GLP-1 COMPOSITIONS AND USES THEREOF

The present invention relates to the field of pharmaceutical compositions comprising the GLP-1 peptide semaglutide.

BACKGROUND

Marketed liquid pharmaceutical compositions comprising the GLP-1 peptide semaglutide comprise preservative and are intended for multiple use. To further improve the ease of use and convenience for patients, it is desirable to develop compositions comprising GLP-1 peptides for single use administration. These compositions should be stable and comfortable to administer to the patient in need.

US2019388502 reports mild pain injection upon subcutaneously injection of phenol free pharmaceutical compositions comprising the GIP/GLP1 co-agonist peptide Tirzepatide and either propylene glycol or sodium chloride.

SUMMARY

In some embodiments the invention relates to a liquid pharmaceutical composition comprising semaglutide, no more than 0.1 %(w/w) phenol and above 6.4 mg/ml sodium chloride. In some embodiments the invention relates to kits comprising the pharmaceutical composition as defined herein. In some embodiments the invention relates to the pharmaceutical composition as defined herein for use in medicine.

DESCRIPTION

The present invention relates to a liquid pharmaceutical composition comprising semaglutide, no more than 0.1 %(w/w) phenol and above 6.4 mg/ml sodium chloride. Surprisingly, the present inventors found that such compositions have improved properties in relation to injection pain experience. In some embodiments the liquid pharmaceutical composition comprises no more than 0.09, alternatively 0.08, alternatively 0.07, alternatively 0.06, alternatively 0.05, alternatively 0.04, alternatively 0.03, alternatively 0.02, alternatively 0.01 %(w/w) phenol. In some embodiments the liquid pharmaceutical composition comprises no phenol. In some embodiments the liquid pharmaceutical composition comprises 5.0-7.0 mg/ml sodium chloride. In some embodiments the liquid pharmaceutical composition comprises about 6.4 mg/ml sodium chloride. In some embodiments the liquid pharmaceutical composition comprises 6.4-7.9 mg/mL sodium chloride, such as 6.4-7.5 mg/ml sodium chloride. In some embodiments the liquid pharmaceutical composition comprises above 7.0,

alternatively above 7.2, alternatively above 7.5, alternatively above 7.7, alternatively above 8, alternatively above 8.2, alternatively above 8.25 mg/ml sodium chloride. In some embodiments the liquid pharmaceutical composition comprises 6.5-12 mg/ml sodium chloride. In some embodiments the liquid pharmaceutical composition comprises 7-12, alternatively 7.5-12, alternatively 8-12 mg/ml sodium chloride. In some embodiments the liquid pharmaceutical composition comprises 7-9.5, alternatively 7-9, alternatively 7-8.25 mg/ml sodium chloride. In some embodiments the liquid pharmaceutical composition comprises 7-10, alternatively 7-9.5, alternatively 8-9, alternatively 8.1-8.9, alternatively 8.1-8.8, alternatively 8.2-8.7, alternatively 8.2-8.6, alternatively 8.2-8.5, alternatively 8.2-8.4, alternatively 8.2-8.3 mg/ml sodium chloride. In some embodiments the liquid pharmaceutical composition comprises 8.25 mg/ml sodium chloride. In some embodiments the liquid pharmaceutical composition

a. is for parenteral administration;

b. is an aqueous solution comprising at least 60 %w/w water; or

c. further comprises a buffer.

In some embodiments the liquid pharmaceutical composition comprises a) semaglutide, such as 0.01-3.5 mg/ml semaglutide or 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) an isotonic agent, d) buffer, e) at least 60% water, and f) histidine. In some embodiments the isotonic agent is sodium chloride. In some embodiments the isotonic agent is sodium chloride.

In some embodiments the liquid pharmaceutical composition comprises a) semaglutide, such as 0.01-3.5 mg/ml semaglutide or 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) sodium chloride as isotonic agent d) buffer, e) at least 60% water, and f) histidine. In some embodiments the liquid pharmaceutical composition comprises a) semaglutide, such as 0.01-3.5 mg/ml semaglutide or 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 2-12 mg/ml sodium chloride, such as 3-12 mg/ml, such as 4-12 mg/l, such as 5-12 mg/ml, such as 6-12 mg/ml, such as 7-12 mg/ml, such as 8-12 mg/ml, such as 8.1-12 mg/ml, such as 8.2-12 mg/ml sodium chloride d) buffer, e) at least 60% water, and f) histidine.

In some embodiments the liquid pharmaceutical composition comprises a) semaglutide, such as 0.1-10 mg/ml semaglutide or 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 5.0-5.0 mg/ml sodium chloride, such as 5.4 or 6.7 mg/ml, d) buffer, e) at least 60% water, and f) histidine.

In some embodiments the liquid pharmaceutical composition comprises a) semaglutide, such as 0.1-10 mg/ml semaglutide or 0.5-10 mg/ml semaglutide, optionally b)

no more than 0.1 %(w/w) phenol, c) sodium chloride, d) phosphate, e) water for injection, f) histidine, and optionally NaOH/HCl to reach pH 7-8, such as pH 7.4.

In some embodiments the liquid pharmaceutical composition comprises a) semaglutide, such as 0.1-10 mg/ml semaglutide or 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) about 6.4 mg/ml sodium chloride, such as 6.7-12 mg/ml, such as 6.72-12 mg/l sodium chloride, d) buffer, e) at least 60% water, and f) histidine.

In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) 3.2 mg/ml semaglutide, optionallyb) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium

chloride, d) buffer, e) at least 97% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.25 mg/ml sodium chloride, d) buffer, e) at least 97% water (such as 97-99%), optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8.

In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate such as sodium acetate or acetic acid, and said composition optionally has a pH of 6-10, such as 7-8.

In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 6.5-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 7-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 7.5-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents

for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.2-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.2-9.5 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.2-9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) 3.2 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the liquid pharmaceutical composition consists or consists essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 97% water (such as 97-99%), optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8. In some embodiments the invention relates to a kit comprising the liquid

pharmaceutical composition consisting or consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8; and an injection device comprising a needle, such as a pre-filled syringe, for administration of said composition to a subject.

In some embodiments the concentration of semaglutide is 0.5-10 mg/ml or 0.01-3.5 mg/ml of said liquid pharmaceutical composition. In some embodiments the concentration of semaglutide is 0.5 mg/ml, alternatively 1 mg/ml, alternatively 1.5 mg/ml, alternatively 2 mg/ml, alternatively 2.5 mg/ml, alternatively 3 mg/ml, alternatively 3.5 mg/ml. In some embodiments the concentration of semaglutide is 3.2 mg/ml of said liquid pharmaceutical composition. In some embodiments, semaglutide is in the form of a pharmaceutically acceptable salt. In some embodiments the liquid pharmaceutical composition is an aqueous solution comprising at least 60 %w/w water, such as at least 70 %w/w water or at least 80 %w/w water. In some embodiments the liquid pharmaceutical composition is an aqueous solution comprising at least 97 %w/w water, such as at least 98%w/w water. In some embodiments the liquid pharmaceutical composition is an aqueous solution comprising 97-99% w/w water. In some embodiments the liquid pharmaceutical composition is an aqueous solution comprising 97-98% w/w water. In some embodiments the liquid pharmaceutical composition comprises a buffer. In some embodiments, the buffer is present in a concentration of 0.01-50 mM of said composition. In some embodiments, the buffer is a phosphate buffer. In some embodiments, the phosphate buffer is selected from the group consisting of sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium phosphate. In some embodiments, the phosphate buffer is disodium hydrogen phosphate dihydrate. In some embodiments, the concentration of the phosphate buffer 1-2 mg/ml, alternatively 1.1-1.9 mg/ml, alternatively 1.2-1.7 mg/ml, alternatively 1.3-1.6 mg/ml, alternatively 1.4-1.5 mg/ml. In some embodiments, the concentration of said phosphate buffer is 1.42 mg/ml. In some embodiments the liquid pharmaceutical composition comprises one or more agents for adjusting pH, such as HCl, NaOH, or acetate such as sodium acetate or acetic acid. In some embodiments the liquid pharmaceutical composition comprises no preservative. In some embodiments the liquid pharmaceutical composition has a pH in the range of 6.0-10.0, alternatively 7-8. In some embodiments the liquid pharmaceutical composition has a pH of 7.4. In some embodiments the liquid pharmaceutical composition is for parenteral administration. In some embodiments the liquid pharmaceutical composition is for subcutaneous administration. In some embodiments the liquid pharmaceutical

composition is for use in an injection device. In some embodiments the liquid pharmaceutical composition has a mild or very mild pain intensity upon administration by injection to a patient. In some embodiments the liquid pharmaceutical composition has a very mild pain intensity upon administration by injection to a patient. In some embodiments the liquid pharmaceutical composition has a VAS score below 33, alternatively below 16 upon administration by injection to a patient. In some embodiments the liquid pharmaceutical composition has a VAS score below 20, alternatively below 15, alternatively below 10 upon administration by injection to a patient.

In some embodiments the invention relates to a liquid pharmaceutical composition further comprising histidine. In some embodiments the concentration of histidine is 0.5-100 mM, alternatively 0.5-50 mM, alternatively 0.5-20 mM, alternatively 0.5-15 mM, alternatively 0.5-10 mM. In some embodiments the concentration of histidine is 2-100 mM, alternatively 2-50 mM, alternatively 2-20 mM, alternatively 2-15 mM, alternatively 2-10 mM. In some embodiments the concentration of histidine is 5-100 mM, alternatively 5-50 mM, alternatively 5-20 mM, alternatively 5-15 mM, alternatively 5-10 mM. In some embodiments the concentration of histidine is 10-100 mM, alternatively 10-50 mM, alternatively 10-20 mM, alternatively 10-15 mM. In some embodiments the invention relates to a liquid pharmaceutical composition, wherein fewer impurities are generated during storage. In some embodiments the invention relates to a liquid pharmaceutical composition, wherein fewer HMWPs are generated during storage. In some embodiments the invention relates to a liquid pharmaceutical composition, wherein fewer hydrophobic impurities 1 are generated during storage. In some embodiments the invention relates to a liquid pharmaceutical composition, wherein fewer hydrophobic impurities 2 are generated during storage. In some embodiments the invention relates to a liquid pharmaceutical composition, wherein an improved chemical stability of the composition is obtained.

In some embodiments the invention relates to a liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, above 6.4 mg/ml sodium chloride and 1-2 mg/ml phosphate buffer. In some embodiments the invention relates to a liquid pharmaceutical composition which is essentially free of phenol, the composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, above 6.4 mg/ml sodium chloride and 1-2 mg/ml phosphate buffer. In some embodiments the invention relates to a liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 7-9 mg/ml sodium chloride and 1-2 mg/ml phosphate buffer. In some embodiments the invention relates to a liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, above 6.4 mg/ml sodium chloride, 0.5-

10 mM histidine, and 1-2 mg/ml phosphate buffer. In some embodiments the invention relates to a liquid pharmaceutical composition being essentially free of phenol, the composition comprising 0.5-3.5 mg/ml semaglutide, above 6.4 mg/ml sodium chloride, 0.5-10 mM histidine, and 1-2 mg/ml phosphate buffer. In some embodiments the invention relates to a liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 7-9 mg/ml sodium chloride, 0.5-10 mM histidine, and 1-2 mg/ml phosphate buffer. In some embodiments the invention relates to a liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 7-9 mg/ml sodium chloride and 1-2 mg/ml disodium hydrogen phosphate dihydrate. In some embodiments the invention relates to a liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 7-9 mg/ml sodium chloride, 0.5-10 mM histidine, and 1-2 mg/ml disodium hydrogen phosphate dihydrate. In some embodiments the invention relates to a liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 8.25 mg/ml sodium chloride and 1.42 mg/ml disodium hydrogen phosphate dihydrate. In some embodiments the invention relates to a liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 8.25 mg/ml sodium chloride, 0.5-10 mM histidine, and 1.42 mg/ml disodium hydrogen phosphate dihydrate.

In some embodiments the invention relates to a kit comprising the liquid pharmaceutical composition according to the invention and instructions for use. In some embodiments the invention relates to a kit comprising the liquid pharmaceutical composition according to the invention and an injection device for administration of said composition to a subject. In some embodiments the injection device is selected from the group consisting of a durable pen and a prefilled pen. In some embodiments the invention relates to a kit comprising the liquid pharmaceutical composition according to the invention and an injection device comprising a needle, such as a pre-filled syringe, for administration of said composition to a subject.

In some embodiments the invention relates to a liquid pharmaceutical composition of the invention for use in medicine. In some embodiments the invention relates to a liquid pharmaceutical composition of the invention for use in the treatment and/or prevention of diabetes, obesity, NASH, Alzheimer's disease and/or cardiovascular diseases. In some embodiments the invention relates to a method for the prevention or treatment of diabetes or obesity, wherein the liquid pharmaceutical composition according to the invention is administered to a subject in need thereof.

Pharmaceutical compositions

The terms “pharmaceutical composition” and “composition” are used interchangeably herein and refer to pharmaceutical compositions suitable for administration to a subject in need thereof.

In some embodiments the composition comprises 0.01-100 mg/ml semaglutide. In some embodiments the composition comprises 0.1-50 mg/ml, such as 0.5-25 mg/ml or 1-15 mg/ml, semaglutide. In some embodiments the composition comprises 0.1-10 mg/ml, such as 0.5-3.5 mg/ml or 1-2 mg/ml semaglutide, such as 0.5 to 2 mg/ml. In some embodiments the composition comprises 0.01-10 mg/ml, such as 0.01-3.5 mg/ml semaglutide. In some embodiments the composition comprises no more than 9 mg/ml, such as no more than 8 mg/ml or no more than 7 mg/ml, semaglutide. In some embodiments the composition comprises no more than 6 mg/ml, such as no more than 5 mg/ml or no more than 4 mg/ml semaglutide. In some embodiments the composition comprises no more than 3 mg/ml, such as no more than 2 mg/ml or no more than 1 mg/ml semaglutide. In some embodiments the composition comprises at least 0.01 mg/ml, such as at least 0.02 mg/ml or at least 0.05 mg/ml semaglutide. In some embodiments the composition comprises 1.34 mg/ml semaglutide. In some embodiments the composition comprises 3.2 mg/ml semaglutide.

In some embodiments the composition of the invention has a pH in the range of 3-10, such as pH 6-10 or 6-9. In some embodiments the composition of the invention has a pH in the range of pH 6.5-8.5, such as pH 7.0-8.2 or 7.0-7.8. In some embodiments pH is measured at 25 °C.

In some embodiments the composition of the invention comprises one or more pharmaceutically acceptable excipients.

In some embodiments the composition of the invention comprises an isotonic agent, such as propylene glycol or sodium chloride. In some embodiments the isotonic agent is propylene glycol and/or sodium chloride. In some embodiments, the isotonic agent is not propylene glycol.

In some embodiments the composition of the invention does not comprise propylene glycol.

In some embodiments the composition of the invention comprises no further isotonic agents.

In some embodiments the composition of the invention comprises 6.5-12, alternatively 7-12, alternatively 7.5-12, alternatively 8-12, alternatively 8.2-12, alternatively 8.25- 12 mg/ml sodium chloride. In some embodiments the composition of the invention comprises 6.5-9.5, alternatively 7-9.5, alternatively 7.5-9.5, alternatively 8-9.5, alternatively

8.2-9.5, alternatively 8.25- 9.5 mg/ml sodium chloride. In some embodiments the composition of the invention comprises 6.5-9, alternatively 7-9, alternatively 7.5-9, alternatively 8-9, alternatively 8.2-9, alternatively 8.25-9 mg/ml sodium chloride. In some embodiments the composition of the invention comprises 6.5-8.5, alternatively 7-8.5, alternatively 7.5-8.5, alternatively 8-8.5, alternatively 8.2-8.5, alternatively 8.25-8.5 mg/ml sodium chloride.

In some embodiments the composition of the invention comprises 6.5-12 mg/ml, such as 7-12 mg/ml or 7.5-12 mg/ml, sodium chloride. In some embodiments the composition of the invention comprises 8-12 mg/ml, such as 8.2-12 mg/ml or 8.25-12 mg/ml, sodium chloride.

In some embodiments the composition of the invention comprises 6.5-9.5 mg/ml, such as 7-9.5 mg/ml or 7.5-9.5 mg/ml, sodium chloride. In some embodiments the composition of the invention comprises 8-9.5 mg/ml, such as 8.2-9.5 mg/ml or 8.25-9.5 mg/ml, sodium chloride.

In some embodiments the composition of the invention comprises 6.5-9 mg/ml, such as 7-9 mg/ml or 7.5-9 mg/ml, sodium chloride. In some embodiments the composition of the invention comprises 8-9 mg/ml, such as 8.2-9 mg/ml or 8.25-9 mg/ml, sodium chloride.

In some embodiments the composition of the invention comprises 6.5-8.5, such as 7-8.5 or 7.5-8.5 mg/ml, sodium chloride. In some embodiments the composition of the invention comprises 8-8.5, such as 8.2-8.5 or 8.25-8.5 mg/ml, sodium chloride.

In some embodiments the composition of the invention comprises 5-6.2, such as 5.2-6.2 or 5.3-6.2 mg/ml, sodium chloride. In some embodiments the composition of the invention comprises 5-6, such as 5.2-6 or 5.3-6 mg/ml, sodium chloride.

In some embodiments the composition of the invention comprises 6.5-7.9, such as 6.6-7.9 or 6.7-7.9 mg/ml, sodium chloride. In some embodiments the composition of the invention comprises 6.5-7.8, such as 6.6-7.8 or 6.7-7.8 mg/ml, sodium chloride.

In some embodiments the composition of the invention comprises 5.4 or 6.72 mg/ml, sodium chloride.

In some embodiments the composition of the invention comprises a buffer, such as phosphate buffer, TRIS, or no buffer. In some embodiments the phosphate buffer is a sodium phosphate buffer, such as disodium hydrogen phosphate.

In some embodiments the composition of the invention comprises no preservative. In some embodiments the composition of the invention is essentially free of preservative.

The composition of the invention is in the form of a liquid pharmaceutical composition. In some embodiments the liquid pharmaceutical composition is a solution or a suspension. In some embodiments the composition of the invention is in the form of a

solution, such as an aqueous solution. In some embodiments the term “aqueous solution” as used herein refers to a solution comprising at least 60 %w/w water. In some embodiments the aqueous solution comprises 60-99 %w/w water. In some embodiments the aqueous solution comprises at least 75 %w/w water, such as at least 80 %w/w water or at least 85 %w/w water. In some embodiments the aqueous solution comprises at least 90 %w/w water, such as at least 92 %w/w water or at least 94 %w/w water. In some embodiments the aqueous solution comprises at least 97 % w/w water such as least 98% w/w water. In some embodiments the aqueous solution comprises 97-98% w/w water. In some embodiments the liquid pharmaceutical composition is made by dissolving powder, such as freeze dried or spray dried powder.

Semaglutide

The GLP-1 peptide semaglutide may be prepared as described in WO2006/097537, Example 4. Semaglutide is also known as N6.26-{18-[N-(17-carboxyheptadecanoyl)-L-γ-glutamyl]-10-oxo-3,6,12,15-tetraoxa-9,18-diazaoctadecanoyl}-[8-(2-amino-2-propanoic acid),34-L-arginine]human glucagon-like peptide 1(7-37), see WHO Drug Information Vol. 24, No. 1, 2010. In some embodiments semaglutide may be present in the composition in its fully or partly ionised form; for example one or more carboxylic acid groups (-COOH) may be deprotonated into the carboxylate group (-COO-) and/or one or more amino groups (-NH2) may be protonated into the -NH3+ group. In some embodiments semaglutide is added to the composition in the form of a salt. In some embodiments semaglutide may be recombinantly produced. In some embodiments semaglutide may be synthetically produced.

Administration and kits

In some embodiments, the composition of the invention is for parenteral administration. In some embodiments the composition is for subcutaneous administration.

In some embodiments the composition of the invention is for administration once weekly. In some embodiments the composition of the invention is for administration once daily, once every second or once every third day.

In some embodiments the invention relates to a kit comprising the pharmaceutical composition as defined herein and instructions for use. In some embodiments the instructions for use comprise the package insert of a drug.

In some embodiments the invention relates to a kit comprising the pharmaceutical composition as defined herein and an injection device. In some embodiments the injection device is selected from the group consisting of a durable pen and a prefilled pen. Examples

of durable pens are NovoPen® 4 or NovoPen® 5 (both from Novo Nordisk A/S, Denmark). An example of a prefilled pen is FlexPen® (Novo Nordisk A/S, Denmark).

Indications

In some embodiments the compositions of the invention are for use in medicine. In some embodiments the composition of the invention may be used for the following medical treatments:

(i) prevention and/or treatment of all forms of diabetes, such as hyperglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, non-insulin dependent diabetes, MODY (maturity onset diabetes of the young), gestational diabetes, and/or for reduction of HbA1c;

(ii) delaying or preventing diabetic disease progression, such as progression in type 2 diabetes, delaying the progression of impaired glucose tolerance (IGT) to insulin requiring type 2 diabetes, and/or delaying the progression of non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes;

(iii) prevention and/or treatment of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; and/or delaying gastric emptying.

(iv) prevention and/or treatment of cardiovascular diseases, such as delaying or reducing development of a major adverse cardiovascular event (MACE) selected from the group consisting of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, revascularisation, hospitalisation for unstable angina pectoris, and hospitalisation for heart failure.

(v) prevention and/or treatment of NASH.

(vi) prevention and/or treatment of Alzheimer's disease.

In some embodiments the indication is (i). In some embodiments the indication is (ii). In a still further particular aspect, the indication is (iii). In a still further particular aspect, the indication is (iv). In a still further particular aspect, the indication is (v). In a still further particular aspect, the indication is (vi). In some embodiments the indication is type 2 diabetes and/or obesity.

In some embodiments the method or use comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions defined herein. In some embodiments the indication is (i) and (iii). In some embodiments the indication is (ii) and (iii).

In some embodiments the invention comprises administration of an effective amount of a GLP-1 peptide. In some embodiments the invention relates to administration of an effective amount of a GLP-1 peptide.

Generally, all subjects suffering from obesity are also considered to be suffering from overweight. In some embodiments the invention relates to a method for treatment or prevention of obesity. In some embodiments the invention relates to use of the composition for treatment or prevention of obesity. In some embodiments the subject suffering from obesity is human, such as an adult human or a paediatric human (including infants, children, and adolescents). Body mass index (BMI) is a measure of body fat based on height and weight. The formula for calculation is BMI = weight in kilograms/height in meters2. A human subject suffering from obesity may have a BMI of ≥30; this subject may also be referred to as obese. In some embodiments the human subject suffering from obesity may have a BMI of ≥35 or a BMI in the range of ≥30 to <40. In some embodiments the obesity is severe obesity or morbid obesity, wherein the human subject may have a BMI of ≥40.

In some embodiments the invention relates to a method for treatment or prevention of overweight, optionally in the presence of at least one weight-related comorbidity. In some embodiments the invention relates to use of the composition for treatment or prevention of overweight, optionally in the presence of at least one weight-related comorbidity. In some embodiments the subject suffering from overweight is human, such as an adult human or a paediatric human (including infants, children, and adolescents). In some embodiments a human subject suffering from overweight may have a BMI of ≥25, such as a BMI of ≥27. In some embodiments a human subject suffering from overweight has a BMI in the range of 25 to <30 or in the range of 27 to <30. In some embodiments the weight-related comorbidity is selected from the group consisting of hypertension, diabetes (such as type 2 diabetes), dyslipidaemia, high cholesterol, and obstructive sleep apnoea.

In some embodiments the invention relates to a method for reduction of body weight. In some embodiments the invention relates to use of the composition for reduction of body weight. A human to be subjected to reduction of body weight according to the present invention may have a BMI of ≥25, such as a BMI of ≥27 or a BMI of ≥30. In some embodiments the human to be subjected to reduction of body weight according to the present invention may have a BMI of ≥35 or a BMI of ≥40. The term “reduction of body weight” may include treatment or prevention of obesity and/or overweight.

In some embodiments, as used herein, specific values given in relation to numbers or intervals may be understood as the specific value or as about the specific value (e.g. plus or minus 10 percent of the specific value).

Embodiments of the invention

The following are non-limiting embodiments of the invention:

1. A liquid pharmaceutical composition comprising semaglutide, no more than 0.1 %(w/w) phenol and above 6.4 mg/ml sodium chloride.
2. A liquid pharmaceutical composition comprising semaglutide, no more than 0.1 %(w/w) phenol and above 6.4 mg/ml sodium chloride and further optionally comprises histidine.
3. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, c) buffer, d) at least 60% water, optionally e) histidine, optionally f) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
4. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
5. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
6. A liquid pharmaceutical composition consisting essentially of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
7. A liquid pharmaceutical composition consisting essentially of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or

more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.

8. A liquid pharmaceutical composition consisting essentially of a) 3.2 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
9. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 97% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
10. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.25 mg/ml sodium chloride, d) buffer, e) at least 97% water (such as 97-99%), optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
11. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate such as sodium acetate or acetic acid, and said composition optionally has a pH of 6-10 such as 7-8.
12. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
13. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
14. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such

as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.

15. A liquid pharmaceutical composition consisting essentially of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
16. A liquid pharmaceutical composition consisting essentially of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such 7-8.
17. A liquid pharmaceutical composition consisting essentially of a) 3.2 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
18. A liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 97% water (such as 97-99%), optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
19. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
20. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
21. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH,

such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.

22. A liquid pharmaceutical composition consisting of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
23. A liquid pharmaceutical composition consisting of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
24. A liquid pharmaceutical composition consisting of a) 3.2 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
25. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 97% water, optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
26. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.25 mg/ml sodium chloride, d) buffer, e) at least 97% water (such as 97-99%), optionally f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
27. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, f) histidine, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate such as sodium acetate or acetic acid, and said composition optionally has a pH of 6-10 such as 7-8.
28. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at

least 60% water, optionally g one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.

29. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
30. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
31. A liquid pharmaceutical composition consisting of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-12 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
32. A liquid pharmaceutical composition consisting of a) 0.5-10 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) 8.1-8.9 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
33. A liquid pharmaceutical composition consisting of a) 3.2 mg/ml semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
34. A liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 97% water (such as 97-99%), optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10 such as 7-8.
35. The liquid pharmaceutical composition according to any one of the previous embodiments, comprising no more than 0.09, alternatively 0.08, alternatively 0.07, alternatively 0.06, alternatively 0.05, alternatively 0.04, alternatively 0.03, alternatively 0.02, alternatively 0.01 %(w/w) phenol.

36. The liquid pharmaceutical composition according to any one of the previous embodiments, wherein the liquid composition is essentially free of phenol.
37. The liquid pharmaceutical composition according to any of the previous embodiments comprising no phenol.
38. The liquid pharmaceutical composition according to any of the previous embodiments comprising above 7.0, alternatively above 7.2, alternatively above 7.5, alternatively above 7.7, alternatively above 8, alternatively above 8.2, alternatively above 8.25 mg/ml sodium chloride.
39. The liquid pharmaceutical composition according to any of the previous embodiments comprising 7-12, alternatively 7.5-12, alternatively 8-12 mg/ml sodium chloride.
40. The liquid pharmaceutical composition according to any of the previous embodiments comprising 7-9.5, alternatively 7-9, alternatively 7-8.25 mg/ml sodium chloride.
41. The liquid pharmaceutical composition according to any of the previous embodiments comprising 7-10, alternatively 7-9.5 alternatively 8-9, alternatively 8.1-8.9, alternatively 8.1-8.8, alternatively 8.2-8.7, alternatively 8.2-8.6, alternatively 8.2-8.5, alternatively 8.2-8.4, alternatively 8.2-8.3 mg/ml sodium chloride.
42. The liquid pharmaceutical composition according to any of the previous embodiments comprising 7-10, such as 7-9.5 or 8-9, mg/ml sodium chloride.
43. The liquid pharmaceutical composition according to any of the previous embodiments comprising 8.1-8.9, such as 8.1-8.8 or 8.2-8.7, mg/ml sodium chloride.
44. The liquid pharmaceutical composition according to any of the previous embodiments comprising 8.2-8.6 or 8.2-8.5 mg/ml sodium chloride.
45. The liquid pharmaceutical composition according to any of the previous embodiments comprising 8.2-8.4 or 8.2-8.3 mg/ml sodium chloride.
46. The liquid pharmaceutical composition according to any of the previous embodiments comprising 8.25 mg/ml sodium chloride.
47. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition
    a. is for parenteral administration;
    b. is an aqueous solution comprising at least 60 %w/w water; or
    c. further comprises a buffer.
48. The liquid pharmaceutical composition according to any of the previous embodiments, wherein the concentration of semaglutide is 0.5-10 mg/ml or 0.01-3.5 mg/ml of said composition.

49. The liquid pharmaceutical composition according to any of the previous embodiments, wherein the concentration of semaglutide is 0.5 mg/ml, alternatively 1 mg/ml, alternatively 1.5 mg/ml, alternatively 2 mg/ml, alternatively 2.5 mg/ml, alternatively 3 mg/ml, alternatively 3.5 mg/ml.
50. The liquid pharmaceutical composition according to any of the previous embodiments, wherein the concentration of semaglutide is 3.2 mg/ml.
51. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said semaglutide is in the form of a pharmaceutically acceptable salt.
52. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition is an aqueous solution comprising at least 60 %w/w water, such as at least 70 %w/w water or at least 80 %w/w water.
53. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition is an aqueous solution comprising at least 97 %w/w water, such as at least 98 %w/w water.
54. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition is an aqueous solution comprising 97-99 % w/w water.
55. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said liquid pharmaceutical composition comprises a buffer.
56. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said buffer is present in a concentration of 0.01-50 mM of said composition.
57. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said buffer is a phosphate buffer.
58. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said phosphate buffer is selected from the group consisting of sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium phosphate.
59. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said phosphate buffer is disodium hydrogen phosphate dihydrate.
60. The liquid pharmaceutical composition according to any of the previous embodiments, wherein the concentration of said phosphate buffer is 1-2 mg/ml,

alternatively 1.1-1.9 mg/ml, alternatively 1.2-1.7 mg/ml, alternatively 1.3-1.6 mg/ml, alternatively 1.4-1.5 mg/ml.

61. The liquid pharmaceutical composition according to any of the previous embodiments, wherein the concentration of said phosphate buffer is 1.42 mg/ml.
62. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition comprises one or more agents for adjusting pH, such as HCl, NaOH, or acetate.
63. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition comprises no preservative.
64. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition has a pH in the range of 6.0-10.0, alternatively 7-8.
65. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition has a pH of 7.4.
66. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition is for parenteral administration.
67. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition is for subcutaneous administration.
68. The liquid pharmaceutical composition according to any of the previous embodiments for use in an injection device.
69. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition has a mild or very mild pain intensity upon administration by injection to a patient.
70. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition has a very mild pain intensity upon administration by injection to a patient.
71. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition has a VAS score below 33, alternatively below 16 upon administration by injection to a patient.
72. The liquid pharmaceutical composition according to any of the previous embodiments, wherein said composition has a VAS score below 20, alternatively below 15, alternatively below 10 upon administration by injection to a patient.
73. The liquid pharmaceutical composition according to any of the previous embodiments further comprising histidine.

74. The liquid pharmaceutical composition according to embodiment 73, wherein the concentration of histidine is 0.5-100 mM, alternatively 0.5-50 mM, alternatively 0.5-20 mM, alternatively 0.5-15 mM, alternatively 0.5-10 mM.
75. The liquid pharmaceutical composition according to any of the previous embodiments, wherein fewer impurities are generated during storage.
76. The liquid pharmaceutical composition according to any of the previous embodiments, wherein fewer HMWPs are generated during storage.
77. The liquid pharmaceutical composition according to any of the previous embodiments, wherein fewer hydrophobic impurities 1 are generated during storage.
78. The liquid pharmaceutical composition according to any of the previous embodiments, wherein fewer hydrophobic impurities 2 are generated during storage.
79. The liquid pharmaceutical composition according to any of the previous embodiments, wherein an improved chemical stability of the composition is obtained.
80. A liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 7-9 mg/ml sodium chloride and 1-2 mg/ml phosphate buffer.
81. A liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 7-9 mg/ml sodium chloride, 0.5-10 mM histidine, and 1-2 mg/ml phosphate buffer.
82. A liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 7-9 mg/ml sodium chloride and 1-2 mg/ml disodium hydrogen phosphate dihydrate.
83. A liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 7-9 mg/ml sodium chloride, 0.5-10 mM histidine, and 1-2 mg/ml disodium hydrogen phosphate dihydrate.
84. A liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 8.25 mg/ml sodium chloride and 1.42 mg/ml disodium hydrogen phosphate dihydrate.
85. A liquid pharmaceutical composition comprising 0.5-3.5 mg/ml semaglutide, no more than 0.1 %(w/w) phenol, 8.25 mg/ml sodium chloride, 0.5-10 mM histidine, and 1.42 mg/ml disodium hydrogen phosphate dihydrate.
86. A kit comprising the liquid pharmaceutical composition according to any one of the preceding embodiments and instructions for use.
87. A kit comprising the liquid pharmaceutical composition according to any one of embodiments 1-85 and an injection device for administration of said composition to a subject.

88. The kit according to embodiment 87, wherein said injection device is selected from the group consisting of a durable pen and a prefilled pen.
89. A kit comprising the liquid pharmaceutical composition as defined in any one of the previous embodiments and an injection device comprising a needle, such as a pre-filled syringe, for administration of said composition to a subject.
90. A kit comprising the liquid pharmaceutical composition consisting essentially of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8; and an injection device comprising a needle, such as a pre-filled syringe, for administration of said composition to a subject.
91. A kit comprising the liquid pharmaceutical composition consisting of a) semaglutide, optionally b) no more than 0.1 %(w/w) phenol, c) above 6.4 mg/ml sodium chloride, d) buffer, e) at least 60% water, optionally g) one or more agents for adjusting pH, such as HCl, NaOH, or acetate, and said composition optionally has a pH of 6-10, such as 7-8; and an injection device comprising a needle, such as a pre-filled syringe, for administration of said composition to a subject.
92. The liquid pharmaceutical composition according to any one of embodiments 1-85 for use in medicine.
93. The liquid pharmaceutical composition according to any one of embodiments 1-85 for use in the treatment and/or prevention of diabetes, obesity, Alzheimer's disease, NASH and/or cardiovascular diseases.
94. The liquid pharmaceutical composition according to any one of embodiments 1-85 for use in the treatment and/or prevention of Alzheimer's disease.
95. The liquid pharmaceutical composition according to any one of embodiments 1-85 for use in the treatment and/or prevention of Alzheimer's disease, NASH and/or cardiovascular diseases.
96. A method for the prevention or treatment of diabetes or obesity, wherein the liquid pharmaceutical composition according to any one of the embodiments 1-85 is administered to a subject in need thereof.
97. A method for the prevention or treatment of Alzheimer's disease, NASH and/or cardiovascular diseases, wherein the liquid pharmaceutical composition according to any one of the embodiments 1-85 is administered to a subject in need thereof

Examples

List of Abbreviations

SDD: Single dose device
VAS: Visual Analog Scale
WFI: water for injection
q.s.: quantum sufficent

General Methods

Preparation of semaglutide compositions for clinical study

Compositions of semaglutide were prepared by dissolving buffer (disodium hydrogen phosphate dihydrate), isotonic agent (propylene glycol or sodium chloride), phenol (optionally) in water. pH of the buffer solution was adjusted to 7.4 by addition of sodium hydroxide and/or hydrochloric acid. Semaglutide was dissolved therein, pH was adjusted to 7.4 using sodium hydroxide and/or hydrochloric acid, and the composition was finally sterilised by filtration through a 0.22 µm sterile filter. The compositions of semaglutide were filled in a pre-filled syringe or a cartridge. All compositions of semaglutide have acceptable stability during shelf life and in-use conditions.

Design of clinical study

Compositions tested were prepared as described in section "*Preparation of semaglutide compositions for clinical study*".

Single-center, crossover, randomized, double-blind studies in healthy men and women comparing the injection site pain experience of the specified products (see Tables 2 and 4) when both products were used to deliver 0.25 mg semaglutide subcutaneously were conducted. Subjects were randomized in a 2×2 scheme evenly to 4 sequences of product and injection side as shown in Table 1.

Table 1: Product and Side of Injection in Abdomen per Treatment.

FORM B: Formulation B as specified in Tables 2 and 4. FORM C/D: Formulation C or D as specified in Tables 2 or 4.

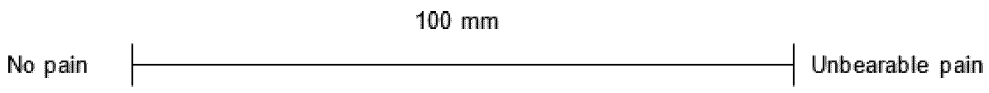
Treatment Short Identifier	Treatment Long Identifier	Ratio Required
	First injection on right side, Second injection on left side	
A	FORM C/D (Right) followed by FORM B (Left)	1
C	FORM B (Right) followed by FORM C/D (Left)	1
	First injection on left side, Second injection on right side	
B	FORM C/D (Left) followed by FORM B (Right)	1
D	FORM B (Left) followed by FORM C/D (Right)	1

The staff member was instructed to select an injection site on the assigned side of the midline, that, according to their judgment based on visual inspection and palpation, has the maximal thickness of subcutaneous fat. The injection with the FORM C/D product was performed as described in the DV3396 pen-injector directions for use, i.e., without making a lifted skin fold. Injection with the FORM B product was performed as described in the PDS290 pen-injector directions for use and the Ypsomed Clickfine AutoProtect, 8 mm x 29G needle instructions for use.

Subjects received two (2) single doses of semaglutide 0.25 mg on one (1) day. The two (2) products were administered at least 30 minutes apart, in the anterior aspect of the abdominal wall on opposite sides of the midline.

The first dose was administered as follows. An unblinded staff member present in the study room started a timer when the other unblinded staff member started the injection. The timer was placed such that it was not visible to the subject. The blinded staff member was not present in the room when the dosing was given. Immediately after dosing the unblinded team left the room and the blinded team took over. This was within the “one minute after injection” timepoint.

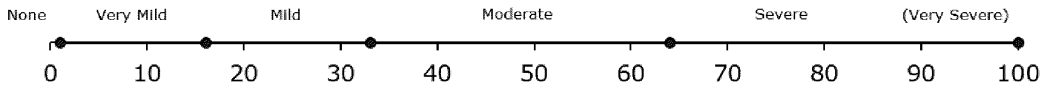
The intensity of injection site pain VAS was filled in by the subjects starting one (1) minute after each injection of the study drug to report the pain intensity experienced in the first minute after the injection. Subjects were instructed to make a vertical line on the VAS (100 mm); the endpoints are “no pain” and “unbearable pain.” The VAS is shown below. The distance (mm) between the endpoint “no pain” and the vertical line on the VAS was recorded. The VAS is a well-validated tool to assess injection-site pain ((Williamson A1, Hoggart B. "Pain: a review of three commonly used pain rating scales." J Clin Nurs. 2005 Aug;14(7):798-804.)).



At least 30 minutes after the first injection, after confirmation from the subject that the pain was entirely gone (to not contaminate the rating of the last injection), the timer was reset, and the last injection was given. In each subject, the two (2) semaglutide injections were performed by the same staff member. If the pain was not gone at 30 minutes, another attempt was made at 60 minutes. If pain was still present at that time, no further attempts were made.

Following the last injection, the same measurement was performed as after the first injection, as described above. Subjects were not allowed to consult their own prior ratings.

A total of 100 subjects were tested and the VAS score is shown as an average of the obtained VAS scores. Using data from the actual trial and statistics, the pain category that best matched a given VAS score was calculated as shown below. The category "Very Severe" was not used and could not be characterised, as well as VAS scores above 83.



Preparation of semaglutide compositions for stability study

Unless otherwise noted, compositions of semaglutide were prepared by dissolving buffer (disodium hydrogen phosphate dihydrate), isotonic agent (sodium chloride) and optionally a stabilizer (histidine) in water. Semaglutide was dissolved therein. pH was adjusted to 7.4 using sodium hydroxide and/or hydrochloric acid, and the composition was finally sterilised by filtration through a 0.22 µm sterile filter. The composition comprising semaglutide and optionally histidine was added to a pre-filled syringe (Ompi #7600002.8506).

Assay (I): Determination of High Molecular Weight Proteins (HMWP) content of semaglutide compositions

Determination of HMWP content was performed using size exclusion chromatography (SE-HPLC) using a Waters Insulin HMWP column with a mobile phase of sodium chloride, sodium phosphate, phosphoric acid and isopropanol, isocratic elution and detection at 280 nm. Content of HMWP is given in % as the combined area of chromatographic peaks eluting earlier than the semaglutide monomer peak (i.e. HMWP peaks), relative to the total area of HMWP and semaglutide monomer peaks.

Assay (II): Determination of Hydrophobic Impurities 1 and 2, hydrophilic and sum of impurities of semaglutide compositions

Determination of Hydrophobic Impurities 1 and 2, hydrophilic impurities and sum of impurities of the semaglutide compositions was performed using reversed phase high performance liquid chromatography (RP-HPLC). The RP-HPLC method was performed on a Kinetex C18 column starting with an isocratic elution followed by a gradient elution using eluent A (90% 0.09M phosphate buffer, pH 3.6 and 10% acetonitrile) and eluent B (60% acetonitrile and 20% isopropanol) from approx 50:50 to 10:90 and back to approx. 50:50 of A:B. Detection was performed at 210 nm.

The Sum of impurities is calculated as the area of all the semaglutide related impurity peaks relative to the total area of semaglutide and semaglutide related impurities peaks and is expressed in percentage. The Sum of impurities is further divided in three groups

- The Hydrophilic impurities are impurity peaks eluted before semaglutide.
- The Hydrophobic impurities 1 are all peaks eluted between semaglutide and the start of the second linear gradient in the chromatogram.
- The Hydrophobic impurities 2 are all peaks eluted between the end of the first isocratic elution in the chromatogram and the start of the third linear gradient

These three impurity groups are individually expressed in percentage relative to the total area of all semaglutide related peaks.

Example 1: Clinical study comparing approved Ozempic® formulation and new SDD formulation

Purpose: To test and compare a new SDD formulation to the approved Ozempic® formulation.

The study was conducted as described in section "*Design of clinical study*". The following two products were compared: FORM B product (Formulation B (Ozempic®), PDS290) and FORM C product (Formulation C, DV3396). The compositions are shown in Table 2. In addition to the difference in semaglutide concentration, the preservative (phenol) is removed from Formulation C, as the product is intended for single injections. To adjust the tonicity of the formulation after removal of phenol, the content of propylene glycol is adjusted from 14.0 mg/ml to 18.5 mg/ml. Changes in composition are highlighted with bold.

Table 2 Changes in composition when compared to semaglutide 1.34 mg/ml

Name of ingredient	Formulation B (PDS290)	Formulation C (DV3396)	Function ingredient
Semaglutide	1.34 mg/ml	**0.5 mg/ml**	Active substance
Disodium hydrogen phosphate dihydrate	1.42 mg/ml	1.42 mg/ml	Buffering agent
Propylene glycol	14.0 mg/ml	**18.5 mg/ml**	Isotonic agent
Phenol	5.50 mg/ml	**N/A**	Preservative
Hydrochloric acid, 2N	q.s	q.s	pH adjustment
Sodium hydroxide, 2N	q.s	q.s	pH adjustment
WFI	To 1.00 ml	To 1.00 ml	Solute
pH	7.4	7.4	

Table 3 VAS scores

Formulation	VAS score	Pain intensity
Formulation B (PDS290)	4.4	Very mild
Formulation C (DV3396)	35.1	Moderate

The VAS scores given in Table 3 were obtained. A low VAS score is associated with low experience of pain. A VAS score of 4.4 mm (very mild pain intensity) was obtained for FORM B product whereas a VAS score of 35.1 mm (moderate pain intensity) was obtained for FORM C product. These results show that the subjects experience increased injection pain with the FORM C product compared to FORM B product.

Example 2: Clinical study comparing approved Ozempic® formulation and new improved SDD formulation

Purpose: To test and compare a new improved SDD formulation to the approved Ozempic® formulation.

The study was conducted as described in section "*Design of clinical study*". The following two products were compared: FORM B product (Formulation B (Ozempic®), PDS290) and FORM D product (Formulation D, DV3396). A new formulation of semaglutide single dose was developed showing acceptable physical and chemical stability. The optimised formulation (named Formulation D) contains sodium chloride (8.25 mg/ml to obtain tonicity) instead of propylene glycol. The compositions are shown in Table 4.

Table 4 Changes in composition when compared to semaglutide 1.34 mg/ml

Name of ingredient	Formulation B (PDS290)	Formulation D (DV3396)	Function ingredient
Semaglutide	1.34 mg/ml	**0.5 mg/ml**	Active substance
Disodium hydrogen phosphate dihydrate	1.42 mg/ml	1.42 mg/ml	Buffering agent
Propylene glycol	14.0 mg/ml	**N/A**	Isotonic agent
Sodium chloride	NA	**8.25 mg/ml**	Isotonic agent
Phenol	5.50 mg/ml	**N/A**	Preservative
Hydrochloric acid, 2N	q.s	q.s	pH adjustment
Sodium hydroxide, 2N	q.s	q.s	pH adjustment
WFI	To 1.00 ml	To 1.00 ml	Solute
pH	7.4	7.4	

Table 5 VAS scores

Formulation	VAS score	Pain intensity
Formulation B (PDS290)	5.7	Very mild
Formulation D (DV3396)	8.3	Very mild

The VAS scores given in Table 5 were obtained. A VAS score of 5.7 mm (very mild pain intensity) was obtained for FORM B product and a VAS score of 8.3 mm (very mild pain intensity) was obtained for FORM D product. These results show that the subjects

experience similar, very mild injection pain with the FORM D product compared to FORM B product. These results indicate that the injection pain experience is independent from the used device but that the different formulations comprising semaglutide have an influence on the experience of pain.

Example 3: Stability study (30 °C)

Compositions comprising semaglutide were prepared as described in "*Preparation of semaglutide compositions for stability study*" and tested using Assay (I) and Assay (II) as described under General Methods. The tested compositions contained semaglutide (0.5 mg/ml), sodium chloride (8.25 mg/ml), disodium hydrogen phosphate dihydrate (1.42 mg/ml), and optionally histidine (0.5, 2 and 10 mM) as specified in Table 6, at pH 7.4 in an aqueous solution. The compositions were added to a pre-filled syringe with staked needle (filling volume 0.5 ml). The filled syringes were stored at 30°C and the chemical stability followed over time. Chemical stability was determined by measuring formation of HMWP as described in Assay (I) after storage at 30°C; the results are provided in Table 7. Formation of semaglutide related impurities was determined as described by Assay (II) after storage at 30°C; the results are provided in Tables 8-11.

Table 6. Compositions tested in Example 3 and Example 4.

Composition no.	**Description**
1	0 mM histidine
2	0.5 mM histidine
3	2 mM histidine
4	10 mM histidine

Table 7. HMWP formation in semaglutide compositions during storage at 30°C.

Composition no.	**HMWP (%)**				
	0 days	**15 days**	**31 days**	**61 days**	**150 days**
1 (0 mM histidine)	0.1	0.3	0.4	0.9	1.0
2 (0.5 mM histidine)	0.1	0.2	0.3	0.7	1.1
3 (2 mM histidine)	0.1	0.2	0.3	0.6	0.8
4 (10 mM histidine)	0.1	0.2	0.2	0.4	0.5

The results presented in Table 7 show that when histidine is present in the composition, less HMWPs are formed during storage; in comparison to the batch produced without histidine, a

maximum HMWP reduction of ~50% is observed after 31 days and up to 150 days with the addition of 10mM histidine. A lower HMWP concentration corresponds to a better stability, i.e. the composition is chemically more stable when histidine is present.

Table 8. Formation of Hydrophobic Impurities 1 in semaglutide compositions during storage at 30°C.

Composition no.	Hydrophobic impurities 1 (%)				
	0 days	15 days	31 days	61 days	150 days
1 (0 mM histidine)	1.5	1.6	1.9	2.2	3.9
2 (0.5 mM histidine)	1.5	1.6	1.8	2.0	3.5
3 (2 mM histidine)	1.5	1.6	1.7	2.1	3.4
4 (10 mM histidine)	1.5	1.5	1.7	2.0	3.3

The results presented in Table 8 show that when histidine is present in the composition, less hydrophobic impurities 1 are formed during storage. A lower hydrophobic impurities 1 concentration corresponds to a better stability, i.e. the composition is chemically more stable when histidine is present.

Table 9. Formation of Hydrophobic Impurities 2 in semaglutide compositions during storage at 30°C.

Composition no.	Hydrophobic impurities 2 (%)				
	0 days	15 days	31 days	61 days	150 days
1 (0 mM histidine)	0.1	0.2	0.4	0.5	1.2
2 (0.5 mM histidine)	0.1	0.1	0.3	0.4	1.0
3 (2 mM histidine)	0.1	0.1	0.2	0.5	0.7
4 (10 mM histidine)	0.1	0.1	0.2	0.3	0.5

The results presented in Table 9 show that when histidine is present in the composition, less hydrophobic impurities 2 are formed during storage; in comparison to the batch produced without histidine, a maximum hydrophobic impurities 2 reduction of ~50% is observed after 31 days and up to 150 days with the addition of 10mM histidine. A lower hydrophobic impurities 2 concentration corresponds to a better stability, i.e. the composition is chemically more stable when histidine is present.

Table 10. Formation of Hydrophilic impurities in semaglutide compositions during storage at 30°C.

Composition no.	Hydrophilic impurities (%)				
	0 days	**15 days**	**31 days**	**61 days**	**150 days**
1 (0 mM histidine)	1.6	1.9	2.1	2.7	4.5
2 (0.5 mM histidine)	1.6	1.9	2.1	2.7	4.5
3 (2 mM histidine)	1.5	1.9	2.1	2.8	4.6
4 (10 mM histidine)	1.5	1.8	2.2	2.8	4.9

The results presented in Table 10 show that when histidine is present in the composition, little to no impact on the formation of hydrophilic impurities is observed. The compositions are therefore similarly stable when histidine is present.

Table 11. Formation of Sum of impurities in semaglutide compositions during storage at 30°C.

Composition no.	Sum of impurities (%)				
	0 days	**15 days**	**31 days**	**61 days**	**150 days**
1 (0 mM histidine)	6.4	3.7	4.4	5.4	13.1
2 (0.5 mM histidine)	6.2	3.6	4.2	5.2	12.4
3 (2 mM histidine)	6.0	3.6	4.1	5.3	12.1
4 (10 mM histidine)	6.0	3.5	4.1	5.0	12.1

The results presented in Table 8-11 show that when histidine is present in the composition the chemical stability of semaglutide is similar or improved as overall less impurities are formed during storage. An improved stability profile (lower impurity levels) can allow for a longer drug product shelf life and/or in-use period.

Example 4: Stability study (5 °C)

Compositions comprising semaglutide were prepared as described in "*Preparation of semaglutide compositions for stability study*" and tested using Assay (I) and Assay (II) as described under General Methods. The tested compositions contained semaglutide (0.5 mg/ml), sodium chloride (8.25 mg/ml), disodium hydrogen phosphate dihydrate (1.42 mg/ml), and optionally histidine (0.5, 2 and 10 mM) as specified in Table 6, at pH 7.4 in an aqueous solution. The compositions were added to a pre-filled syringe with staked needle (filling volume 0.5 ml). The filled syringes were stored at 5°C and the chemical stability followed over time.

Chemical stability was determined by measuring formation of HMWP as described in Assay (I) after storage at 5°C; the results are provided in Table 12. Formation of semaglutide related impurities was determined as described by Assay (II) after storage at 5°C; the results are provided in Tables 13-16.

Table 12. HMWP formation in semaglutide compositions during storage at 5°C.

Composition no.	HMWP (%)			
	0 days	150 days	184 days	366 days
1 (0 mM histidine)	0.1	0.2	0.2	0.3
2 (0.5 mM histidine)	0.1	0.1	0.2	0.3
3 (2 mM histidine)	0.1	0.1	0.2	0.3
4 (10 mM histidine)	0.1	0.1	0.1	0.2

The results presented in Table 12 supports the general trend for the data obtained at 30°C shown in Table 7.

Table 13. Formation of Hydrophobic Impurities 1 in semaglutide compositions during storage at 5°C.

Composition no.	Hydrophobic impurities 1			
	0 days	150 days	184 days	366 days
1 (0 mM histidine)	1.5	1.6	1.9	1.8
2 (0.5 mM histidine)	1.5	1.5	1.6	1.6
3 (2 mM histidine)	1.5	1.5	1.6	1.5
4 (10 mM histidine)	1.5	1.5	1.6	1.6

The results presented in Table 13 supports the general trend for the data obtained at 30°C shown in Table 8.

Table 14. Formation of Hydrophobic Impurities 2 in semaglutide compositions during storage at 5°C.

Composition no.	Hydrophobic impurities 2			
	0 days	150 days	184 days	366 days
1 (0 mM histidine)	0.1	0.1	0.1	0.2
2 (0.5 mM histidine)	0.1	0.1	0.1	0.2

Composition no.	Hydrophobic impurities 2			
	0 days	150 days	184 days	366 days
3 (2 mM histidine)	0.1	0.1	0.1	0.2
4 (10 mM histidine)	0.1	0.1	0.1	0.1

The results presented in Table 14 supports the general trend for the data obtained at 30°C shown in Table 9.

Table 15. Formation of Hydrophilic impurities in semaglutide compositions during storage at 5°C.

Composition no.	Hydrophilic impurities			
	0 days	150 days	184 days	366 days
1 (0 mM histidine)	1.6	1.6	1.5	1.9
2 (0.5 mM histidine)	1.6	1.7	1.6	1.8
3 (2 mM histidine)	1.5	1.6	1.6	1.8
4 (10 mM histidine)	1.5	1.7	1.6	1.9

The results presented in Table 15 supports the general trend for the data obtained at 30°C shown in Table 10.

Table 16. Formation of Sum of impurities in semaglutide compositions during storage at 5°C.

Composition no.	Sum of impurities			
	0 days	150 days	184 days	366 days
1 (0 mM histidine)	3.2	3.4	3.5	3.9
2 (0.5 mM histidine)	3.1	3.4	3.3	3.6
3 (2 mM histidine)	3.0	3.3	3.3	3.5
4 (10 mM histidine)	3.0	3.3	3.3	3.6

The results presented in Table 16 supports the general trend for the data obtained at 30°C shown in Table 11.

The results presented in Table 12-16 show that when histidine is present in the composition the chemical stability of semaglutide at long term storage conditions indicate improvement in alignment with results obtained at 30°C. An improved stability profile (lower impurity levels) can allow for a longer drug product shelf life (typically at least 3 years) and/or in-use period.

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.