

METHODS FOR TREATING SHORT BOWEL SYNDROME AND/OR HIGH OUTPUT OSTOMY

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims priority to, and the benefit of, U.S. Provisional Application No. 63/111,869, filed November 10, 2020, which is hereby incorporated by reference in its entirety.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

10 The contents of the text file submitted electronically herewith are incorporated herein by reference in their entirety: A computer readable format copy of the Sequence Listing (Filename: "NMT-027PC_ST25.txt"; Date recorded: November 10, 2021; File size: 8,090 bytes).

BACKGROUND

15 Ostomy surgery is a procedure that allows bodily waste to pass through a surgically created stoma into a prosthetic, such as an ostomy bag on the outside of the body. An ostomy may be necessary in the case of birth defects, cancer, inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), or severe abdominal or pelvic trauma, for example. In some cases, the patient has a surgical removal of a large portion of the small intestine (e.g., due to Crohn's disease, or necrotizing enterocolitis in the case of young children) leading to
20 short bowel syndrome (SBS), a malabsorption disorder caused by a lack of functional small intestine.

25 Patients with a jejunostomy (i.e., end jejunostomy) have major problems of dehydration, electrolyte depletion, and nutritional challenges, largely due to a large volume of stomal output. Some SBS patients fail to adapt adequately and have high ostomy outputs from the time of surgery, and may experience intestinal failure. Intestinal failure generally requires i.v. fluid and parenteral nutritional support. Improved treatment of SBS as well as conditions requiring ostomy surgery are critical for reversing or preventing intestinal failure and/or ameliorating the need for parenteral nutritional support and/or frequent i.v. fluids. In the various embodiments, this disclosure meets these objectives.

DETAILED DESCRIPTION

The present invention provides methods and compositions for treating short bowel syndrome and/or high output ostomy. The invention comprises administering to a patient in need a long-acting Glucagon-like peptide 1 (GLP-1) receptor agonist. In embodiments, the
5 long-acting Glucagon-like peptide 1 (GLP-1) receptor agonist is the exenatide-XTEN fusion protein known as vutolnatide. In various embodiments, the method reduces ostomy output, reduces requirement for parenteral nutrition and/or frequent i.v. fluid support, and/or ameliorates acute intestinal failure. In some embodiments, the method of the present invention reduces high urine and/or stool output in a patient having short bowel syndrome,
10 including end jejunostomy patients.

In some embodiments, the patient is an end jejunostomy patient experiencing a high output ostomy (HOO). HOO is defined herein as more than about 1.5 L of fluid from the ostomy in a 24-hour period. In some embodiments, the patient is losing at least about 2 L of fluid from the ostomy in a 24-hour period, or at least about 2.5 L, or at least about 3 L, or at
15 least about 3.5 L, or at least about 4 L of fluid from the ostomy in a 24-hour period.

Under normal circumstances, 9 to 10 liters of fluid enter the jejunum each day, including both oral intake and gastrointestinal secretions from oral, gastric, duodenal, and biliopancreatic sources. The jejunum absorbs approximately 6 L, and the ileum another 2.5 liters, leaving approximately 1 to 1.5 liters of fluid entering the colon per day. Almost all of
20 this fluid and the electrolytes it contains are absorbed in the colon, leaving approximately 100 milliliters excreted in feces daily. Thus, diversion of the fecal stream at the level of the ileocecal valve would be expected to produce approximately 1 to 1.5 liters of stool output per day containing approximately 200 mEq of sodium, 100 mEq of chloride, and 10 mEq of potassium. Diversion at a higher level will result in significantly more fluid and electrolyte
25 losses.

Fluid and electrolyte losses can be offset in part by increased oral intake. In addition, in the case of SBS, the remaining small intestine often compensates by increasing the efficiency of fluid and electrolyte absorption, a process termed adaptation, which occurs within weeks to months. This adaptation process is a combination of: (1) changes in mucosal
30 morphology - mucosal hypertrophy and hyperplasia of remaining intestines that increases its

absorptive capacity; (2) changes in small bowel electrolyte transport; and (3) alterations in motility - slowing transit through the bowel increases time available for absorption (Rowe, K. et al., *Proc (Bayl. Univ. Med. Cent.)*, 33(2):218-226, 2020).

In various embodiments, the patient has Short Bowel Syndrome (SBS). In some
5 embodiments, the patient having SBS has high output of urine and/or stool. SBS is a life-
altering condition caused by a significant shortening of the gastrointestinal (GI) tract, often
from surgical removal of a large portion of the small intestine. In some embodiments, a
patient having SBS has an intact colon (i.e., where the remaining ends of the intestine are
stitched together). In other embodiments, a patient having SBS does not have an intact colon,
10 and the patient relies on a permanent ostomy. If the shortened GI tract cannot properly absorb
nutrients, the patient may need to rely on total parenteral nutrition (TPN) to manage
nutritional needs. TPN involves intravenous infusion for up to several hours every day
which, aside from the negative impact on quality of life, carries side effects as well as high
risk of systemic infections. Further, high output ostomy can be a severe and chronic result
15 of short bowel syndrome. In some embodiments, the patient has an end jejunostomy. In
various embodiments, the patient to be treated does not have active Crohn's disease or IBD.
For example, in various embodiments, if the patient has a history of Crohn's disease or IBD,
the patient is in remission.

Patients with SBS and HOO are at risk for intestinal failure. Three types of intestinal
20 failure can be distinguished. Type 1 acute intestinal failure (IF) is self-limiting and common
following abdominal surgery, and the necessity of i.v. fluid and nutritional support is short
(<28 days). Type 2 IF is also acute in onset and reversible, but requires more than 28 days
of intravenous fluid and/or nutritional support and is often associated with septic, metabolic
and complex nutritional complications. Finally, type 3 IF is characterized as chronic IF,
25 frequently irreversible and requires long term or even lifelong therapy with intravenous fluid
and/or TPN. In various embodiments, the subject may be experiencing or at risk of Type 1,
Type 2, or Type 3 Intestinal Failure.

In accordance with this disclosure, the patient's condition is ameliorated by
administration of a long-acting GLP-1 receptor agonist. Glucagon-like peptide-1 (GLP-1) is
30 a hormone that is produced by L-cells in the ileum. As an incretin hormone, GLP-1

stimulates insulin secretion in a glucose-dependent process, and it tonically suppresses glucagon release and lowers postprandial glucagon excursions (Schirra, J., et al., *Gut*; 55:243-251, 2006). GLP-1 is also a regulator of fasting and postprandial gastroduodenal motility. GLP-1 also regulates several GI functions, such as decreasing gastric acid secretion, and slowing GI transit and motility. GLP-1 (e.g., GLP-1 (7-37)) and exenatide are peptide GLP-1 receptor agonists that can be delivered for pharmaceutical intervention. In various embodiments, the GLP-1 receptor agonist may have from one to five, or from one to three amino acid substitutions with respect to human GLP-1 peptide or exenatide.

In accordance with embodiments of this disclosure, the GLP-1 receptor agonist is a long-acting GLP-1 receptor agonist unit dose providing an effective concentration of the GLP-1 receptor agonist in circulation for at least about one week or at least about two weeks upon a single subcutaneous injection. In some embodiments, the long-acting GLP-1 receptor agonist formulation is vurolenatide. In accordance with this disclosure, a large AUC of GLP-1 agonist (e.g., as achieved herein by a long-acting GLP-1 agonist such as vurolenatide) is believed to be superior for treatment of SBS or HOO as compared to providing spikes (e.g., one or more times daily) in levels of GLP-1 receptor agonist.

The long-acting GLP-1 receptor agonist may be created using various chemical polymers, which can be conjugated to the GLP-1 receptor agonist to enhance the pharmacokinetic (PK) properties. Exemplary PK properties include longer terminal half-life, larger area under the curve, increased time in which the blood concentration remains within the therapeutic window, increased time between consecutive doses, and decreased dose in moles over time. In some embodiments, the GLP-1 agonist is conjugated or fused to a chemical polymer, such as polyethylene glycol (PEG), polylactides (PLA), polyglycolides (PGA), poly(lactide-co-glycolide) (PLGA), poly(ϵ -caprolactone) (PCL), polyglyconate, polyanhydrides, polyorthoesters, poly(dioxanone), and polyalkylcyanoacrylates. In some embodiments, the GLP-1 receptor agonist is acylated.

In other embodiments, the GLP-1 receptor agonist is fused to a half-life extension polypeptide, such as albumin amino acid sequence, a transferrin amino acid sequence, an immunoglobulin Fc domain amino acid sequence (e.g., IgG1 or IgG4 Fc domain), an elastin-like peptide amino acid sequence, or an unstructured polypeptide as disclosed in U.S. Patent

No. 8,957,021, which is hereby incorporated by reference. An exemplary unstructured polypeptide is AE864XTEN, and is exemplified in SEQ ID NO: 1 (vurolenatide). Other half-life extension polypeptides are disclosed in US 8,748,380, US 10,233,228, US 10,501,524, and US 9,458,218, which are hereby incorporated by reference in its entirety. Exemplary
5 fusions may include linker sequences, such as sequences of from 4 to 40 amino acids (e.g. 4 to 20), and which are optionally composed predominately of serine and glycine amino acids.

In some embodiments, the long-acting GLP-1 receptor agonist is an exenatide or GLP-1 peptide fusion with a half-life extension polypeptide at the C-terminus. In some embodiments, the long-acting GLP-1 receptor agonist comprises the amino acid sequence
10 of SEQ ID NO: 1.

In some embodiments, the long-acting GLP-1 receptor agonist (such as the long-acting GLP-1 receptor agonist of SEQ ID NO: 1) is administered at a unit dose of about 12 mg to about 250 mg, or a unit dose of about 25 mg to about 200 mg. For example, the unit dose may be about 50 mg to about 150 mg. Exemplary unit doses include about 25 mg, about
15 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, and about 200 mg. The route of administration of the long-acting GLP-1 receptor agonist is by parenteral administration, such as subcutaneous injection. In some embodiments, the long-acting GLP-1 receptor agonist is administered by intravenous injection.

In some embodiments, the long-acting GLP-1 receptor agonist is administered about
20 once weekly, or about twice monthly, or about once monthly. The treatment regimen may be continued during the time that the patient exhibits HOO, or as needed to reduce reliance on TPN or frequent i.v. fluid support. In various embodiments, the patient is administered at least two doses of the long-acting GLP-1 agonist. In some embodiments, the patient is administered at least three, or at least four, or at least five, or at least six doses of the long-
25 acting GLP-1 receptor agonist. In some embodiments, the subject receives about 10 doses of the long-acting GLP-1 receptor agonist or less, or receives about 8 doses of the long-acting GLP-1 receptor agonist, or less. In still other embodiments, therapy with the long-acting GLP-1 receptor agonist is continuous. In some embodiments, the subject receives life-long administration of the long-acting GLP-1 receptor agonist. In some embodiments, during
30 therapy, the patient exhibits an average daily reduction of ostomy output of at least about

10% from baseline, or at least about 20% from baseline. In some embodiments, during treatment, the patient's parenteral support is reduced by at least about 10% from baseline, or at least about 20% from baseline, or at least about 30% from baseline, or at least about 50% from baseline. In various embodiments, the improvement from baseline is observed in the first 24 hours or first 48 hours of treatment. In various embodiments, the long-acting GLP-1 receptor agonist therapy described herein provides improvement in bowel movement frequency and form, for example, bowel movements become no longer substantially meal-related. In some embodiments, the long-acting GLP-1 receptor agonist therapy described herein reduces diarrhea occurrences, for example, reduces, eliminates or avoids chronic unrelenting diarrhea. These improvements in some embodiments occur after the first dose of the long-acting GLP-1 receptor agonist. Accordingly, the therapy described herein can substantially improve bowel habits, nutritional status, and quality of life for SBS patients.

In some aspects and embodiments, this disclosure provides a method for treating a patient having short bowel syndrome. The method comprises administering to the patient by subcutaneous injection a unit dose (as described herein) of the long-acting GLP-1 receptor agonist of SEQ ID NO: 1. In various embodiments, the administration is from about once weekly to about once monthly. For example, the patient having SBS may have an end jejunostomy, and the patient may be experiencing high output ostomy (as described above). In exemplary embodiments, the unit dose of the long-acting GLP-1 agonist is about 50 mg to about 150 mg. For example, the unit dose may be about 50 mg, about 100 mg, or about 150 mg. In some embodiments, the long-acting GLP-1 receptor agonist is administered about twice weekly, about once weekly, or about twice monthly, or about once monthly. In some embodiments, about 50 mg, or about 100 mg, or about 150 mg are administered once or twice weekly. In some embodiments, about 50 mg, or about 100 mg, or about 150 mg are administered once or twice monthly. Thus, in exemplary embodiments, about 50 mg, or about 100 mg, or about 150 mg are administered about twice monthly. In some embodiments, about 150 mg of the GLP-1 receptor agonist is administered about monthly.

In various embodiments, the patient does not experience substantial adverse effects from the drug, such as substantial symptoms of nausea, vomiting, hypoglycemia, pancreatitis, liver injury, and/or kidney function. In various embodiments, the adverse

effects (such as nausea and vomiting) are significantly less than observed with agents such as liraglutide or exenatide.

In another aspect, this disclosure provides a unit dose composition of a long-acting GLP-1 receptor agonist defined by SEQ ID NO: 1, the unit dose composition comprising
5 from about 12.5 mg to about 200 mg of the long acting GLP-1 receptor agonist formulated for subcutaneous administration. In various embodiments, the unit dose may be about 50 mg to about 150 mg. Exemplary unit doses include about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, and about 200 mg. The unit dose may be suspended in an appropriate physiological solution, *e.g.*, saline or other
10 pharmacologically acceptable solvent or a buffered solution, and may optionally comprise a surfactant. Pharmaceutically acceptable carriers include water, saline, and glycerol. In some embodiments, the formulation may comprise fixed oils, polyethylene glycol, propylene glycol or other solvents. In some embodiments, the solvent is water.

The pharmaceutical compositions of the disclosure may be conveniently presented
15 in unit dose forms containing a predetermined amount of the active agent of the disclosure per dose. Auto-injectors such as an “injection pen” are spring-loaded syringes designed to deliver a dose of a particular drug. By design, injection pens are easy to use and are intended for self-administration by patients, or administration by untrained personnel. Injection pens are designed to overcome the hesitation associated with self-administration of the needle-
20 based drug delivery device. The injection pen keeps the needle tip shielded prior to injection and also has a passive safety mechanism to prevent accidental firing (injection). Injection depth can be adjustable or fixed and a function for needle shield removal may be incorporated. By pressing a button, the syringe needle is automatically inserted into the subcutaneous tissue and the drug is delivered. Once the injection is completed some injection
25 pens have a visual or audible indication to confirm that the full dose has been delivered.

In some embodiments, the injection pen contains from one to ten unit doses or from one to five unit doses. In some embodiments, the unit doses are no more than about 1 mL, no more than about 1.5 mLs, or no more than about 2 mLs in volume (whether or not contained or delivered by an injection pen). The injection pen may contain at least four unit
30 doses (*e.g.*, about 3, about 4, about 5, about 6, about 7, or about 8 unit doses).

As used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the content clearly dictates otherwise.

As used herein, the term “about” means $\pm 10\%$ of an associated numerical value.

Embodiments of the disclosure are now described with reference to the following
5 examples.

EXAMPLES

This Example follows a drug administration of subcutaneous delivery of 50 milligrams of study drug (long-acting GLP-1 receptor agonist of SEQ ID NO: 1) on Day 1, with the patient to be evaluated over a 48-hour period.

10 A 61-year-old female patient (7 years post-extensive bowel resection) presenting with severe malabsorption secondary to short bowel syndrome and a high output end jejunostomy was accepted for a clinical trial. Baseline stool output measurement was 22,508 milliliters for the 48 hours prior to the first dose of study drug. She was emptying her ostomy bag 8-10 times each day and several times at night. The patient had difficulty maintaining
15 adequate hydration and nutrition with frequent modifications to her daily parenteral support (PS) and nutrition (total daily PS = 2L). On admission to the study, the patient weighed 51.6 kg with a BMI of 19.4; baseline physical exam was unremarkable aside from ostomy and surgical scar; laboratory screening showed normal electrolytes, total protein and albumin with hemoglobin/hematocrit of 10.5/33.2.

20 On Day 1 of the study, the patient was administered (by subcutaneous injection) 50 milligrams of the study drug and followed for 48 hours. The patient's total stool output measurement in the 48 hours following the initial dose of study drug was 12,550 milliliters, reflecting a total stool output reduction of about 44% from baseline. Three days following the first dose of study drug, the patient's parenteral support was decreased by 500 milliliters
25 per day (a 25% reduction) and was maintained at that level for the duration of the trial.

A second subcutaneous administration of study drug was given at 50 milligrams on Day 15. Within 48 hours of the second dose of study drug, the patient's total stool output was 13,950 milliliters, reflecting a 38% reduction from baseline. Two weeks following the second dose of study drug, the patient's body weight increased to 54.3 kg (from the 51.6 kg

baseline). Overall, the patient remained improved for the duration of the 28 days clinical trial period.

In summary, this patient with longstanding SBS and a high output end jejunostomy demonstrated an immediate and remarkable clinical response to a dose of 50 mg
5 subcutaneous injection of study drug.

SEQUENCES

SEQ ID NO: 1

Exenatide fused to AE864XTEN

5 HEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGSPAGSPTSTEEGTSESATP
ESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGTSESATP
ESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSESATPESGPGTSTEPSE
10 GSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGTSESATP
ESGPGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSTEPSEGSAPGTSTEPSE
GSAPGTSESATPESGPGTSESATPESGPGSPAGSPTSTEEGTSESATPESGPGSEPATSG
SETPGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSE
GSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSESATP
15 ESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSE
GSAPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGSPAGSPTSTEEGTSESATP
ESGPGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSG
SETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSG
SETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATP
20 ESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPT
STEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSE
GSAPG

CLAIMS

What is claimed is:

1. A method for treating short bowel syndrome and/or high output ostomy, the method comprising administering to a patient in need thereof a long-acting GLP-1 receptor agonist.
- 5 2. The method of claim 1, wherein the patient has a high output ostomy.
3. The method of claim 1 or 2, wherein the patient has an end jejunostomy.
4. The method of any one of claims 1 to 3, wherein the long-acting GLP-1 agonist is an exenatide or GLP-1 fusion with a half-life extension polypeptide.
5. The method of claim 4, wherein the half-life extension polypeptide is fused to the C-terminus of the exenatide or GLP-1.
- 10 6. The method of claim 4 or 5, wherein the half-life extension polypeptide comprises an albumin amino acid sequence, a transferrin amino acid sequence, elastin-like peptide amino acid sequence, or is an unstructured polypeptide.
7. The method of claim 6, wherein administration of the GLP-1 receptor agonist composition results in an effective amount of the GLP-1 receptor agonist in circulation for at least about one week upon subcutaneous injection.
- 15 8. The method of claim 7, wherein the long-acting GLP-1 receptor agonist is administered by subcutaneous injection.
9. The method of any one of claims 6 to 8, wherein the long-acting GLP-1 receptor agonist comprises the amino acid sequence of SEQ ID NO: 1.
- 20 10. The method of claim 9, wherein the long-acting GLP-1 receptor agonist is administered at a unit dose of about 12 milligrams to about 250 milligrams.
11. The method of claim 10, wherein the unit dose is about 50 mg to about 150 mg.

12. The method of claim 10, wherein the unit dose is about 50 mg.
13. The method of claim 10, wherein the unit dose is about 100 mg.
14. The method of claim 10, wherein the unit dose is about 150 mg.
15. The method of any one of claims 1 to 14, wherein the long-acting GLP-1 receptor agonist is administered about once weekly.
16. The method of any one of claims 1 to 14, wherein the long-acting GLP-1 receptor agonist is administered about twice monthly.
17. The method of any one of claims 1 to 14, wherein the long-acting GLP-1 receptor agonist is administered about once monthly.
18. The method of any one of claims 1 to 17, wherein the patient exhibits an average daily reduction of ostomy output of at least about 10% from baseline, or at least about 20% from baseline.
19. The method of claim 18, wherein parenteral support is reduced by at least about 10% from baseline, or at least about 20% from baseline, or at least about 30% from baseline.
20. The method of any one of claims 1 to 19, wherein the patient does not experience substantial adverse effects, such as symptoms of nausea, vomiting, hypoglycemia, pancreatitis, liver injury, and/or kidney function.
21. A method for treating a patient having short bowel syndrome, the method comprising administering to the patient by subcutaneous injection a unit dose of from about 12.5 mg to about 200 mg of the long-acting GLP-1 receptor agonist of SEQ ID NO: 1, the administration being from about once weekly to about once monthly.
22. The method of claim 21, wherein the patient has an end jejunostomy.
23. The method of claim 21, wherein the patient has a high output ostomy.

24. The method of any one of claims 21 to 23, wherein subcutaneous administration of the GLP-1 receptor agonist unit dose results in an effective amount of the GLP-1 receptor agonist in circulation for at least about one week.
25. The method of any one of claims 21 to 24, wherein the unit dose is about 50 mg to
5 about 150 mg.
26. The method of claim 25, wherein the unit dose is about 50 mg.
27. The method of claim 25, wherein the unit dose is about 100 mg.
28. The method of claim 25, wherein the unit dose is about 150 mg.
29. The method of any one of claims 21 to 28, wherein the long-acting GLP-1 receptor
10 agonist is administered about once weekly.
30. The method of any one of claims 21 to 28, wherein the long-acting GLP-1 receptor agonist is administered about twice monthly.
31. The method of any one of claims 21 to 28, wherein the long-acting GLP-1 receptor agonist is administered about once monthly.
- 15 32. The method of any one of claims 21 to 31, wherein the patient does not experience substantial adverse effects, such as symptoms of nausea, vomiting, hypoglycemia, pancreatitis, liver injury, and/or kidney function.
33. A unit dose composition of a long-acting GLP-1 receptor agonist defined by SEQ ID NO: 1, the unit dose composition comprising from about 12.5 mg to about 200 mg of the
20 long acting GLP-1 receptor agonist formulated for subcutaneous administration.
34. The unit dose composition of claim 33, wherein the unit dose is about 50 mg.
35. The unit dose composition of claim 33, wherein the unit dose is about 100 mg.
36. The unit dose composition of claim 33, wherein the unit dose is about 150 mg.

37. The unit dose composition of any one of claims 33 to 36, wherein the unit dose is contained in an injection pen.
38. The unit dose composition of claim 37, wherein the injection pen contains at least four unit doses.
- 5 39. The unit dose composition of any one of claims 33 to 38, wherein the unit doses are no more than about 1 mL or no more than about 2 mLs in volume.