Claims:

Claim 1. A process for manufacturing a stable liquid pharmaceutical formulation comprising a glucagon-like peptide 2 (GLP-2) analogue, wherein the GLP-2 analogue is represented by the formula:

ZP1848 H-HGEGTFSSELATILDALAARDFIAWLIATKITDKKKKKK-NH2 (SEQ ID NO: 1) or

ZP1846 H-HGEGSFSSELSTILDALAARDFIAWLIATKITDKKKKKK-NH2 (SEQ ID NO: 7);
or a pharmaceutically acceptable salt or derivative thereof;

wherein the liquid pharmaceutical formulation comprises the GLP-2 analogue at a concentration of about 2 mg/mL to about 30 mg/mL and excipients comprising (i) a histidine buffer present at a concentration of about 5 mM to about 50 mM, (ii) mannitol as a non-ionic tonicity modifier present at a concentration of about 90 mM to about 360 mM and with (iii) arginine q.s. to provide a formulation having a pH of about 6.6 to about 7.4;

wherein the process comprises:

(a) mixing the excipients with a first volume of water for injection to provide an excipient solution at 70-90% of the volume of a final liquid formulation;

(b) adding the GLP-2 analogue drug substance to the excipient solution to provide a solution of the excipients and the GLP-2 analogue at 70-90% of the volume of a final liquid formulation; and

(c) adjusting the pH and the volume of the liquid composition as needed to provide a liquid formulation at 100% of the volume of the final liquid pharmaceutical formulation;

wherein the process provides a final aqueous liquid pharmaceutical formulation comprising a glucagon-like peptide 2 (GLP-2) analogue.

Claim 2. The process of claim 1, wherein the process does not require stirring when the GLP-2 drug substance is added to the excipient solution.

Claim 3. The process of claim 1 or claim 2, wherein the GLP-2 analogue drug

substance is added as a lyophilized composition.

Claim 4. The process of any one of claims 1 to 3, wherein adjusting the volume of the liquid composition in step (c) comprises a first addition of water for injection to adjust the pH and a second addition of water for injection to increase the volume of the liquid composition towards the final volume, optionally wherein adjusting the pH of the liquid composition is carried out by adding arginine and/or acetic acid.

Claim 5. The process of any one of the preceding claims, wherein the excipient solution is at about 80% the volume of a final liquid formulation and the first and second additions each add about 10% of the volume of a final liquid formulation.

Claim 6. The process of any one of claims 1 to 4, wherein the excipient solution is at about 75% the volume of a final liquid formulation and the first and second additions each add about 15% and about 10% of the volume of a final liquid formulation.

Claim 7. The process of any one of the preceding claims, wherein the drug substance is added in 1-5 portions, preferably 3 portions.

Claim 8. The process of any one of the preceding claims, further comprising sterile filtering the final liquid pharmaceutical formulation.

Claim 9. The process of any one of the preceding claims, further comprising dividing the final liquid pharmaceutical formulation into doses.

Claim 10. The process of any one of the preceding claims, further comprising quality control testing the final liquid pharmaceutical formulation and comparing results of the quality control testing with a reference.

Claim 11. The process of any one of the preceding claims, wherein the process uses a batch size of 10-50 litres of final liquid pharmaceutical formulation, and optionally a batch size of 10-20 litres of final liquid pharmaceutical formulation, and optionally a batch size of 20-50 litres of final liquid pharmaceutical formulation.

Claim 12. The process of any one of the preceding claims, wherein the process is carried out in a 10 litre or a 20 litre tank.

Claim 13. The process of any one of the preceding claims, wherein

(i) mechanical stirring is used in step (b) to dissolve the GLP-2 analogue drug substance, e.g. using a stirrer wing; and/or

(ii)the process is carried out under nitrogen.

Claim 14. The process of any one of the preceding claims, wherein the process comprises performing a visual control after step (a) to determine whether the excipients have (fully) dissolved and/or wherein the process comprises performing a visual control after step (b) to determine whether the GLP-2 analogue and the excipients have substantially completely dissolved and/or wherein the process comprises performing a visual control after step (c) to determine whether the process has produced a solution of the GLP-2 analogue and excipients.

Claim 15. The process of any one of the preceding claims, wherein step (b) comprises washing a vessel or transfer bag/container that contained the lyophilized GLP-2 analogue to remove any residual GLP-2 analogue.

Claim 16. The process of any one of the preceding claims, wherein

(i) the addition of the GLP-2 analogue in step (b) reduces foaming of the composition comprising the GLP-2 analogue and the excipients and/or formation of residual lumps of the GLP-2 analogue. to secure visual control of clear solution at the end of the process; and/or

(ii) the addition of the GLP-2 analogue in step (b) reduces the level of covalently linked high molecular weight species in the final liquid pharmaceutical formulation.

Claim 17. The process of any one of the preceding claims, wherein the GLP-2 analogue is in the form of an acetate salt represented by the formula:

H-HGEGTFSSELATILDALAARDFIAWLIATKITDKKKKKK-NH_2 acetate (SEQ ID NO: 1).

Claim 18. The process of claim 17, wherein the acetate salt of a glucagon-like peptide 2 (GLP-2) analogue has the formula:

(H-HGEGTFSSELATILDALAARDFIAWLIATKITDKKKKKK-NH_2), x(CH_3COOH) where x is 1.0 to 8.0; or

(H-HGEGSFSSELSTILDALAARDFIAWLIATKITDKKKKKK-NH_2), x(CH_3COOH) where x is 1.0 to 8.0.

Claim 19. The process of claim 18, wherein in the formula of acetate salt of the glucagon-like peptide 2 analogue, x is from 2.0 to 6.0.

Claim 20. The process of any one of the preceding claims, wherein the formulation is stable for at least 18 months when stored at 2-8ºC.

Claim 21. The process of any one of the preceding claims, wherein the histidine buffer is present at a concentration of about 5 mM to about 25 mM.

Claim 22. The process of claim 21, wherein the histidine buffer is present at a concentration of about 15 mM.

Claim 23. The process of any one of the preceding claims, wherein mannitol is present as the non-ionic tonicity modifier at a concentration of about 150 mM to about 250 mM.

Claim 24. The process of any one of the preceding claims, wherein the formulation has a pH of about 6.8 to about 7.2.

Claim 25. The process of claim 24, wherein the formulation has a pH of about 7.0.

Claim 26. The process of any one of the preceding claims, wherein the formulation comprises the GLP-2 analogue, or the pharmaceutically acceptable salt thereof; at a concentration of about 20 mg/mL, histidine buffer at a concentration of about 15 mM, mannitol at a concentration of about 230 mM, and arginine q.s. to provide a pH of about 7.0.

Claim 27. The process of any one of the preceding claims, wherein the histidine buffer is L-histidine and/or the mannitol is D-mannitol.

Claim 28. The process of any one of the preceding claims, further comprising loading the formulation into a pre-filled syringe, an injection pen or an injector device.

Claim 29. The process of any one of the preceding claims, wherein the process

reduces the formation of covalently bonded oligomeric products of the glucagon-like peptide 2 (GLP-2) analogue in a stable liquid pharmaceutical formulation.

Claim 30. Use of a formulation for reducing the formation of covalently bonded oligomeric products of a glucagon-like peptide 2 (GLP-2) analogue, wherein the GLP-2 analogue is represented by the formula:

ZP1848 H-HGEGTFSSELATILDALAARDFIAWLIATKITDKKKKKK-NH_2 (SEQ ID NO: 1) or

ZP1846 H-HGEGSFSSELSTILDALAARDFIAWLIATKITDKKKKKK-NH_2 (SEQ ID NO: 7);

or a pharmaceutically acceptable salt thereof;

wherein the liquid pharmaceutical formulation comprises the GLP-2 analogue at a concentration of about 2 mg/mL to about 30 mg/mL and excipients comprising (i) a histidine buffer present at a concentration of about 5 mM to about 50 mM, (ii) mannitol as a non-ionic tonicity modifier present at a concentration of about 90 mM to about 360 mM and with (iii) arginine q.s. to provide a formulation having a pH of about 6.6 to about 7.4;

wherein the use comprises:

(a) mixing the excipients with a first volume of water for injection to provide an excipient solution at 70-90% of the volume of a final liquid formulation;

(b) adding the GLP-2 analogue drug substance to the excipient solution to provide a solution of the excipients and the GLP-2 analogue at 70-90% of the volume of a final liquid formulation; and

(c) adjusting the pH and the volume of the liquid composition as needed to provide a liquid formulation at 100% of the volume of the final liquid pharmaceutical formulation;

wherein the process provides a final aqueous liquid pharmaceutical formulation comprising a glucagon-like peptide 2 (GLP-2) analogue.