An alternative amylin analogue incorporating N-methylated residues and having a reduced tendency to fibrillation, designated IAPP-GI, has been described by Yan et al. (PNAS, 103(7), 2046-2051, 2006; Angew. Chem. Int. Ed. 2013, 52, 10378-10383; WO2006/042745). IAPP-GI appears to have lower activity than native amylin, however.

WO 2018/046719 describes amylin analogues having, inter alia, a lactam bridge instead of a disulfide bridge, N-methylated residues, and a deletion corresponding to the residues Asn21 and Asn22 of native human amylin. Such analogues have considerably lower tendency towards fibrillation than native amylin, while also having higher potency than the analogues described by Yan et al. (supra). They are typically amenable to formulation at, or near to, physiological pH. However, there is a need to develop improved formulations for these analogues, especially to provide stable formulations capable of long-term storage without undue fibrillation or degradation of the active monomeric form of the peptide.

Summary

Broadly, the disclosure is based on studies described in the examples that led to surprising findings regarding aqueous formulations of the amylin analogue, that are particularly suitable for long term storage. In particular, it was found that a low buffer concentration and a particular pH range are unexpectedly significant for optimal stability.

The disclosure provides a stable aqueous liquid pharmaceutical formulation comprising an amylin analogue, which is:
[19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNT-Hyp-NH_2
wherein "[19CD]" represents 19-carboxy-nonadecanoyl and "()" shown after the amino acid residues indicate residues whose side chains participate in an intramolecular lactam bridge;
or a pharmaceutically acceptable salt and/or derivative thereof;
wherein the formulation comprises:

(a) the amylin analogue at a concentration of from 0.4 mg/ml to 25 mg/ml; and

(b) a buffer at a concentration of 0.5 mM to 25 mM;

wherein the formulation has a pH of 5.8 to 6.9.

Claims:

1. A stable aqueous liquid pharmaceutical formulation comprising an amylin analogue, which is:
[19CD]-isoGlu-RD()GTATK()ATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNT-Hyp-NH_2
wherein "[19CD]" represents 19-carboxy-nonadecanoyl and "()" shown after the amino acid residues indicate residues whose side chains participate in an intramolecular lactam bridge;

or a pharmaceutically acceptable salt thereof;

wherein the formulation comprises:

(a) the amylin analogue at a concentration of from 0.4 mg/ml to 25 mg/ml; and

(b) a buffer at a concentration of 0.5 mM to 25 mM;

wherein the formulation has a pH of 5.8 to 6.9.

2. The stable aqueous liquid formulation of claim 1, wherein the amylin analogue is present at a concentration of at least 0.4 mg/ml, at least 0.5 mg/ml, at least 0.6 mg/ml, at least 1.2 mg/ml, or at least 2.5 mg/ml.

3. The stable aqueous liquid formulation of any one of the preceding claims, wherein the amylin analogue is present at up to 25 mg/ml, up to 20 mg/ml, up to 15 mg/ml, or up to 10 mg/ml.

4. The stable aqueous liquid formulation of any one of the preceding claims, wherein the amylin analogue is present at a concentration of 3 mg/ml to 12 mg/ml, e.g. 3 mg/ml to 7 mg/ml or 8 mg/ml to 12 mg/ml, e.g. about 5 mg/ml or about 10 mg/ml.

5. The stable aqueous liquid formulation of any one of the preceding claims, wherein the buffer is present at a concentration of 0.5 mM to 20 mM, e.g. 0.5 mM to 15 mM, e.g. 1 mM to 15 mM, e.g. 1 mM to 12 mM.

6. The stable aqueous liquid formulation of any one of the preceding claims, wherein the buffer is present at a concentration of 3 mM to 7 mM or 8 mM to 12 mM, e.g. about 5 mM or about 10 mM.

7. The stable aqueous liquid formulation of any one of the preceding claims, wherein the buffer is phosphate, histidine or citrate.

8. The stable aqueous liquid formulation of any one of claims 1 to 6, wherein the buffer is TRIS buffer, and wherein the buffer is present at 15 mM to 25 mM, e.g. 17 mM to 23 mM, e.g. about 20 mM.

9. The stable aqueous liquid formulation of any one of the preceding claims, wherein the pH is 6.2 to 6.8, e.g. 6.4 to 6.6, e.g. about 6.5.

10. The stable aqueous liquid formulation of any one of the preceding claims, further comprising a tonicity modifier.

11. The stable aqueous liquid formulation of any one of the preceding claims, wherein the formulation is stable at 2-8°C for at least 6 months, at least 12 months, at least 18 months or at least 24 months.

12. The stable aqueous liquid formulation of any one of the preceding claims, wherein the formulation displays no turbidity, or aggregation, fibrillation or gelling of the amylin analogue, after storage at 2-8°C for at least 6 months, at least 12 months, at least 18 months or at least 24 months.

13. The stable aqueous liquid formulation of any one of the preceding claims, wherein at least 80%, more preferably at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% of the amylin analogue remains in intact monomeric form in the formulation after it has been stored at 2-8°C for at least 6 months, at least 12 months, at least 18 months or at least 24 months.

14. The stable aqueous liquid formulation of any one of the preceding claims, wherein the amylin analogue is provided as a chloride salt.

15. The stable aqueous liquid formulation of any one of the preceding claims, wherein the formulation is formulated for administration to a subject by injection, e.g.

wherein the injection is subcutaneous injection.