorded as ‘Grade 2”.

Examples of Grades:

Grade 1 – Mild: I noticed the symptom. It did not keep me from doing my normal activities.

Grade 2 – Moderate: I noticed the symptom and it kept me from doing some of my normal activities.

Grade 3 – Severe: I really noticed the symptom and it kept me from doing activities that I wanted or needed to do.

Grade 4 – Very severe: The symptom made me unable to perform basic self-care functions such as washing myself **OR** medical or surgical intervention was needed to prevent serious consequences.

Daily diary page day 0 (start of trial therapy)
Day after start: _____

Subject ID:_____

Date:____/____/_____ Check here is no side effects present: ☐
Highest temperature of the day:____°F

Check if symptom present	Event	Date of Onset	Intensity	Action taken	Medications	Date Resolved
☐	Fever					
☐	Abdominal Pain					
☐	Diarrhea					
☐	Nausea/Vomiting					
☐	Blood in Stool					
☐	Other 1					
☐	Other 2					
☐	Other 3					
☐	Other 4					

Grade 1 – Mild: I noticed the symptom. It did not keep me from doing my normal activities.
Grade 2 – Moderate: I noticed the symptom and it kept me from doing some of my normal activities.
Grade 3 – Severe: I really noticed the symptom and it kept me from doing activities that I wanted or needed to do.
Grade 4 – Very severe: The symptom made me unable to perform basic self-care functions such as washing myself **OR** medical or surgical intervention was needed to prevent serious consequences.

Completed by: _____

APPENDIX G: DAILY GLUCOSE DIARY

Daily Glucose Diary

Week 1 2 3 4 5 6 (please circle)

Please measure glucose daily first thing in the morning before eating or drinking anything but water.

Day (date)	Time	Glucose level
1.		
2.		
3.		
4.		
5.		
6.		
7.		

If you measure a glucose level below 3.9 mmol/L (70 mg/dL) , please start measuring your glucose values every 15 minutes and follow the hypoglycemic protocol

APPENDIX H: HYPOGLYCEMIC PROTOCOL AND REPORTING FORM

Hypoglycemic protocol and reporting form

Please measure your blood glucose anytime if you feel symptoms of hypoglycemia, which can be hunger, shakiness, nervousness, sweating, dizziness or light-headedness, sleepiness, confusion, difficulty speaking, anxiety, weakness.

If you have a plasma glucose level < 3.9 mml/L (70- mg/dl) one of these quick-fix foods should be consumed right away to raise blood glucose:

- 1/2 cup, or 4 ounces, of any fruit juice
- 1/2 cup, or 4 ounces, of a regular— not diet—soft drink
- 1 cup, or 8 ounces, of milk
- 5 or 6 pieces of hard candy
- 1 tablespoon of sugar or honey

You should continue to measure your glucose level every 15 min until it is > 3.9 mmol/L (70 mg/dL) and fill the values in the hypoglycemia reporting form. Please fill out a new form for each event if > 60 minutes apart.

Hypoglycemia reporting form

Day (date)	Time	Glucose level	Symptoms	What did you eat/drink when after you measured a plasma glucose level < 3.9 mml/L (70- mg/dl)	Last meal/snack before hypoglycemia episode (what did you eat/snack and when did you eat it?)	Activity preceding hypoglycemic episode

Was the hypoglycemic episode so severe that you could not care for yourself and needed help from others?

0 Yes 0 No

If yes:

Who assisted in the treatment of the hypoglycemic episode (i.e., medical person or non-medical person)?

Where was the treatment administered (in clinic/emergency room/hospital or other)?

What type of treatment was provided by other person (i.e., oral carbohydrates, glucagon, IV glucose or other)?

Were symptoms alleviated after administration of treatment?