for treatment of short bowel syndrome under the names Gattex (in the US) and Revestive (in Europe).

WO 2006/117565 (Zealand Pharma A/S) describes GLP-2 analogues which comprise one of more substitutions as compared to [hGly2]GLP-2 and which improved biological activity *in vivo* and/or improved chemical stability, e.g. as assessed in *in vitro* stability assays.

Among the molecules disclosed in WO 2006/117565 is ZP1848 (glepaglutide) which has been designed to be stable in liquid formulations. Dosage regimes for GLP-2 analogues including ZP1848 and its metabolites are described in WO 2018/229252, which also shows that these compounds are effective to increase longitudinal growth of the intestines.

Use of GLP-2 analogues, including ZP1848, to treat conditions associated with bile acid synthesis, liver bile acid content, or intestinal bile acid content is described in WO 2020/020904.

Ready-to use formulations of ZP1848 are described in WO 2020/065064.

Summary

Clearance of teduglutide is impaired in subjects with renal dysfunction, and in particular in patients with moderate or severe renal impairment, or end stage renal disease (ESRD). Consequently, it is recommended that the normal dose of teduglutide is reduced by 50% for patients with moderate renal impairment, severe renal impairment, or ESRD. See, for example, Nave, R et al., Eur. J. Clin. Pharmacol. 2013, 69(5): 1149-1155, Summary of Product Characteristics of Revestive® (European Medicines Agency), European Medicines Agency (2012) European Public Assessment Report of Revestive®.

Since ZP1848 is also a GLP-2 analogue, similar considerations might reasonably be expected to apply.

Surprisingly, though, it has been found that ZP1848 is cleared normally in patients with renal impairment. As a result, there is no need to adjust the dosage of ZP1848 depending on a patient's renal function. This provides a number of benefits. Firstly, it means that patients with impaired renal function are able to receive a full therapeutically effective dose without undesirable side effects, e.g. caused by over-exposure to the active agent. In addition, it obviates the need to test a patient's renal function before prescribing ZP1848, resulting in more efficient and economical treatment. Furthermore, safety should be

improved in the event that a patient already receiving ZP1848 develops a form of renal impairment, since there should be no need to adjust their dose to take account of the renal event.

Thus, in a first example, the disclosure provides ZP1848 or a pharmaceutically acceptable salt thereof for use in prophylaxis or treatment of a condition responsive thereto in a subject with at least moderate renal impairment, wherein no dose adjustment of ZP1848 or said salt is required. In another aspect, it is referred to the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for prophylaxis or treatment of a condition responsive thereto in a subject with at least moderate renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides a method of prophylaxis or treatment of a condition responsive thereto in a subject with at least moderate renal impairment, comprising administering ZP1848 or a pharmaceutically acceptable salt thereof to said subject, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for prophylaxis or treatment of a condition responsive thereto in a subject with at least moderate renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

The term "at least moderate" renal impairment is used in this specification to include subjects having moderate renal impairment, severe renal impairment, or ESRD.

Thus, the subject would typically require an adjusted dose of teduglutide, if teduglutide were to be prescribed for treatment of the same condition. The subject may or may not previously have been treated with teduglutide, e.g. at an adjusted dose.

In a further example, the disclosure provides ZP1848 or a pharmaceutically acceptable salt thereof for use in prophylaxis or treatment of a condition responsive thereto in a subject for whom an adjusted dose of teduglutide would be indicated as a result of renal impairment, wherein no dose adjustment of ZP1848 or said salt is required. In another aspect, it is referred to the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for prophylaxis or treatment of a condition responsive thereto in a subject for whom an adjusted dose of teduglutide would

be indicated as a result of renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides a method of prophylaxis or treatment of a condition responsive to ZP1848 in a subject for whom an adjusted dose of teduglutide would be indicated as a result of renal impairment, comprising administering ZP1848 or a pharmaceutically acceptable salt thereof to said subject, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for prophylaxis or treatment of a condition responsive thereto in a subject for whom an adjusted dose of teduglutide would be indicated as a result of renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

Thus, the subject may have at least moderate renal impairment, e.g. moderate renal impairment, severe renal impairment, or ESRD.

The subject would typically require an adjusted dose of teduglutide, if teduglutide were to be prescribed for treatment of the same condition. The subject may or may not previously have been treated with teduglutide, e.g. at an adjusted dose.

In a further example, the disclosure provides ZP1848 or a pharmaceutically acceptable salt thereof for use in prophylaxis or treatment of a condition responsive thereto in a subject who has received an adjusted dose of teduglutide due to renal impairment, wherein no dose adjustment of ZP1848 or said salt is required. In another aspect, it is referred to the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for prophylaxis or treatment of a condition responsive thereto in a subject who has received an adjusted dose of teduglutide due to renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides a method of prophylaxis or treatment of a condition responsive to ZP1848 in a subject who has received an adjusted dose of teduglutide due to renal impairment, comprising administering ZP1848 or a pharmaceutically acceptable salt thereof to said subject, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for prophylaxis or treatment of a condition responsive thereto in a subject who has received an adjusted dose of teduglutide due to renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

Thus the subject will previously have received teduglutide, at an adjusted dose, for treatment of the same condition. Typically, the subject has at least moderate renal impairment, e.g. moderate renal impairment, severe renal impairment, or ESRD.

The condition to be treated may be any condition therapeutically responsive to treatment with a GLP-2 analogue, e.g. where treatment results in amelioration of one or more symptoms, amelioration of underlying pathology, delay of onset, and/or inhibition of progression. Thus prophylaxis may be considered treatment or therapy.

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Such conditions include stomach and bowel-related disorders such as ulcers, digestion disorders, malabsorption syndromes, short-gut syndrome, inflammatory bowel disease, celiac sprue (for example arising from gluten induced enteropathy or celiac disease), tropical sprue, hypogammaglobulinemic sprue, enteritis, regional enteritis (Crohn's disease), ulcerative colitis, small intestine damage or short bowel syndrome (SBS).

Use for the treatment of short bowel syndrome (SBS) may be of particular interest, especially in a subject receiving parenteral support (PS).

Further conditions include stomach and bowel-related disorders such radiation enteritis, infectious or post-infectious enteritis, or small intestinal damage due to toxic or other chemotherapeutic agents. In this case, treatment with the GLP-2 analogue may optionally be combined with one or more anti-cancer therapies, and may therefore comprise adminstering one or more chemotherapeutic agent(s) to the subject or treating the subject with radiation therapy.

Thus the condition may be a side effect of chemotherapy or radiation treatment in a human subject.

The terms "subject" and "patient" are used interchangeably in this specification. It will be understood that the subject (or patient) is a mammal, and typically a human.

ZP1848 is also effective in increasing intestinal mass and longitudinal intestinal growth, particularly in the small intestine.

Thus, in a further example, the disclosure provides ZP1848 or a pharmaceutically acceptable salt thereof for use in increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject with at least moderate renal impairment, wherein no dose adjustment of ZP1848 or said salt is required. In another aspect, it is referred to the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject with at least moderate renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides a method of increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject with at least moderate

renal impairment, comprising administering ZP1848 or a pharmaceutically acceptable salt thereof to said subject, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for increasing intestinal mass and/or promoting

or increasing longitudinal intestinal growth in a subject with at least moderate renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

Thus, the subject would typically require an adjusted dose of teduglutide, if teduglutide were to be used for the same purpose. The subject may or may not previously have been treated with teduglutide, e.g. at an adjusted dose.

In a further example, the disclosure provides ZP1848 or a pharmaceutically acceptable salt thereof for use in increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject for whom an adjusted dose of teduglutide would be indicated as a result of renal impairment, wherein no dose adjustment of ZP1848 or said salt is required. In another aspect, it is referred to the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject for whom an adjusted dose of teduglutide would be indicated as a result of renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides a method of increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject for whom an adjusted dose of teduglutide would be indicated as a result of renal impairment, comprising administering ZP1848 or a pharmaceutically acceptable salt thereof to said subject, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject for whom an adjusted dose of teduglutide would be indicated as a result of renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

Thus, the subject may have at least moderate renal impairment, e.g. moderate renal impairment, severe renal impairment, or ESRD.

The subject would typically require an adjusted dose of teduglutide, if teduglutide were to be prescribed for the same purpose. The subject may or may not previously have been treated with teduglutide, e.g. at an adjusted dose.

In a further example, the disclosure provides ZP1848 or a pharmaceutically acceptable salt thereof for use in increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject who has received an adjusted dose of teduglutide due to renal impairment, wherein no dose adjustment of ZP1848 or said salt is required. In another aspect, it is referred to the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject who has received an adjusted dose of teduglutide due to renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides a method of increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject who has received an adjusted dose of teduglutide due to renal impairment, comprising administering ZP1848 or a pharmaceutically acceptable salt thereof to said subject, wherein no dose adjustment of ZP1848 or said salt is required.

The disclosure further provides the use of ZP1848 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth in a subject who has received an adjusted dose of teduglutide due to renal impairment, wherein no dose adjustment of ZP1848 or said salt is required.

Thus the subject will previously have received teduglutide, at an adjusted dose, e.g. for the same purpose. Typically, the subject has at least moderate renal impairment, e.g. moderate renal impairment, severe renal impairment, or ESRD.

In such examples, the subject may be affected by a condition in which increasing intestinal mass and/or promoting or increasing longitudinal intestinal growth is desirable, e.g. therapeutic. This may include any of the conditions set out elsewhere in this specification, but especially subjects affected by short bowel syndrome (SBS), e.g. those receiving parenteral support.

In a further aspect, the disclosure provides a pharmaceutical kit comprising ZP1848 or a pharmaceutically acceptable salt thereof and information that no dose adjustment of ZP1848 is required for subjects having at least moderate renal impairment. In another aspect, it is referred to a pharmaceutical kit comprising ZP1848 or a pharmaceutically acceptable salt thereof and information that no dose adjustment of ZP1848 is required for subjects having at least moderate renal impairment.

The ZP1848 or pharmaceutically acceptable salt will typically be provided as a pharmaceutical composition, comprising ZP1848 or said salt in combination with a pharmacetically acceptable carrier or excipient.

The kit may comprise one or more individual measured doses of ZP1848 or said salt, wherein each individual measured dose is an anadjusted dose as described elsewhere in this specification.

The individual doses may be for administration via a dosing regime as described elsewhere in this specification.

The kit may further comprise one or more chemotherapeutic agents, which may be provided in a separate pharmaceutical composition to ZP1848 or salt thereof.

It will be understood that subjects treated according to any example of the disclosure will typically receive ZP1848 or a pharmaceutically acceptable salt thereof instead of teduglutide (and any other GLP-2 receptor agonist), i.e. ZP1848 or the relevant salt will typically be the sole GLP-2 receptor agonist used for treatment of the subject. Similarly the compositions and kits defined herein typically contain ZP1848 or the relevant salt as the sole GLP-2 receptor agonist.

In the context of the present disclosure, an "adjusted" dose is a dose which has been reduced to take account of renal impairment. Thus, the dose of teduglutide is reduced by 50% when administered to subjects with at least moderate renal impairment to account for impaired clearance of the drug from the system of such patients, and to avoid over-exposure of the patient to the drug.

For ZP1848 and salts thereof, there is no need to adjust the dose to account for renal impairment in the patient. Thus, the dose for such subjects can be the same as that which would be provided to an otherwise equivalent subject with normal renal function. This may be referred to as the "normal", "standard", or "unadjusted" dose. It will be understood that a small amount of variation may nevertheless be permitted, e.g. +/- 10%, without being considered an "adjusted" dose. Typically an "adjusted" dose would vary by more than 30%, e.g. more than 40%, e.g. about 50%.

It will, of course, be understood that the "normal" dose may be determined depending on the particular subject, e.g. depending on their age, sex, weight, disease status, etc. and/or on the intended dosage regime. Again, such variations should not be considered to result in an "adjusted" dose within the meaning of the disclosure. Rather, "adjusted" should be construed to mean "adjusted for considerations of renal function" or similar, unless the context demands otherwise.

Administration may be according to any suitable dosing regime.

For example, administration may be once daily.

However, as descibed in WO 2018/229252, ZP1848 has an unexpectedly long half-life which may enable alternative regimes such as once or twice weekly adminstration,

especialy when delivered by subcutaneous injection. Without wishing to be bound by theory, it is believed that the half life of ZP1848 may be due to the combination of the formation of a subcutaneous depot and the formation of metabolites which are slowly released from the subcutaneous depot and which are also agonistic on the GLP-2 receptor. The subcutaneous depot may be formed on administration through a reaction between the lysine tail of ZP1848 and hyaluronic acid in the subcutaneous compartment.

Thus the dosing regime may comprise a plurality or course of doses separated in time by 2 days, 2.5 days, 3 days, 3.5 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days or 12 days. In a preferred example, the doses are separated in time by 3 days, 3.5 days, 4 days, 5 days, 6 days, 7 days or 8 days. In a preferred example, doses are separated in time by 3 days, 3.5 days, 4 days or 7 days. As will be appreciated in the art, the time between doses may be varied to some extent so that each and every doses is not separated by precisely the same time. This will often be directed under the discretion of the physician. Thus, doses may be separated in time by a clinically acceptable range of times, e.g. from about 2 days to about 10 days, or from about 3 or 4 days to about 7 or 8 days.

A typical "normal" or "unadjusted" dose may be in the range between 0.5 mg and 25 mg inclusive per subject per administration.

For example, it may be between 1 mg and 20 mg inclusive per subject per dose, e.g. between 1 mg and 10 mg inclusive per subject per dose, e.g. between 2 mg and 7 mg inclusive per subject per dose, e.g. between 5 mg and 7 mg inclusive per subject per dose, or between 2 mg and 5 mg inclusive per per subject per dose.

Alternatively, it may be between 5 mg and 15 mg inclusive per subject per dose, e.g. between 7 mg and 12 mg inclusive per subject per dose, e.g. between 9 mg and 11 mg inclusive per subject per dose.

In some examples, the dose of the GLP-2 analogues used in accordance with the present disclosure is about 10 mg per subject per dose (where "about" signifies +/- 10%).

In some examples, the dose of the GLP-2 analogues used in accordance with the present disclosure is a fixed dose of 10 mg per subject.

Such doses may be appropriate for any dosage regime, but particularly a once or twice weekly regime.

In a course of treatment, the doses taken by the patient may either be the same or different in accordance with the instructions from the physician.

In some cases, it may be desirable to divide a total dose into a plurality (e.g. two or three) separate doses or administrations, for example for administration at spaced apart injection sites, for example spacing the injection sites at least 5 cm apart. Such spatially separate adminstrations wiil typically be provided at substantially the same time, e.g. on the same day, within one hour of each other, or even closer in time.

Examples of the present disclosure will now be described by way of example and not limitation However, various further example and examples of the present disclosure will be apparent to those skilled in the art in view of the present disclosure.

Unless context dictates otherwise, the descriptions and definitions of the features set out above are not limited to any particular example or example of the disclosure and apply equally to all examples and examples which are described.

Detailed Description of the Invention

Throughout the description and claims the conventional one-letter and three-letter codes for natural amino acids are used. All amino acid residues in the compounds described are typically of the L-configuration.

Compounds

ZP1848 is a peptide having the formula:

H-HGEGTFSSELATILDALAARDFIAWLIATKITDKKKKKK-NH_2

as described e.g. in WO 2006/117565. It will be understood that the N-terminal "H-" indicates a free N-terminal amine (NH_2-) group. The C-terminal "NH_2-" indicates a C-terminal amide group. The terms ZP1848 and glepaglutide may be used interchangeably.

The invention encompasses the use of pharmaceutically acceptable salts of ZP1848, as described in more detail below. Any suitable salt may be used, although acetate may be preferred.

When ZP1848 is injected into the subcutaneous (SC) compartment, two functionally active