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(54) Title: FREEZE DRIED COMPOSITIONS

(57) Abstract: The invention relates to a solid composition obtainable by freeze drying an aqueous composition comprising (i) a hyaluronidase, (ii) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and (iii) a drug. The invention also relates to a reconstituted aqueous composition obtainable by reconstituting the solid composition of the invention, and a process for making the solid composition of the invention.

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FREEZE DRIED COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 63/333,557 filed on April 22, 2022 and to European Patent Application No. EP22173920.4, filed on May 17, 2022, the entire contents of both of which are expressly incorporated herein by reference in their entirety.

TECHNICAL FIELD

The present invention relates to a solid composition obtainable by freeze drying an aqueous composition comprising (i) a hyaluronidase, (ii) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and (iii) a drug, as described herein. The present invention also relates to a reconstituted aqueous composition obtainable by reconstituting the solid composition of the invention, and a process for making the solid composition of the invention.

BACKGROUND AND RELATED ART

When a drug is to be administered by subcutaneous or intramuscular injection it may also be desirable to formulate it or to administer it with a hyaluronidase to increase dispersion and absorption of the drug. Hyaluronidase may also be used to achieve other effects – for example, the administration of a hyaluronidase may reduce the bump formed by the administration of high volumes of a pharmaceutical composition at injection sites. However, storing hyaluronidases in pharmaceutical compositions comprising a drug, for example compositions comprising rilpivirine, for many weeks, months or years represents a significant challenge. When stored at room temperature for extended time-periods, hyaluronidases may unfold and degrade rapidly. Thus, it is also desirable to provide compositions comprising a drug and a hyaluronidase, in which the hyaluronidase is stable during storage for many weeks, months or years, in particular at room temperature, e.g. at 20-25°C.

SUMMARY OF THE INVENTION

In a first aspect the invention relates to a solid composition obtainable by freeze drying (synonymous with “lyophilising”) an aqueous composition comprising (i) a hyaluronidase, (ii) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and (iii) a drug.

In a second aspect the invention relates to a reconstituted aqueous composition obtainable by reconstituting the solid composition according to the first aspect.

In a third aspect there is provided a method for the treatment or prevention of a disease or disorder in a subject, the method comprising administering to the subject the reconstituted aqueous composition according to the second aspect.

In a fourth aspect there is provided a reconstituted aqueous composition according to the second aspect for use in the treatment or prevention of a disease or disorder in a subject.

In a fifth aspect there is provided the use of the reconstituted aqueous composition according to the second aspect, for the manufacture of a medicament for treating or preventing a disease or disorder in a subject.

In a sixth aspect there is provided a solid composition according to the first aspect for use in the treatment or prevention of a disease or disorder in a subject.

In a seventh aspect there is provided the use of the solid composition according to the first aspect for the manufacture of a medicament for treating or preventing a disease or disorder in a subject.

In an eighth aspect, there is provided use of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof for stabilising a hyaluronidase in a solid composition comprising a drug.

In a ninth aspect there is provided a method for stabilising a hyaluronidase in a solid composition, the method comprising freeze drying an aqueous composition comprising the hyaluronidase, cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and a drug.

In a tenth aspect there is provided a kit comprising (i) the solid composition according to the first aspect, and (ii) a diluent.

In an eleventh aspect there is provided a kit comprising: (i) the solid composition according to the first aspect, and (ii) a composition comprising one or more other drugs, and optionally (iii) a diluent.

BRIEF DESCRIPTION OF THE FIGURES

The invention will be described, by way of example only, with reference to the accompanying figures.

Figure 1: Hyaluronidase melting temperature studies and cellulose derivative concentration

Figure 2: Drug particle size under different storage conditions

Figure 3: Rilpivirine particle size and hyaluronidase stability studies under different storage conditions

Figure 4: Viscosity studies

Figure 5: Injection force studies

These figures are explained further in the “Examples” section.

DISCLOSURE OF THE INVENTION

This application has been drafted in sections to aid readability. However, this does not mean that each section is to be read in isolation. To the contrary, unless otherwise specified, each section is to be read with cross-referencing to the other sections, i.e. taking the entire application as a whole. No artificial separation of embodiments is intended, unless explicitly stated.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the invention

In a first aspect the invention relates to a solid composition obtainable by freeze drying an aqueous composition comprising (i) a hyaluronidase, (ii) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and (iii) a drug.

In a second aspect the invention relates to a reconstituted aqueous composition obtainable by reconstituting the solid composition according to the first aspect.

Freeze drying is a process in which an aqueous composition is initially frozen. During the initial freezing step, the water forms solid ice crystals and the composition concentrates leading to the separation of two phases. The pressure is then reduced during a primary drying stage, and the ice sublimes. The temperature may be increased in the primary drying stage to increase the rate of sublimation. In a secondary drying stage, the temperature of the composition is increased slowly to promote the removal of residual water and provide a solid composition. Solid compositions obtainable by freeze drying can be referred to by multiple terms, including “lyophilised powder”, “lyophilised cake”, “cake”, “freeze dried cake”, “freeze dried powder” and “freeze dried product”. In an embodiment, the solid composition obtainable by freeze drying is a lyophilized cake, or cake or freeze-dried cake.

A hyaluronidase is an enzyme that degrades hyaluronic acid (HA) e.g. in the skin and lowers the viscosity of hyaluronan in the extracellular matrix. Because of this property, it can be used to increase dispersion and absorption of injected active pharmaceutical ingredients and/or to enable administration of larger volumes subcutaneously. Enzymatic activity of hyaluronidase, including rHuPH20, can be defined by units per mL (U/mL) or by total enzyme activity in a particular formulation (U).

The term “hyaluronidase” as used herein means any enzyme that degrades hyaluronic acid and lowers the viscosity of hyaluronan in the extracellular matrix.

In an embodiment, the hyaluronidase is recombinant hyaluronidase. In a preferred embodiment, the hyaluronidase is recombinant human hyaluronidase, e.g. rHuPH20. In an embodiment, rHuPH20 is defined by the amino acid sequence available under CAS Registry No. 757971-58-7. Further information regarding rHuPH20 is provided in Int. Pat. Publ. No. WO2004/078140. In an embodiment, the amino acid sequence of rHuPH20 comprises SEQ ID NO: 1. In some embodiments, the hyaluronidase is a variant of rHuPH20 having an amino acid sequence of rHuPH20 that comprises SEQ ID NO: 2, namely residues 36-482 of wild type human hyaluronidase. In some embodiments, the hyaluronidase is a variant of rHuPH20 having an amino acid sequence that comprises SEQ ID NO: 3. In some embodiments, the hyaluronidase is a variant of rHuPH20 having an amino acid sequence that comprises SEQ ID NO: 4. In some embodiments, the hyaluronidase is a variant of rHuPH20 having an amino acid sequence that comprises SEQ ID NO: 5.

SEQ ID NO: 1: rHuPH20	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRIN ATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAK KDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIEL VQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHLW GYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTALY PSIYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVFAYTRIV FTDQVLKFLSQDELVYTFGETVALGASGIVIWGTLSIMRSMKSCLL LDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSSDYL HLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCK EKADVKDTDAVDVCIADGVCIDAFLKPPMETEEP
SEQ ID NO: 2: rHuPH20 variant 1	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRIN ATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAK KDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIEL VQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHLW GYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTALY PSIYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVFAYTRIV FTDQVLKFLSQDELVYTFGETVALGASGIVIWGTLSIMRSMKSCLL LDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSSDYL HLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCK EKADVKDTDAVDVCIADGVCIDAFLKPPMETEEPQIFY
SEQ ID NO: 3: rHuPH20 variant 2	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRIN ATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAK KDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIEL VQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHLW GYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTALY PSIYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVFAYTRIV FTDQVLKFLSQDELVYTFGETVALGASGIVIWGTLSIMRSMKSCLL LDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSSDYL HLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCK EKADVKDTDAVDVCIADGVCIDAFLKPPMETEEPQIF
SEQ ID NO: 4: rHuPH20 variant 3	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRIN ATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAK KDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIEL VQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHLW GYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTALY PSIYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVFAYTRIV

	FTDQVLKFLSQDELVYTFGETVALGASGIVIWGTLSIMRSMKSCLL LDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSSDYL HLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCK EKADVKDTDAVDVCIADGVCIDAFLKPPMETEEPQI
SEQ ID NO: 5: rHuPH20 variant 4	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRIN ATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAK KDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIEL VQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHLW GYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTALY PSIYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVFAYTRIV FTDQVLKFLSQDELVYTFGETVALGASGIVIWGTLSIMRSMKSCLL LDNYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSSDYL HLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCK EKADVKDTDAVDVCIADGVCIDAFLKPPMETEEPQ

In an embodiment, the concentration of the hyaluronidase in the aqueous composition or the reconstituted aqueous composition is from about 10 to about 10,000 U/mL, or from about 100 to about 10,000 U/mL, or from about 500 to about 10,000 U/mL, or from about 500 to about 5,000 U/mL, or from about 500 to about 2500 U/mL, or from about 1000 to about 2500 U/mL, or from about 1500 to about 2500 U/mL. Preferably, the concentration of the hyaluronidase in the aqueous composition or the reconstituted aqueous composition is from about 1800 to about 2200 U/mL (e.g. about 2000 U/mL).

In an embodiment, the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is a carboxymethyl cellulose (CMC) or a pharmaceutically acceptable salt thereof, preferably wherein the CMC is not cross-linked. In an embodiment, the CMC or a pharmaceutically acceptable salt of CMC is a pharmaceutically acceptable salt of CMC. Pharmaceutically acceptable salts of CMC means those where the counterion is pharmaceutically acceptable. The pharmaceutically acceptable salts are meant to comprise the therapeutically active non-toxic base addition salt forms which CMC is able to form. Preferred pharmaceutically acceptable salts of CMC include sodium CMC and potassium CMC. In a particularly preferred embodiment, the CMC or a pharmaceutically acceptable salt thereof is sodium CMC, particularly non-cross-linked sodium CMC. In another embodiment, the CMC or a pharmaceutically acceptable salt thereof is CMC. Examples of CMCs that may be used in the invention are carmellose sodium, 40 mPa.s

(parenteral grade), available from Ashland, and Blanose CMC 7LF PH or Blanose 7LP EP, available from Ashland.

The CMC or a derivative thereof or a pharmaceutically acceptable salt thereof can have any degree of substitution (DS). The DS is the average number of carboxymethyl groups per cellulose unit. In a preferred embodiment, the DS is from about 0.4 to about 1.5. In an embodiment, the CMC or a pharmaceutically acceptable salt thereof has a DS of from about 0.5 to about 1, for example from about 0.65 to about 0.95 such as about 0.7.

In an embodiment, the CMC or a pharmaceutically acceptable salt thereof has a viscosity of from about 10 mPa.s to about 100 mPa.s in an aqueous solution of 1% (w/v) at room temperature. In an embodiment, the CMC or a pharmaceutically acceptable salt thereof has a viscosity of from about 20 mPas to about 60 mPa.s in an aqueous solution of 1% (w/v) at room temperature. In an embodiment, the CMC or a pharmaceutically acceptable salt thereof has a viscosity of from about 30 mPa.s to about 50 mPa.s in an aqueous solution of 1% (w/v) at room temperature, for example about 40 mPa.s in an aqueous solution of 1% (w/v) at room temperature.

In an embodiment, the CMC or a pharmaceutically acceptable salt thereof has a viscosity of from about 10 mPa.s to about 100 mPa.s in an aqueous solution of 2% (w/v) at room temperature. In an embodiment, the CMC or a pharmaceutically acceptable salt thereof has a viscosity of from about 20 mPas to about 60 mPa.s in an aqueous solution of 2% (w/v) at room temperature. In an embodiment, the CMC or a pharmaceutically acceptable salt thereof has a viscosity of from about 30 mPa.s to about 50 mPa.s in an aqueous solution of 2% (w/v) at room temperature, for example about 40 mPa.s in an aqueous solution of 2% (w/v) at room temperature.

In an embodiment, the molecular weight of the CMC or a pharmaceutically acceptable salt thereof is from about 50 kDa to about 2,000 kDa. In an embodiment, the molecular weight of the CMC or a pharmaceutically acceptable salt thereof is from about 50 kDa to about 1,000 kDa. In an embodiment, the molecular weight of the CMC or a pharmaceutically acceptable salt thereof is from about 70 kDa to about 900 kDa. In a preferred embodiment, the molecular weight of the CMC or a pharmaceutically acceptable salt thereof is from about 90 kDa to about 750 kDa. In a most preferred embodiment, the molecular weight of the CMC or a pharmaceutically acceptable salt thereof is from about 70 kDa to about 110 kDa, for example about 90 kDa.

The inventors have surprisingly found that the addition of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to the aqueous compositions of the invention increases the melting temperature (T_m) of a hyaluronidase (Example 1a). This is indicative of improved stability of the hyaluronidase on storage.

The inventors have also found that the addition of a cellulose (e.g. CMC) or a derivative thereof, or a pharmaceutically acceptable salt thereof, to the aqueous compositions of the invention which comprise a hyaluronidase leads to a decrease in the loss of hyaluronidase activity, decrease in aggregation of the hyaluronidase, and/or decrease in oxidation of the hyaluronidase in the reconstituted aqueous composition of the invention, such as following storage of the freeze dried product under stress test conditions (Examples 5 and 7). This is indicative of improved stability on storage.

In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 1 mg/mL to about 100 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 1 mg/mL to about 75 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 1 mg/mL to about 50 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 1 mg/mL to about 25 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 5 mg/mL to about 25 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 5 mg/mL to about 15 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 5 mg/mL to about 10 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In a most preferred embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 1 mg/mL to about 5 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically

acceptable salt thereof, e.g. about 3 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is sodium CMC and the aqueous composition or the reconstituted aqueous composition comprises the sodium CMC in any one of the amounts specified in the paragraph directly above. In a preferred embodiment, the CMC or a pharmaceutically acceptable salt thereof is sodium CMC and the aqueous composition or the reconstituted aqueous composition has any of the degrees of substitution, viscosities and molecular weights specified herein.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 0.002 mg to about 5 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 0.01 mg to about 5 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 0.05 mg to about 2.5 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 0.1 mg to about 2 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In a preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 0.1 mg to about 1 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In a more preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 0.1 mg to about 0.25 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase, e.g. about 0.15 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In another more preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 0.05 mg to about 0.25 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase, e.g. about

0.15 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

In a preferred embodiment, the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is sodium CMC and the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises any one of the ratios of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to hyaluronidase, specified in the paragraph directly above.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises a cryoprotectant. In an embodiment the cryoprotectant is a sugar, sugar alcohol, or amino acid or a pharmaceutically acceptable salt thereof, preferably wherein the sugar is not a monosaccharide. Pharmaceutically acceptable salts of the cryoprotectant means those where the counterion is pharmaceutically acceptable. The pharmaceutically acceptable salts are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which a given sugar, sugar alcohol or an amino acid is able to form. In an embodiment the cryoprotectant is a sugar or sugar alcohol, preferably wherein the sugar is not a monosaccharide. Suitable sugars and sugar alcohols include mannitol, lactose, sucrose, trehalose, sorbitol, dextrose, fructose, maltose, xylitol and raffinose. Preferably, the sugar or sugar alcohol is selected from mannitol and sucrose. More preferably, the sugar or sugar alcohol is sucrose. Suitable amino acids or pharmaceutically acceptable salts thereof include arginine, glycine and histidine or a pharmaceutically acceptable salt thereof. In an embodiment, the amino acid or a pharmaceutically acceptable salt thereof is selected from arginine and glycine or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the amino acid or a pharmaceutically acceptable salt thereof is arginine (e.g. arginine HCl). In an embodiment, the aqueous composition (and, therefore, the solid composition) or the reconstituted aqueous composition additionally comprises two cryoprotectants. In an embodiment, the aqueous composition (and, therefore, the solid composition) or the reconstituted aqueous composition additionally comprises two cryoprotectants, wherein one cryoprotectant is a sugar or sugar alcohol and the other cryoprotectant is an amino acid or a pharmaceutically acceptable salt thereof.

The inventors surprisingly found that when the drug is in the form of particles suspended in the aqueous composition, the particle size distribution in the reconstituted aqueous

compositions according to the invention was similar to that in the aqueous composition prior to the freeze drying (see e.g. Example 4).

In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 1 mg/mL to about 200 mg/mL of the cryoprotectant. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 1 mg/mL to about 175 mg/mL of the cryoprotectant. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 1 mg/mL to about 150 mg/mL of the cryoprotectant. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 20 mg/mL to about 150 mg/mL of the cryoprotectant.

In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises a cryoprotectant which is a sugar or sugar alcohol in an amount of from about 25 mg/mL to about 150 mg/mL. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises a cryoprotectant which is a sugar or sugar alcohol in an amount of from about 25 mg/mL to about 125 mg/mL cryoprotectant. In a preferred embodiment, the aqueous composition or the reconstituted aqueous composition comprises a cryoprotectant which is a sugar or sugar alcohol in an amount of from about 50 mg/mL to about 100 mg/mL cryoprotectant. In another preferred embodiment, the aqueous composition or the reconstituted aqueous composition comprises a cryoprotectant which is a sugar or sugar alcohol in an amount of from about 75 mg/mL to about 125 mg/mL, e.g. about 100 mg/mL. In an embodiment, the cryoprotectant is sucrose.

In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises a cryoprotectant which is an amino acid or a pharmaceutically acceptable salt thereof in an amount of from about 1 mg/mL to about 100 mg/mL. In a preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a cryoprotectant which is an amino acid or a pharmaceutically acceptable salt thereof in an amount of from about 10 mg/mL to about 50 mg/mL. In a more preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a cryoprotectant which is an amino acid or a pharmaceutically acceptable salt thereof in an amount of from about 25 mg/mL to about 35 mg/mL, e.g. about 30 mg/mL. In an embodiment, the cryoprotectant is arginine, preferably arginine HCl.

In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises two cryoprotectants, wherein the total amount of the two cryoprotectants is from about 25 mg/mL to about 150 mg/mL, preferably wherein the two cryoprotectants are a sugar or sugar alcohol and an amnio acid. In a preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises two cryoprotectants, wherein the total amount of the two cryoprotectants is from about 50 mg/mL to about 125 mg/mL, preferably wherein the two cryoprotectants are a sugar or sugar alcohol and an amino acid.

In a preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises sucrose and cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In a more preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises sucrose and sodium CMC.

In a preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises arginine or a pharmaceutically acceptable salt thereof and cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof. In a more preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises arginine hydrochloride and sodium CMC.

In an embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:1 (w/w) to about 1:100 (w/w). In an embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:1 (w/w) to about 1:50 (w/w). In an embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:1 (w/w) to about 1:40 (w/w). In a preferred embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a

consequence, the solid composition) or the reconstituted aqueous composition is from about 1:8 (w/w) to about 1:40 (w/w). In an embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:8 (w/w) to about 1:35 (w/w), e.g. about 1:10 (w/w) to about 1:33 (w/w).

In an embodiment, the cryoprotectant is arginine or a pharmaceutically acceptable salt thereof, e.g. arginine HCl, and the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:1 (w/w) to about 1:15 (w/w). In an embodiment, the cryoprotectant is arginine or a pharmaceutically acceptable salt thereof, e.g. arginine HCl, and the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:2 (w/w) to about 1:15 (w/w). In an embodiment, the cryoprotectant is arginine or a pharmaceutically acceptable salt thereof, e.g. arginine HCl, and the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:4 (w/w) to about 1:11 (w/w). In a preferred embodiment, the cryoprotectant is arginine or a pharmaceutically acceptable salt thereof, e.g. arginine HCl, and the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:9 (w/w) to about 1:11 (w/w). In a preferred embodiment, the cryoprotectant is arginine or a pharmaceutically acceptable salt thereof, e.g. arginine HCl, and the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:5 (w/w) to about 1:10 (w/w).

In an embodiment, the cryoprotectant is sucrose, and the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:30 (w/w) to about 1:50 (w/w). In an embodiment, the cryoprotectant is sucrose, and the ratio of cellulose or a derivative thereof, or a

pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:30 (w/w) to about 1:40 (w/w). In a preferred embodiment, the cryoprotectant is sucrose, and the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:30 (w/w) to about 1:35 (w/w).

The aqueous composition or the reconstituted aqueous composition comprises water, e.g. sterile water for injection.

In an embodiment, the pH of the aqueous composition or the reconstituted aqueous composition is from about 5 to about 7. In an embodiment, the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 7. In an embodiment, the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 6.5. In a preferred embodiment, the pH of the aqueous composition or the reconstituted aqueous composition is about 6. The pH of the aqueous composition or the reconstituted aqueous composition may be adjusted by, for example, varying the type and/or amount of buffering agent and/or pH adjusting agent present in the aqueous composition.

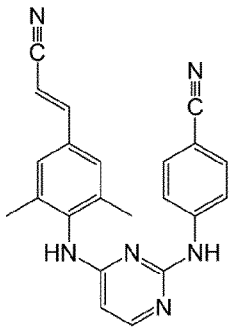
The term “drug” includes any substance that is biologically active. The substance may be free base, free acid or pharmaceutically acceptable salt thereof, and also encompasses tautomers, solvates (e.g. hydrates) and crystalline or amorphous solid forms thereof, and the like. The term “drug” also includes prodrugs. In an embodiment, the drug is not a biologic. By “biologic” it is meant a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition, for example, of human beings. In an embodiment, the drug is not an antibody. In another embodiment, the drug has a molecular weight (MW) of less than 1000 Da. In another embodiment, the drug has a molecular weight (MW) of less than 1000 Da and is not a biologic.

In an embodiment, the drug is selected from drugs for treatment of chronic and long-term diseases and disorders, for example for treatment of chronic viral infection (such as

chronic infection with Varicella-zoster virus, measles virus, human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, hepatitis D virus or human cytomegalovirus), cancer, psychiatric diseases and disorders, mood disorders (such as bipolar, cyclothymic or depression), diabetes, hypertension, abnormal cholesterol and triglyceride levels, inflammatory disorders (such as allergy, asthma, autoimmune diseases, coeliac disease, hepatitis, inflammatory bowel disease, Crohn disease, gout, myositis, scleroderma, rheumatoid arthritis, lupus vasculitis, ankylosing spondylitis or chronic obstructive pulmonary disease), cystic fibrosis, multiple sclerosis, autoimmune disorders, neurodegenerative disorders (such as Parkinson Disease or Alzheimer disease), chronic pain, inherited metabolic disorders or epilepsy.

In a preferred embodiment, the drug is rilpivirine (TMC278), or a pharmaceutically acceptable salt thereof, preferably rilpivirine.

Rilpivirine (4-[[4-[[4-[(1E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile; TMC278) has the following structural formula:



By “rilpivirine” it is meant rilpivirine having the structural formula shown above, i.e. the free base form.

Pharmaceutically acceptable salts of rilpivirine means those where the counterion is pharmaceutically acceptable. The pharmaceutically acceptable salts are meant to comprise the therapeutically active non-toxic acid addition salt forms which rilpivirine is able to form. These salt forms can conveniently be obtained by treating rilpivirine with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetri

carboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzene sulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

In an embodiment, the aqueous composition comprises the drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises the drug in the form of micro- or nanoparticles suspended in the aqueous composition or the reconstituted aqueous composition.

Two embodiments having preferred drug particle sizes are contemplated herein.

In the first preferred drug particle size embodiment, the particles have a D_v90 of less than or about 2 µm. In this embodiment, the particles may have a D_v90 of from about 100 nm to about 2 µm. In this embodiment, the particles may have a D_v90 of from about 200 nm to about 2 µm, for example, of from 200 nm to about 2 µm. In this embodiment, the particles may have a D_v90 of from about 300 nm to about 2 µm, for example, of from 300 nm to about 2 µm. In this embodiment, the particles may have a D_v90 of from about 400 nm to about 2 µm, for example, of from 400 nm to about 2 µm. In this embodiment, the particles may have a D_v90 of from about 500 nm to about 2 µm, for example, of from 500 nm to about 2 µm. Preferably in this embodiment, the particles have a D_v90 of from about 500 nm to about 1,600 nm, for example, of from 500 nm to about 1,600 nm or a D_v90 of from about 500 nm to about 1,000 nm, for example, of from 500 nm to about 1,000 nm, for example about 800 nm. More preferably in this embodiment, the particles have a D_v90 of about 500 nm to about 700 nm, for example about 500 nm to about 650 nm, and most preferably from about 525 nm to about 644 nm.

The term "D_v90" as used herein refers to the diameter below which 90% by volume of the particle population is found. The term "D_v50" as used herein refers to the diameter below which 50% by volume of the particle population is found. The term "D_v10" as used herein refers to the diameter below which 10% by volume of the particle population is found.

In the first preferred particle size embodiment, the particles may have a D_v50 of less than or about 1,000 nm. In this embodiment, the particles may have a D_v50 of from about 10 nm to about 1,000 nm. In this embodiment, the particles may have a D_v50 of from about 50 nm to about 700 nm. In this embodiment, the particles may have a D_v50 of from about 100 nm to about 600 nm. In this embodiment, the particles may have a D_v50 of from about

150 nm to about 500 nm. Preferably in this embodiment, the particles have a D_v50 of from about 200 nm to about 500 nm.

In the first preferred particle size embodiment, the particles may have a D_v10 of less than or about 500 nm. In this embodiment, the particles may have a D_v10 of from about 10 nm to about 500 nm. In this embodiment, the particles may have a D_v10 of from about 25 nm to about 400 nm. In this embodiment, the particles may have a D_v10 of from about 50 nm to about 300 nm. In this embodiment, the particles may have a D_v10 of from about 50 nm to about 200 nm. Preferably in this embodiment, the particles have a D_v10 of from about 75 nm to about 200 nm.

Preferably in this embodiment, the particles have a D_v90 of from about 500 nm to about 1,600 nm, a D_v50 of from about 200 nm to about 500 nm and a D_v10 of from about 75 nm to about 200 nm.

Alternatively, the particles have a D_v90 of from about 500 nm to about 1,000 nm, a D_v50 of from about 200 nm to about 500 nm and a D_v10 of from about 75 nm to about 200 nm.

Alternatively, the particles have a D_v90 of from about 500 nm to about 700 nm, a D_v50 of from about 200 nm to about 500 nm and a D_v10 of from about 75 nm to about 200 nm.

In the second preferred drug particle size embodiment, the particles may have a D_v90 of from about 1 µm to about 10 µm. In this embodiment, the particles may have a D_v90 of from about 2 µm to about 9 µm. In this embodiment, the particles may have a D_v90 of from about 3 µm to about 8 µm. In this embodiment, the particles may have a D_v90 of from about 3 µm to about 7 µm. Preferably in this embodiment, the particles have a D_v90 of from about 4 µm to about 6 µm. Most preferably in this embodiment, the particles have a D_v90 of about 5 µm to about 6 µm, e.g. about 5 µm or about 6 µm.

In the second preferred particle size embodiment, the particles have a D_v50 of less than or about 3 µm. In this embodiment, the particles may have a D_v50 of less than 2.5 µm. In this embodiment, the particles may have a D_v50 of from about 1 µm to about 2.5 µm. In this embodiment, the particles may have a D_v50 of from about 1.2 µm to about 2.2 µm. Preferably in this embodiment, the particles have a D_v50 of from about 1.5 µm to about 2.2 µm. Further preferably in this embodiment, the particles have a D_v50 of from about 1.5 µm to about 2 µm.

In the second preferred particle size embodiment, the particles may have a D_v10 of less than or about 1000 nm. In this embodiment, the particles may have a D_v10 of from about 10 nm to about 1000 nm. In this embodiment, the particles may have a D_v10 of from about 100 nm to about 700 nm. In this embodiment, the particles may have a D_v10 of from about 200 nm to about 600 nm. Preferably in this embodiment, the particles have a D_v10 of from about 300 nm to about 500 nm.

Preferably in this embodiment, the particles have a D_v90 of from about 4 µm to about 6 µm, a D_v50 of from about 1.5 µm to about 2 µm and a D_v10 of from about 300 nm to about 500 nm.

Preferably in this embodiment, the particles have a D_v90 of from about 5 µm to about 6 µm, a D_v50 of from about 1.5 µm to about 2.2 µm and a D_v10 of from about 300 nm to about 500 nm.

The inventors surprisingly found that in compositions of the invention particle size distribution of the drug particles was similar to that in the aqueous composition prior to the freeze drying.

The D_v10, D_v50 and D_v90 as used herein are determined by routine laser diffraction techniques, e.g. in accordance with ISO 13320:2009.

Laser diffraction relies on the principle that a particle will scatter light at an angle that varies depending on the size the particle and a collection of particles will produce a pattern of scattered light defined by intensity and angle that can be correlated to a particle size distribution. A number of laser diffraction instruments are commercially available for the rapid and reliable determination of particle size distributions. For example, particle size distribution may be measured by the conventional Malvern MastersizerTM 3000 particle size analyser from Malvern Instruments. The Malvern MastersizerTM 3000 particle size analyser operates by projecting a helium-neon gas laser beam through a transparent cell containing the particles of interest suspended in an aqueous solution. Light rays which strike the particles are scattered through angles which are inversely proportional to the particle size and a photodetector array measures the intensity of light at several predetermined angles and the measured intensities at different angles are processed by a computer using standard theoretical principles to determine the particle size distribution.

Laser diffraction values may be obtained using a wet dispersion of the particles in distilled water.

Other methods that are commonly used in the art to measure D_v10, D_v50 and D_v90 include disc centrifugation, scanning electron microscope (SEM), sedimentation field flow fractionation and photon correlation spectroscopy.

In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 0.01 to about 500 mg/mL of the drug. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 1 to about 500 mg/mL of the drug. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 10 to about 500 mg/mL of the drug. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 100 to about 500 mg/mL of the drug. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 150 to about 450 mg/mL of the drug. In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 200 to about 400 mg/mL of the drug. In a preferred embodiment, the aqueous composition or the reconstituted aqueous composition comprises from about 250 to about 350 mg/mL of the drug, e.g. about 300 mg/mL.

In an embodiment, the amount of the drug in the aqueous composition (and, therefore, the solid composition) or reconstituted aqueous composition is from about 0.03 mg to about 28800 mg, or from about 3 mg to about 28800 mg, or from about 30 mg to about 28800 mg, or from about 300 mg to about 28800 mg, or from about 900 mg to about 28800 mg (e.g. from about 900 mg to about 14400 mg, or from about 900 mg to about 7200 mg, or from about 900 mg to about 4500 mg, or from about 900 mg to about 3600 mg), preferably from about 1200 mg to about 14400 mg, preferably from about 1350 mg to about 13200 mg, preferably from about 1500 mg to about 12000 mg, (e.g. from about 3000 mg to about 12000 mg), preferably from about 1800 mg to about 10800 mg (e.g. from about 2700 mg to about 10800 mg, or from about 1800 mg to about 3600 mg), most preferably from about 1800 mg to about 7200 mg, or from about 1800 mg to about 4500 mg, or from about 2700 mg to about 4500 mg, or from about 3600 mg to about 4500 mg. The indicated “mg” corresponds to mg of the drug in its free base form. Thus, by way of example, 1 mg of rilpivirine (i.e. rilpivirine in its free base form) corresponds to 1.1 mg of rilpivirine hydrochloride.

In an embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:1 (w/w) to about 20:1 (w/w). In an embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:1 (w/w) to about 10:1 (w/w). In an embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 2:1 (w/w) to about 10:1 (w/w). In an embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 2:1 (w/w) to about 7:1 (w/w). In a preferred embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 3:1 (w/w) to about 6:1 (w/w).

In a preferred embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:1 (w/w) to about 15:1 (w/w). In a particularly preferred embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:1 (w/w) to about 5:1 (w/w), for example about 3:1 (w/w). In another particularly preferred embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 8:1 (w/w) to about 12:1 (w/w), for example about 10:1 (w/w).

In an embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:1 (w/w) to about 1:10 (w/w). In an embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:2 (w/w) to about 1:10 (w/w). In an embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:2 (w/w) to about 1:7 (w/w). In a preferred embodiment, the ratio of drug to cryoprotectant in the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition is from about 1:3 (w/w) to about 1:6 (w/w).

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises one or more surface modifiers. When the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises a drug in the form of particles as defined herein, the one or more surface modifiers is adsorbed to the surface of the particles.

The surface modifier may be selected from known organic and inorganic pharmaceutical excipients, including various polymers, low molecular weight oligomers, natural products and surfactants. Particular surface modifiers that may be used in the invention include nonionic and anionic surfactants. Representative examples of surface modifiers include gelatin, casein, lecithin, salts of negatively charged phospholipids or the acid form thereof (such as phosphatidyl glycerol, phosphatidyl inosite, phosphatidyl serine, phosphatic acid, and their salts such as alkali metal salts, e.g. their sodium salts, for example egg phosphatidyl glycerol sodium, such as the product available under the tradename Lipoid™ EPG), gum acacia, stearic acid, benzalkonium chloride, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives; polyoxyethylene stearates, colloidal silicon dioxide, sodium dodecylsulfate bile salts such as sodium taurocholate, sodium desoxytaurocholate, sodium desoxycholate; methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose, magnesium aluminate silicate, polyvinyl alcohol (PVA), poloxamers, such as Pluronic™ F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide; tyloxapol; Vitamin E-TGPS (α -tocopheryl polyethylene glycol succinate, in particular α-tocopheryl polyethylene glycol 1000 succinate); poloxamines, such as Tetronic™ 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine; dextran; lecithin; dioctyl ester of sodium sulfosuccinic acid such as the products sold under the tradename Aerosol OT™ (AOT); sodium lauryl sulfate (Duponol™ P); alkyl aryl polyether sulfonate available under the tradename Triton™ X-200; polyoxyethylene sorbitan fatty acid esters (Tweens™ 20, 40, 60 and 80); sorbitan esters of fatty acids (Span™ 20, 40, 60 and 80 or Arlacel™ 20, 40, 60 and 80); polyethylene glycols (such as those sold under the tradename Carbowax™ 3550 and 934); sucrose stearate and sucrose distearate mixtures such as the product available under the tradename Crodesta™ F110 or Crodesta™ SL-40; hexyldecyl trimethyl ammonium chloride (CTAC); polyvinylpyrrolidone (PVP). If desired, two or more surface modifiers can be used in combination.

In an embodiment, the surface modifier is selected from a poloxamer, α-tocopheryl polyethylene glycol succinate, polyoxyethylene sorbitan fatty acid ester, and salts of negatively charged phospholipids or the acid form thereof. In an embodiment, the surface modifier is selected from Pluronic™ F108, Vitamin E TGPS(α-tocopheryl polyethylene glycol succinate, in particular a-tocopheryl polyethylene glycol 1000 succinate), polyoxyethylene sorbitan fatty acid esters such as Tween™ 80, and phosphatidyl glycerol, phosphatidyl inosite, phosphatidyl serine, phosphatic acid, and their salts such as alkali metal salts, e.g. their sodium salts, for example egg phosphatidyl glycerol sodium, such as the product available under the tradename Lipoid™ EPG.

In a preferred embodiment, the surface modifier is a poloxamer, in particular Pluronic™ F108. Pluronic™ F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula HO-$[CH_2CH_2O]_x$-$[CH(CH_3)CH_2O]_y$-$[CH_2CH_2O]_z$-H in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag Nonionic™ 1108-F and Synperonic™ PE/F108. In one embodiment, the surface modifier comprises a combination of a polyoxyethylene sorbitan fatty acid ester and a phosphatidyl glycerol salt (in particular egg phosphatidyl glycerol sodium).

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of a poloxamer. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 5 mg/mL to about 100 mg/mL of a poloxamer. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 5 mg/mL to about 70 mg/mL of a poloxamer. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 5 mg/mL to about 60 mg/mL of a poloxamer.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 5 mg/mL to about 25 mg/mL of a poloxamer. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 5 mg/mL to about 20 mg/mL of a poloxamer, e.g. about 20 mg/mL. In a preferred embodiment, the aqueous composition (and, as a consequence, the solid

composition) or the reconstituted aqueous composition comprises from about 5 mg/mL to about 15 mg/mL of a poloxamer, e.g. about 10 mg/mL.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 20 mg/mL to about 60 mg/mL of a poloxamer. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 25 mg/mL to about 60 mg/mL of a poloxamer. In a particularly preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 40 mg/mL to about 60 mg/mL of a poloxamer, e.g. about 50 mg/mL.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a poloxamer and a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, wherein when drug has a Dv90 of less than about 1600 nm the ratio of the drug to poloxamer is less than about 15:1 (w/w). In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a poloxamer and a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer is from about 15:1 (w/w) to about 3:1 (w/w). In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a poloxamer and a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, wherein when the drug has a Dv90 of less than about 1600 nm the ratio of the drug to poloxamer is from about 15:1 (w/w) to about 4:1 (w/w). In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a poloxamer and a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer is from about 15:1 (w/w) to about 6:1 (w/w). In a preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a poloxamer and a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer is about 6:1 (w/w).

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition and a poloxamer, the ratio of the drug to poloxamer is more than about 15:1 (w/w), and the drug has a Dv90 of from about 1 µm to about 10 µm, from about 2 µm to about 9 µm, from about 3 µm to about 8 µm, or from about 3 µm to about 7 µm. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, and a poloxamer, the ratio of the drug to poloxamer is from about 15:1 (w/w) to about 60: (w/w)1, and the drug has a Dv90 of from about 1 µm to about 10 µm, from about 2 µm to about 9 µm, from about 3 µm to about 8 µm, or from about 3 µm to about 7 µm. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, and a poloxamer, the ratio of the drug to poloxamer is from about 20:1 (w/w) to about 60:1 (w/w), and the drug has a Dv90 of from about 1 µm to about 10 µm, from about 2 µm to about 9 µm, from about 3 µm to about 8 µm, or from about 3 µm to about 7 µm. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, and a poloxamer, the ratio of the drug to poloxamer is from about 30:1 (w/w) to about 60:1 (w/w), and the drug has a Dv90 of from about 1 µm to about 10 µm, from about 2 µm to about 9 µm, from about 3 µm to about 8 µm, or from about 3 µm to about 7 µm. In a preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, and a poloxamer, the ratio of the drug to poloxamer is about 30:1 (w/w), and the drug has a Dv90 of from about 1 µm to about 10 µm, from about 2 µm to about 9 µm, from about 3 µm to about 8 µm, or from about 3 µm to about 7 µm, e.g. from about 4 µm to about 6 µm.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, and a poloxamer, the ratio of the drug to poloxamer is less than about 15:1 (w/w), and the

drug has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, and a poloxamer, the ratio of the drug to poloxamer is from about 3:1 (w/w) to about 15:1 (w/w), and the drug has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, and a poloxamer, the ratio of the drug to poloxamer is 4:1 (w/w) to about 15:1 (w/w), and the drug has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, and a poloxamer, the ratio of the drug to poloxamer is 6:1 (w/w) to about 15:1 (w/w), and the drug has a Dv90 of from about 500 nm to about 1600 nm. In a preferred embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition, and a poloxamer, the ratio of the drug to poloxamer is about 6:1 (w/w), and the drug has a Dv90 of from about 500 nm to about 1600 nm, e.g. about 500 nm to about 700 nm.

In an embodiment, the relative amount (w/w) of drug to the surface modifier is from about 1:1 (w/w) to about 40:1 (w/w). In an embodiment, the relative amount (w/w) of drug to the surface modifier is from about 1:1 (w/w) to about 35:1 (w/w). In an embodiment, the relative amount (w/w) of drug to the surface modifier is from about 15:1 (w/w) to about 35:1 (w/w). In an embodiment, the relative amount (w/w) of drug to the surface modifier is from about 25:1 (w/w) to about 35:1 (w/w), e.g. about 30:1 (w/w). The surface modifier is preferably a poloxamer.

In an embodiment, the relative amount (w/w) of drug to the surface modifier is from about 5:1 to about 25:1. In an embodiment, the relative amount (w/w) of drug to the surface modifier is from about 10:1 to about 20:1. In an embodiment, the relative amount (w/w) of drug to the surface modifier is from about 13:1 to about 17:1, e.g. about 15:1. The surface modifier is preferably a poloxamer.

In an embodiment, the relative amount (w/w) of drug to the surface modifier (e.g. a poloxamer) is less than about 15:1. In a preferred embodiment, the relative amount (w/w) of drug to the surface modifier (e.g. a poloxamer) is less than about 12:1.
In an embodiment, the relative amount (w/w) of drug to the surface modifier is from about 1:2 to about 20:1, in particular from about 1:1 to about 10:1, such as from about 4:1 to about 8:1, e.g. from about 4:1 to about 6:1, preferably about 6:1. The surface modifier is preferably a poloxamer.

In an embodiment, the aqueous composition or the reconstituted aqueous composition comprises a drug as defined herein in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition and one or more surface modifiers as defined herein wherein the amount of the drug is at least about 50% by weight of the particles, at least about 80% by weight of the particles, at least about 85% by weight of the particles, at least about 90% by weight of the particles, at least about 95% by weight of the particles, or at least about 99% by weight of the particles, in particular ranges between 80% and 90% by weight of the particles or ranges between 85% and 90% by weight of the particles.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises a buffering agent and/or a pH adjusting agent. Particular buffers are the salts of weak acids. Buffering and pH adjusting agents that can be added may be selected from tartaric acid, maleic acid, glycine, sodium lactate/lactic acid, ascorbic acid, sodium citrates/citric acid, sodium acetate/acetic acid, sodium bicarbonate/carbonic acid, sodium succinate/succinic acid, sodium benzoate/benzoic acid, sodium phosphates, tris(hydroxymethyl)aminomethane, sodium bicarbonate/sodium carbonate, ammonium hydroxide, benzene sulfonic acid, benzoate sodium/acid, diethanolamine, glucono delta lactone, hydrochloric acid, hydrogen bromide, lysine, methanesulfonic acid, monoethanolamine, sodium hydroxide, tromethamine, gluconic, glyceric, gluratic, glutamic, ethylene diamine tetraacetic (EDTA), triethanolamine, including mixtures thereof. In an embodiment, the buffer is a sodium phosphate buffer, e.g. sodium dihydrogen phosphate monohydrate. In an embodiment the pH adjusting agent is sodium hydroxide. In a preferred embodiment, the aqueous composition or the reconstituted aqueous composition comprises a buffering agent and a pH adjusting agent, wherein the buffering agent is sodium dihydrogen phosphate monohydrate and the pH adjusting agent is sodium hydroxide.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises a chelating agent. In an embodiment the chelating agent is selected form sodium citrate, sodium EDTA, citric acid and malic acid. In a preferred embodiment, the chelating agent is citric acid, e.g. citric acid monohydrate.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition additionally comprises an antioxidant. In an embodiment, the antioxidant is methionine. In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition comprises from about 1.0 mg/mL to about 2.0 mg/mL of the antioxidant (e.g. methionine), for example about 1.5 mg/mL.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition does not comprise an isotonizing agent.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition does not comprise glucose.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition does not comprise mannitol.

In an embodiment, the aqueous composition (and, as a consequence, the solid composition) or the reconstituted aqueous composition does not comprise a polyvinyl pyrrolidone (PVP).

The aqueous composition and the reconstituted aqueous composition may usefully have osmolality suitable to reduce pain on subcutaneous injection. For example, in an embodiment, the aqueous composition and reconstituted aqueous composition has an osmolality of from about 280 mOsm/kg to about 600 mOsm/kg. In an embodiment, the aqueous composition and reconstituted aqueous composition has an osmolality of from about 280 mOsm/kg to about 300 mOsm/kg. In a preferred embodiment, the aqueous composition and reconstituted aqueous composition has an osmolality of about 290 mOsm/kg.

In an embodiment, the aqueous composition or the reconstituted aqueous composition of the invention may be housed in a container with an inert gas. The inert gas may, for example, be nitrogen.

The following particular embodiments are also part of the invention.

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
a hyaluronidase;
a drug; and
CMC or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 7, optionally from about 6 to about 6.5.

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug; and
sodium CMC,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 6.5.

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug; and
sodium CMC,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 6.5, and
wherein the aqueous composition comprises from about 0.5 mg sodium CMC per 100 U rHuPH20 to about 2 mg sodium CMC per 100 U rHuPH20,

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug; and

sodium CMC,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 6.5, and
wherein the aqueous composition comprises from about 0.05 mg sodium CMC per 100 U rHuPH20 to about 0.25 mg sodium CMC per 100 U rHuPH20,

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
a hyaluronidase;
a drug;
CMC or a pharmaceutically acceptable salt thereof; and
a cryoprotectant,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 7, optionally from about 6 to about 6.5.

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug;
CMC; and
a sugar or sugar alcohol,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 6.5.

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug;
sodium CMC; and
mannitol and/or sucrose,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 6.5,
wherein the aqueous composition or the reconstituted aqueous composition comprises from about 0.5 mg sodium CMC per 100 U rHuPH20 to about 2 mg sodium CMC per 100 U rHuPH20, and

wherein the ratio of sodium CMC to mannitol or sucrose is from about 1:4 (w/w) to about 1:11 (w/w).

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug;
sodium CMC; and
sucrose,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 6.5,
wherein the aqueous composition or the reconstituted aqueous composition comprises from about 0.05 mg sodium CMC per 100 U rHuPH20 to about 0.25 mg sodium CMC per 100 U rHuPH20, and
wherein the ratio of sodium CMC to sucrose is from about 1:30 (w/w) to about 1:35 (w/w).

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug;
CMC; and
an amino acid or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 6.5.

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug;
sodium CMC; and
arginine HCl,
wherein the pH of the aqueous composition or the reconstituted aqueous composition is from about 6 to about 6.5,
wherein the aqueous composition or the reconstituted aqueous composition comprises from about 0.05 mg sodium CMC per 100 U rHuPH20 to about 0.25 mg sodium CMC per 100 U rHuPH20, and

wherein the ratio of sodium CMC to arginine HCl is from about 1:9 (w/w) to about 1:11 (w/w).

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug;
sodium CMC;
sucrose; and
poloxamer 338,
optionally wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer 338 is from about 3:1 (w/w) to about 15:1 (w/w), e.g. about 6:1 (w/w).

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
from about 1800 to about 2200 U/mL rHuPH20;
from about 250 to about 350 mg/mL of a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition;
from about 1 mg/mL to about 5 mg/mL sodium CMC;
from about 75 mg/mL to about 125 mg/mL sucrose; and
from about 5 mg/mL to about 60 mg/mL poloxamer 338,
optionally wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer 338 is from about 3:1 (w/w) to about 15:1 (w/w), e.g. about 6:1 (w/w).

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:
rHuPH20;
a drug;
sodium CMC;
arginine HCl; and
poloxamer 338,
optionally wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer 338 is from about 3:1 (w/w) to about 15:1 (w/w), e.g. about 6:1 (w/w).

In a particular embodiment, the aqueous composition or the reconstituted aqueous composition comprises:

from about 1800 to about 2200 U/mL rHuPH20;
from about 250 to about 350 mg/mL of a drug in the form of particles suspended in the aqueous composition or the reconstituted aqueous composition;
from about 1 mg/mL to about 5 mg/mL sodium CMC;
from about 25 mg/mL to about 35 mg/mL arginine HCl; and
from about 5 mg/mL to about 60 mg/mL poloxamer 338,
optionally wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer 338 is from about 3:1 (w/w) to about 15:1 (w/w), e.g. about 6:1 (w/w).

The invention also relates to the freeze dried compositions corresponding to the particular embodiments above.

In any of the particular embodiments, the aqueous composition or the reconstituted aqueous composition may additionally further comprise an antioxidant (e.g. methionine), optionally in an amount of from about 1.0 mg/mL to about 2.0 mg/mL (e.g. 1.5 mg/mL). I

Unless specified otherwise, in any of the particular embodiments above the particles may have a Dv90 of from about 1 µm to about 10 µm (e.g. about 5 µm to about 6 µm). Alternatively, unless specified otherwise, in any of the particular embodiments above the particles may have a Dv90 of from about 500 nm to about 1600 nm (e.g. about 500 nm to about 700 nm).

The invention also relates to a solid composition comprising (i) a hyaluronidase, (ii) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and (iii) a drug. The solid composition may optionally have features (e.g. excipients, amounts and pH) and combinations of features as described herein in relation to the aqueous composition and solid composition of the first aspect of the invention. Thus, purely by way of example, the invention also relates to a solid composition comprising (i) a hyaluronidase, (ii) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, (iii) a drug, and (iv) a cryoprotectant as defined in relation to the first aspect of the invention.

Reconstitution of the solid composition

The solid composition of the invention may be reconstituted to provide a reconstituted aqueous composition. Thus, the second aspect of the invention relates to a reconstituted aqueous composition obtainable by reconstituting the solid composition as defined herein.

For the avoidance of doubt, the reconstituted aqueous composition comprises the same components in the same amounts as the aqueous composition in the first aspect of the invention that is subsequently freeze dried to provide the solid composition of the first aspect of the invention. Thus, all of the embodiments described in the first aspect of the invention in relation to the aqueous composition apply equally to the reconstituted aqueous composition of the second aspect of the invention. The volume of the reconstituted aqueous composition is not necessarily the same as the volume of the aqueous composition in the first aspect of the invention, so the concentrations of components in these compositions may differ from each other. For example, the aqueous composition in the first aspect of the invention could have a concentration of a component of 300 mg/mL, but if it is reconstituted in double the volume after lyophilisation, the concentration of that component in the reconstituted aqueous composition would be 150 mg/mL.

In an embodiment, the reconstituting comprises adding an aqueous dispersion medium to the solid composition as defined herein, the aqueous dispersion medium being preferably water.

In an embodiment, the dispersion medium comprises one or more other active agents, in particular one or more other antiretroviral agents, in particular one or more other antiretroviral agents of another class, for example an antiretroviral of the INSTI class, for example cabotegravir.

In another embodiment, the aqueous dispersion medium is an aqueous solution of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, e.g. CMC or a pharmaceutically acceptable salt thereof. In another embodiment, the aqueous dispersion medium is an aqueous solution of sodium CMC.

Lyophilisation

The aqueous composition described herein can be transformed into the solid composition of the invention by freeze drying the aqueous composition using standard procedures known in the art. An example procedure is provided below:

Vials are filled with the aqueous composition. Lyophilisation is performed on a laboratory scale freezedryer (LyoStar3, SP Scientific, USA). Freezing is conducted at –40 °C (shelf inlet temperature) for 60 minutes including equilibrating steps at +5 °C then –5 °C for

15 minutes each. An annealing step at –20°C (shelf inlet temperature) for 90 minutes is implemented. The shelf temperature ramp rates from the freezing set-point to the primary drying shelf temperature setting are 1 °C/min throughout the process. The shelf inlet temperature set-point during primary drying is about -20°C and secondary drying is about 25 °C. The holding time (soak period) of these steps is 600 minutes respectively 60 minutes to allow a modulation in water content in the samples. The chamber pressure during primary and secondary drying is about 100 mTorr for primary drying step and about 300 mTorr for the secondary drying step. Product temperatures during freeze drying are measured using wired thermocouples. Each thermocouple wire is positioned bottom-centre of the vial to obtain both a representative temperature monitoring in the product and an accurate endpoint detection of the ice sublimation phase.

Uses of the compositions of the invention

The reconstituted aqueous composition can be used to treat or prevent a disease or disorder in a subject, i.e. the reconstituted aqueous composition is for use in therapy.

Thus, in a third aspect the invention relates to a method for the treatment or prevention of a disease or disorder in a subject, the method comprising administering to the subject the reconstituted aqueous composition as defined herein. In a fourth aspect the invention relates to the reconstituted aqueous composition as defined herein for use in the treatment or prevention of a disease or disorder in a subject. In a fifth aspect invention relates to use of the reconstituted aqueous composition as defined herein for the manufacture of a medicament for treating or preventing a disease or disorder in a subject. In a sixth aspect there is provided a solid composition as defined herein for use in the treatment or prevention of a disease or disorder in a subject. In a seventh aspect there is provided the use of the solid composition as defined herein for the manufacture of a medicament for treating or preventing a disease or disorder in a subject.

In a preferred embodiment, the subject is a human.

The drug is present (and is administered to the subject) in a therapeutically effective amount. By “therapeutically effective amount” it is meant an amount sufficient to provide a therapeutic effect.

In an embodiment, the disease or disorder is chronic and long-term diseases and disorders, for example chronic viral infection (such as chronic infection with Varicella-

zoster virus, measles virus, HIV, hepatitis B virus, hepatitis C virus, hepatitis D virus or human cytomegalovirus), cancer, psychiatric diseases and disorders, mood disorders (such as bipolar, cyclothymic or depression), diabetes, hypertension, abnormal cholesterol and triglyceride levels, inflammatory disorders (such as allergy, asthma, autoimmune diseases, coeliac disease, hepatitis, inflammatory bowel disease, Crohn disease, gout, myositis, scleroderma, rheumatoid arthritis, lupus vasculitis, ankylosing spondylitis or chronic obstructive pulmonary disease), cystic fibrosis, multiple sclerosis, autoimmune disorders, neurodegenerative disorders (such as Parkinson's Disease or Alzheimer's disease), chronic pain, inherited metabolic disorders or epilepsy.

In an embodiment, the disease or disorder is HIV infection. In an embodiment, the HIV is HIV type 1 (HIV-1). When the disease or disorder is HIV infection, the drug is preferably rilpivirine or a pharmaceutically acceptable salt thereof, more preferably rilpivirine.

In an embodiment, the reconstituted aqueous composition is administered to the subject intermittently such that the time interval between administrations (i.e. the dosing interval) is about three months to about two years. In an embodiment, the time interval is about three months to about eighteen months. In an embodiment, the time interval is about three months to about one year. In an embodiment, the time interval is about three months to about six months. In an embodiment, the time interval is about six months to about one year. In an embodiment, the time interval is about one year. In an embodiment, the time interval is about three months. In an embodiment, the time interval is about six months.

In an embodiment, the reconstituted aqueous composition is administered to the subject intermittently such that the time interval between administrations (i.e. the dosing interval) is about three months, or of about four months, or of about five months, or of about six months or, of about seven months, or of about eight months, or of about nine months, or of about ten months, or of about eleven months, or of about one year, or of about one year to about two years.

In a preferred embodiment, the reconstituted aqueous composition is administered to the subject intermittently such that the time interval between administrations is as defined in any of the embodiments above and the drug is rilpivirine or a pharmaceutically acceptable salt thereof.

In an embodiment, the reconstituted aqueous composition is administered by subcutaneous injection or intramuscular injection. In an embodiment, the reconstituted aqueous composition is administered by intramuscular injection. In a preferred embodiment, the reconstituted aqueous composition is administered by subcutaneous injection.

In another embodiment, the reconstituted aqueous composition is administered by a manual injection process.

In an embodiment, each administration comprises up to about 600 mL of the reconstituted aqueous composition described herein. In another embodiment, each administration comprises from about 3 mL to about 600 mL of the reconstituted aqueous composition. In another embodiment each administration comprises from about 3 mL to about 150mL of the reconstituted aqueous composition. In another embodiment, each administration comprises from about 3 mL to about 150mL of the reconstituted aqueous composition. In another embodiment, each administration comprises from about 5 mL to about 150mL of the reconstituted aqueous composition. In another embodiment, each administration comprises from about 5 mL to about 100 mL of the reconstituted aqueous composition. In another embodiment, each administration comprises from about 5 mL to about 50 mL of the reconstituted aqueous composition. In another embodiment, each administration comprises from about 5 mL to about 25 mL of the reconstituted aqueous composition. In another embodiment, each administration comprises from about 5 mL to about 20 mL of the reconstituted aqueous composition. In another embodiment, each administration comprises from about 5 mL to about 10 mL of the reconstituted aqueous composition.

In an embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises up to about 150 mL of the reconstituted aqueous composition described herein. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 3 mL to about 150mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 3 mL to about 100mL of the reconstituted aqueous composition. In another embodiment, each administration comprises from about 3 mL to about 25 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 3 mL to about 15mL of the reconstituted aqueous composition. In another embodiment, the

drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 5 mL to about 25 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 6 mL to about 20 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 6 mL to about 18 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 6 mL to about 15 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 6 mL to about 12 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 9 mL to about 18 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 9 mL to about 15 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises from about 9 mL to about 12 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises about 3 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises about 6 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises about 7 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises about 9 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises about 12 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises about 15 mL of the reconstituted aqueous composition. In another embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises about 18 mL of the reconstituted aqueous composition. In a preferred embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and each administration comprises about 3 mL, about 7 mL, or about 15 mL of the reconstituted aqueous composition.

In an embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and is for the treatment of HIV infection, wherein the dose of rilpivirine or pharmaceutically acceptable salt thereof to be administered may be calculated on a basis of from about 300 mg to about 1200 mg/month, or from about 450 mg to about 1200 mg/month, or from about 450 mg to about 900 mg/month, or from about 600 mg to about 900 mg/month, or from about 450 mg to about 750 mg/month, or about 450 mg/month, or about 600 mg/month, or about 750 mg/month, or about 900 mg/month. Doses for other dosing regimens can readily be calculated by multiplying the monthly dose with the number of months between each administration. For example, in case of a dose of 450 mg/month, and in case of a time interval of 6 months between each administration, the dose of rilpivirine or pharmaceutically acceptable salt thereof to be administered in each administration is 2700 mg. The indicated "mg" corresponds to mg of rilpivirine (i.e. rilpivirine in its free base form). Thus, by way of example, 1 mg of rilpivirine (i.e. rilpivirine in its free base form) corresponds to 1.1 mg of rilpivirine hydrochloride.

In an embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and is for the treatment of HIV infection, wherein the dose of rilpivirine or pharmaceutically acceptable salt thereof to be administered may be calculated on a basis of from about 300 mg to about 1200 mg/4 weeks (28 days), or from about 450 mg to about 1200 mg/4 weeks (28 days), or from about 450 mg to about 900 mg/4 weeks (28 days), or from about 600 mg to about 900 mg/4 weeks (28 days), or from about 450 mg to about 750 mg/4 weeks (28 days) or about 450 mg/4 weeks (28 days), or about 600 mg/4 weeks (28 days), or about 750 mg/4 weeks (28 days) or about 900 mg/4 weeks (28 days). Doses for other dosing regimens can readily be calculated by multiplying the week or day dose with the number of weeks between each administration. For example, in case of a dose of 450 mg/4 weeks (28 days), and in case of a time interval of 24 weeks between each administration, the dose of rilpivirine or pharmaceutically acceptable salt thereof to be administered in each administration is 2700 mg. Or for example, in case of a dose of 750 mg/4 weeks (28 days), and in case of a time interval of 24 weeks between each administration, the dose of rilpivirine or pharmaceutically acceptable salt thereof to be administered in each administration is 4500 mg. The indicated "mg" corresponds to mg of rilpivirine (i.e. rilpivirine in its free base form). Thus, by way of example, 1 mg of rilpivirine (i.e. rilpivirine in its free base form) corresponds to 1.1 mg of rilpivirine hydrochloride.

In an embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof, and the rilpivirine or pharmaceutically acceptable salt thereof in the reconstituted aqueous

composition is used in an amount such that the blood plasma concentration of rilpivirine in the subject is kept at a level above about 12 ng/ml, preferably ranging from about 12 ng/ml to about 100 ng/ml, more preferably from about 12 ng/ml to about 50 ng/ml for at least 3 months after administration, or at least 6 months after administration, or at least 9 months after administration, or at least 1 year after administration, or at least 2 years after each administration. In a preferred embodiment, the rilpivirine or pharmaceutically acceptable salt thereof in the reconstituted aqueous composition is used in an amount such that the blood plasma concentration of rilpivirine in the subject is kept at a level of from about 12 ng/ml to about 100 ng/ml for at least 6 months.

In an embodiment, the drug is rilpivirine or pharmaceutically acceptable salt thereof and is for the prevention of HIV infection, wherein each administration of rilpivirine or pharmaceutically acceptable salt thereof may comprise the same dosing as for therapeutic applications as described above.

In an embodiment, the reconstituted aqueous composition comprises a drug as defined herein and is used in combination with one or more other drugs, in particular one or more other antiretroviral agents, in particular one or more other antiretroviral agents of another class, such as for example an antiretroviral of the INSTI class, such as for example cabotegravir.

In an embodiment, said one or more other antiretroviral agents, e.g. cabotegravir, is administered as an intramuscular or subcutaneous injection, in particular as an injectable micro- or nanosuspension, at a time interval of about three months to about two years. In an embodiment, said one or more other antiretroviral agent, e.g. cabotegravir, is administered at the same intermittent time interval as the reconstituted aqueous composition described herein, e.g. the reconstituted aqueous composition and the other antiretroviral agent are administered intermittently at a time interval of about three months, or of about four months, or of about five months or of about six months or of about seven months or of about eight months or of about ten months or of about eleven months or of about one year or of about one year to about 2 years. In an embodiment the reconstituted aqueous composition and the one or more other antiretroviral agents, e.g. cabotegravir, are administered simultaneously or sequentially by intramuscular or subcutaneous injection, in particular subcutaneous injection. In an embodiment, the reconstituted aqueous composition and the one or more other antiretroviral agents, e.g. cabotegravir, are administered simultaneously, in particular by subcutaneous injection. In an

embodiment, the reconstituted aqueous composition and the one or more other antiretroviral agents, e.g. cabotegravir, are administered sequentially, in particular by subcutaneous injection. In an embodiment, the reconstituted aqueous composition is administered first followed by a cabotegravir injection.

As used herein the term "treatment of HIV infection" relates to the treatment of a subject infected with HIV. The term "treatment of HIV infection" also relates to the treatment of diseases associated with HIV infection, for example AIDS, or other conditions associated with HIV infection including thrombocytopaenia, Kaposi's sarcoma and infection of the central nervous system characterized by progressive demyelination, resulting in dementia and symptoms such as, progressive dysarthria, ataxia and disorientation, and further conditions where HIV infection has also been associated with, such as peripheral neuropathy, progressive generalized lymphadenopathy (PGL), and AIDS-related complex (ARC).

As used herein the term "prevention of HIV infection" relates to the prevention or avoidance of a subject (who is not infected with HIV) becoming infected with HIV. The source of infection can be various, a material containing HIV, in particular a body fluid that contains HIV such as blood or semen, or another subject who is infected with HIV. Prevention of HIV infection relates to the prevention of the transmission of the virus from the material containing HIV or from the HIV infected individual to an uninfected person, or relates to the prevention of the virus from entering the body of an uninfected person. Transmission of the HIV virus can be by any known cause of HIV transfer such as by sexual transmission or by contact with blood of an infected subject, e.g. medical staff providing care to infected subjects. Transfer of HIV can also occur by contact with HIV infected blood, e.g. when handling blood samples or with blood transfusion. It can also be by contact with infected cells, e.g. when carrying out laboratory experiments with HIV infected cells.

The term "treatment of HIV infection" refers to a treatment by which the viral load of HIV (represented as the number of copies of viral RNA in a specified volume of serum) is reduced. The more effective the treatment, the lower the viral load. Preferably the viral load should be reduced to as low levels as possible, e.g. below about 200 copies/mL, in particular below about 100 copies/mL, more in particular below 50 copies/mL, if possible below the detection limit of the virus. Reductions of viral load of one, two or even three orders of magnitude (e.g. a reduction in the order of about 10 to about 10^2, or more, such

as about 10^3) are an indication of the effectiveness of the treatment. Another parameter to measure effectiveness of HIV treatment is the CD4 count, which in normal adults ranges from 500 to 1500 cells per µL. Lowered CD4 counts are an indication of HIV infection and once below about 200 cells per µL, AIDS may develop. An increase of CD4 count, e.g. with about 50, 100, 200 or more cells per µL, is also an indication of the effectiveness of anti-HIV treatment. The CD4 count in particular should be increased to a level above about 200 cells per µL, or above about 350 cells per µL. Viral load or CD4 count, or both, can be used to diagnose the degree of HIV infection. Another parameter to measure effectiveness of HIV treatment is keeping the HIV infected subject virologically suppressed (HIV-1 RNA < 50 copies/mL) when on the treatment according to the present invention.

The term "treatment of HIV infection" and similar terms refer to that treatment that lowers the viral load, or increases CD4 count, or both, or keeps the HIV infected subject virologically suppressed, as described above. The term "prevention of HIV infection" and similar terms refer to that situation where there is a decrease in the relative number of newly infected subjects in a population in contact with a source of HIV infection such as a material containing HIV, or a HIV infected subject. Effective prevention can be measured, for example, by measuring in a mixed population of HIV infected and non- infected individuals, if there is a decrease of the relative number of newly infected individuals, when comparing non- infected individuals treated with a pharmaceutical composition of the invention, and non-treated non-infected individuals. This decrease can be measured by statistical analysis of the numbers of infected and non-infected individuals in a given population over time.

Uses of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof for stabilising a hyaluronidase

In an eighth aspect, there is provided use of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof for stabilising a hyaluronidase in a solid composition, in particular a freeze dried composition, comprising a drug.

In a ninth aspect there is provided a method for stabilising a hyaluronidase in a solid composition comprising a drug, the method comprising freeze drying an aqueous composition comprising the hyaluronidase, the drug and cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof.

The cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof in the eighth or ninth aspects of the invention may be any one of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof defined in relation to the first aspect of the invention.

The solid composition in the eighth or ninth aspects of the invention may be any one of the solid compositions as defined in relation to the first aspect of the invention.

The hyaluronidase in the eighth or ninth aspects of the invention may be any one of the hyaluronidases as defined in relation to the first aspect of the invention.

The drug in the eighth or ninth aspects of the invention may be any one of the drugs as defined in relation to the first aspect of the invention.

Kits

In a tenth aspect there is provided a kit comprising: (i) the solid composition of the invention as described herein, and (ii) a diluent, in particular a diluent to reconstitute the solid composition (i).

In an eleventh aspect there is provided a kit comprising: (i) the solid composition of the invention as described herein, and (ii) a composition comprising one or more other drugs, in particular one or more other antiretroviral agents, in particular one or more other antiretroviral agents of another class, such as for example an antiretroviral of the INSTI class, such as for example cabotegravir, and optionally (iii) a diluent, in particular a diluent to reconstitute the solid composition (i).

GENERAL DEFINITIONS

The term “comprising” encompasses “including” as well as “consisting”, e.g. a composition “comprising” X may consist exclusively of X or may include something additional, e.g. X + Y. The term “comprising” used herein also encompasses “consisting essentially of”, e.g. a composition “comprising” X may consist of X and any other components that do not materially affect the essential characteristics of the composition.

The term “about” in relation to a numerical value Y is optional and means, for example, Y ± 10%.

When a time interval is expressed as a specified number of months, it runs from a given numbered day of a given month to the same numbered day of the month that falls the specified number of months later. Where the same numbered day does not exist in the month that falls the specified number of months later, the time interval runs into the following month for the same number of days it would have run if the same numbered day would exist in the month that falls the specified number of months later.

When a time interval is expressed as a number of years, it runs from a given date of a given year to the same date in the year that falls the specified number of years later. Where the same date does not exist in the year that falls the specified number of years later, the time interval runs for the same number of days it would have run if the same numbered day would exist in the month that falls the specified number of months later. In other words, if the time interval starts on 29th February of a given year but ends in a year where there is no 29th February, the time period ends instead on 1st March in that year. The term “about” in relation to such a definition means that the time interval may end on a date that is ± 10% of the time interval.

In an embodiment, the time interval may start up to 7 days before or after the start of the time interval and end up to 7 days before or after the end of the time interval.

All references cited herein are incorporated by reference in their entirety.

The invention will now be described with reference to the following examples. For the avoidance of doubt, these examples do not limit the scope of the invention. Modifications may be made whilst remaining within the scope and spirit of the invention.

EXAMPLES

Example 1a – Hyaluronidase melting temperature studies

This example compares the T_m of a hyaluronidase in various compositions, each having a different combination of excipients and/or pH.

A higher T_m indicates higher thermal stability. A T_m of from about 25 to about 30 °C higher than the intended long term storage conditions targeted to provide optimal thermodynamic stability of the hyaluronidase.

A composition A comprising the following excipients was prepared:

-
- Sodium dihydrogen phosphate monohydrate (2 mg/mL)
- Citric acid monohydrate (1 mg/mL)
- rHuPH20 (2000 U/mL)
- Sodium hydroxide (varied to provide required pH)
- Water for injection (q.s. ad 1 mL)

Compositions 1-5 were prepared by adding the component(s) shown in Table 1 below to the composition A, and adjusting the pH to 6.0, 6.5, or 7.0 as necessary by varying the amount of the sodium hydroxide in the composition.

Composition	Additional component	pH	T_m / °C
1	-	6.5	48.44
2	-	7	47.6
3	Sodium CMC (25 mg/mL)	6.0	54.1
4	Sodium CMC (25 mg/mL)	6.5	54.06
5	Sodium CMC (25 mg/mL)	7	50.41

Table 1: T_m studies

Compositions 1-5 were prepared as set out above and then stored in a refrigerator at 5 °C for between 2 days and 2 weeks. The T_m for the hyaluronidase was then measured for each of the compositions straight away. The T_m was calculated using nano differential scanning fluorimetry (nDSF) assays. nDSF uses the intrinsic tryptophan and tyrosine fluorescence to monitor hyaluronidase unfolding.

The T_m values in this example were measured using nDSF assays as follows.

A Prometheus NT.Plex instrument controlled by PR.ThermControl-CFR software was used to run all nDSF assays. A temperature range of 20–95 °C with a temperature gradient of 1 °C/min was used when measuring the samples. An excitation power of 95% was used in all cases. The instrument determined the fluorescence ratio of 350 nm (tryptophan) and 330 nm (tyrosine) of the hyaluronidase during a heat ramp to 95 °C. The unfolding onset temperature (T_{on}) and the inflection points (T_m) of the present unfolding transitions were then calculated from the unfolding curve.

To enable high throughput sample testing, the nanoDSF instrument was operated in combination with a robotic autosampler. The autosampler performs loading and transfer of the capillary chips from a 384-well plate for nanoDSF measurements. The preparation of the 384-well plate was automated using a Tecan Fluent 760 liquid handling system in combination with custom-made sample holders for 2R vials that were typically provided for sample testing.

The results are shown in Table 1.

Example 1b – Hyaluronidase melting temperature under different storage conditions

This example compares the fluorescence emission spectra of rHuPH20 compositions after storage under different conditions. Fluorescence emission spectroscopy uses a beam of light which is absorbed by a hyaluronidase, causing a fluorophore in the ground state to be excited to a higher energy state, thereby resulting in emission. For a hyaluronidase such as rHuPH20, the fluorescence of tryptophan may be used to measure a change in tertiary hyaluronidase structure during or after storage under different conditions, and thus quantify the thermal stability of the hyaluronidase. The maximum emission wavelengths for folded and unfolded rHuPH20 are 330 nm and 350 nm, respectively.

Compositions 6-10 were prepared by adding the component(s) shown in Table 2 below to composition A of Example 1a, and adjusting the pH to 6.0, 6.5, or 7.0 as necessary by varying the amount of the sodium hydroxide in the composition.

The spectra of the compositions were collected immediately after storage at 5 °C and after storage at 40 °C for one and two weeks. In addition to peak maximum and minimum, the intensity ratio 350/330 nm was calculated and plotted as a function of storage time. The slope of this curve was used to have a semi-quantitative assessment and comparison among compositions.

Composition preparation

200 µl of each composition was dispensed manually into an UV-STAR®, COC, 96-well flat-bottom microplate.

The fluorescence emission spectrum of the samples was measured before and after stressing via a Tecan plate reader (Infinite 200). The following method parameters were used:

Temperature:

- Parameter (on), temperature = 25.0 °C

Wait for temperature:

- Parameter minimum = 24.5 °C; maximum = 25.5 °C

Fluorescence intensity scan:

- Scan selection (emission scan)
- Mode (top)
- Excitation wavelengths: from = 280 nm; bandwidth: 230…315: 5 nm; 316…850: 9 nm
- Emission wavelengths: from = 310 nm; to = 420 nm; step = 1 nm; bandwidth: 280…850: 20 nm; 111 measurements
- Integration: lag time = 0 µs; integration time = 20 µs
- Read: number of flashes = 25; settle time = 0 ms
- Gain (manual = 95)
- Label: name = Label1

The results are shown in Table 2, below.

Composition	Additional component	pH	Slope 350 nm / 330 nm
6	-	6.5	
7	-	7	
8	Sodium CMC (25 mg/mL)	6	–0.00035
9	Sodium CMC (25 mg/mL)	6.5	0.001466
10	Sodium CMC (25 mg/mL)	7	0.003267

Table 2: Slope of the ratio between 350 nm / 330 nm versus time

Example 2 – Hyaluronidase melting temperature studies under different storage conditions

This example compares the T_m of a hyaluronidase in various compositions under different storage conditions.

A composition B comprising the following excipients was prepared:

- rHuPH20 (2000 U/mL)
- Sodium dihydrogen phosphate monohydrate (2 mg/mL)
- Citric acid monohydrate (1 mg/mL)
- Poloxamer 338 (50 mg/mL)
- Sodium hydroxide (q.s. for pH 6)
- Water for injection (q.s. ad 1 mL)

Compositions 11-14 were then prepared by adding the component(s) as shown in Table 3 to the composition B, and the pH was adjusted to 6.0 by varying the amount of sodium hydroxide in the composition.

Composition	**Additional component 1**	**Additional component 2**	**T_m (t = 0) / °C**	**T_m (t = 0) SD (n = 3) / °C / °C**	**T_m (t = 1 week at 40 °C) / °C**	**T_m (t = 1 week at 40 °C) SD (n = 3) / °C**
11	Sucrose (100 mg/mL)	Sodium CMC (10 mg/mL)	54.86	0.04	55.28	0.25
12	Mannitol (50 mg/mL)	Sodium CMC (5 mg/mL)	54.38	0.05	54.54	0.12
13	Mannitol (50 mg/mL)	Sodium CMC (10 mg/mL)	54.06	0.05	54.18	0.07
14	-	-	<47	-	-	-

"-" in the T_m columns means that the hyaluronidase was denatured due to the applied temperature stress.

Table 3: T_m under different storage conditions

Compositions 11-14 were prepared as set out above and then stored in a refrigerator at 5 °C between 2 days and 2 weeks. The T_m values in this example were measured straight away (i.e. "t=0") and after storage for 1 week at 40 °C using the method described in Example 1a.

The pH of the compositions was remeasured immediately before the T_m values were measured. The remeasured pH was 5.93, 5.96, and 5.92 for compositions 11, 12, and 13, respectively.

The results are shown in Table 3. Where a T_m value at t = 1 week at 40 °C is not displayed (i.e. "–"), the hyaluronidase had decomposed.

Example 3 – Sodium CMC concentration

This example examines the dependence of T_m on sodium CMC concentration.

A composition C comprising the following excipients was prepared:

- rHuPH20 (2000 U/mL)
- Sodium dihydrogen phosphate monohydrate (2 mg/mL)
- Citric acid monohydrate (1 mg/mL)
- Poloxamer 338 (50 mg/mL)
- Sodium hydroxide (q.s for pH 6)
- Mannitol (50 mg/mL) or sucrose (100 mg/mL)
- Water for injection (q.s. ad 1 mL)

Compositions 15-20 were then prepared by adding sodium CMC shown in Table 4 below to the above composition C, and the pH was adjusted to 6.0 by varying the amount of sodium hydroxide in the composition.

Composition	Sodium CMC concentration / mg/mL	Sugar/sugar alcohol
15	5	Mannitol (50 mg/mL)
16	5	Sucrose (100 mg/mL)
17	10	Mannitol (50 mg/mL)
18	10	Sucrose (100 mg/mL)
19	15	Mannitol (50 mg/mL)
20	15	Sucrose (100 mg/mL)

Table 4: Sodium CMC concentration

Compositions 15-20 were prepared as set out above and then stored in a refrigerator at 5 °C between 2 days and 2 weeks. T_m values were then measured using the method described in Example 1a.

The results are shown in Figure 1.

Example 4 – Particle size distributions of compositions

In this example aqueous compositions according to the invention comprising drug nanoparticles in suspension were freeze dried to explore the effect of this process on the particle size of the drug in the corresponding reconstituted aqueous compositions. The freeze dried compositions were reconstituted instantly, i.e. at time t=0, and after storage for 1 month, and after storage for 6 months under various conditions.

Aqueous compositions of a drug (rilpivirine) in the form of nanoparticles (having Dv10 of about 96.5 nm, Dv50 of about 224 nm, and Dv90 of about 509 nm) with the following excipients were prepared:

- Nanoparticulate rilpivirine (300 mg/mL)
- rHuPH20 (2000 U/mL)
- Sodium phosphate monohydrate (2 mg/mL)
- Citric acid monohydrate (1 mg/mL)
- Poloxamer 338 (50 mg/mL)
- Sodium hydroxide (q.s. for pH 6)
- Water for injection (q.s. ad 1 mL)

Additional component(s) as shown in Table 5 were added, and the pH was adjusted to 6.0 using sodium hydroxide.

Composition	Additional component 1	Additional component 2
21	Sucrose (100 mg/mL)	Sodium CMC (10 mg/mL)
22	Mannitol (50 mg/mL)	Sodium CMC (10 mg/mL)

Table 5: Additional components

The compositions were freeze dried and reconstituted with water to provide 9 mL of the reconstituted aqueous composition at time t=0, freeze dried and reconstituted with water to

provide 9 mL of the reconstituted aqueous composition after being stored under conditions of 25 °C/60% RH and 40 °C/75% RH for 1 month, and freeze dried and reconstituted with water to provide 9 mL of the reconstituted aqueous composition after being stored under conditions of 25 °C/60% RH for 6 months. The drug particle sizes were measured in all instances following the method below. The volume-based particle size distribution of the drug suspensions was determined by means of wet dispersion laser diffraction, using a Malvern Mastersizer 3000 laser diffraction (Malvern Instruments) and Hydro MV wet dispersion module.

The results are shown in Figure 2.

At time t=0, i.e. following freeze drying and reconstituting straight away, the particle size was preserved in the compositions.

Example 5 – Freeze drying and hyaluronidase stability studies under different storage conditions

This example explores the effect that freeze drying aqueous compositions comprising a hyaluronidas and rilpivirine has on hyaluronidase stability in the corresponding reconstituted aqueous compositions. The freeze dried compositions were reconstituted instantly, i.e. at time t=0, after storage for 1 month, and after storage for 6 months under various conditions.

Aqueous compositions 21 and 22, as described in Example 4 above, were prepared. These compositions were freeze dried and reconstituted with water to provide 9 mL of the reconstituted aqueous composition after being stored under conditions of 25 °C/60% RH for 1 month and 6 months.

Hyaluroidase stability was evaluated through one or more of the following: (i) activity (bioassay method); (ii) quantification/aggregation (size-exclusion chromatography/SEC); and (iii) purity (reversed-phase liquid chromatography/RP-LC).

SEC is a size exclusion chromatographic separation method whereby a column is used to distribute the molecules within the solution flowing through according to their broad size range. Monomers, aggregates and fragments elute at different times from the column and hence their relative proportions in a sample can be quantified using a standard UV detector.

The results are shown in Table 7.

Composition	Hyaluronidase activity	Hyaluronidase quantification/ aggregation (SEC) (µg/mL)	RP-LC Ox2* (Area%)		RP-LC Ox1* (Area%)	
	% loss after 6 months @25 °C	% difference of the t6M @25 °C and t1M @5 °C	t = 1 month at 25 °C	t = 6 months at 25 °C	t = 1 month at 25 °C	t = 6 months at 25 °C
21	-	0	1.5	2.1	20.4	25.7
22	-	**-31.0**	0.6	1.8	20.4	24.2

* Ox1 and Ox2 are oxidised forms of rHuPH20. Ox1 retains more enzymatic activity than Ox2. Ox1 and Ox2 are less active than rHuPH20.

Table 7: Hyaluronidase stability

The appearance of both compositions was acceptable. The freeze dried compositions both had a relatively low water content (<1% as determined by Karl Fisher). IR analysis confirmed that the samples were homogenous. Identical IR spectra were obtained for samples from the top, middle, and bottom of the vials of freeze dried compositions 21 and 22.

Example 6 - Freeze drying and collapse temperature studies under different storage conditions

This example explores the effect that freeze drying aqueous compositions comprising a hyaluronidase and rilpivirine has on collapse temperature (T_c).

Aqueous compositions 21 and 22, as described in Example 4 above, were prepared. The compositions were then freeze dried. The collapse temperature was determined.

The results are shown in Table 8.

Composition	Additional component 1	Additional component 2	Approximate onset of T_c / °C	
			Fast ramp	Medium ramp with annealing
21	Sucrose (100 mg/mL)	Sodium CMC (10 mg/mL)	-16.0	-
22	Mannitol (50 mg/mL)	Sodium CMC (10 mg/mL)	-	-7.2

Table 8: Collapse temperatures (T_c)

Example 7 – Freeze drying, hyaluronidase stability, and rilpivirine particle size studies under different storage conditions

This example explores the effect that freeze drying aqueous compositions comprising a hyaluronidase and rilpivirine has on collapse temperature, hyaluronidase stability, viscosity and injection force in the corresponding reconstituted aqueous compositions. The freeze dried compositions were reconstituted instantly, i.e. at time t=0, after storage for 2 weeks, 1 month, and after storage for 3 months under various conditions.

Aqueous compositions of either (i) rilpivirine nanoparticles (having Dv10 of about 75-200 nm, Dv50 of about 200-500 nm, and Dv90 of about 500-1600 nm, i.e. “nano”) or (ii) rilpivirine microparticles (having Dv10 of about 0.2-0.6 µm, Dv50 of about 1.0-2.5 µm and Dv90 of about 4.0-6.5 µm, i.e. “micro”) with the following excipients were prepared:

- Rilpivirine (300 mg/mL)
- rHuPH20 (2000 U/mL)
- Sodium phosphate monohydrate (2 mg/mL)
- Citric acid monohydrate (1 mg/mL)
- Poloxamer 338 (see Table 9)
- Sodium hydroxide (q.s. for pH 6)
- Water for injection (q.s. ad 1 mL)

Additional component(s) as shown in Table 9 were added, and the pH was adjusted to 6.0 using sodium hydroxide.

The compositions were freeze dried and the collapse temperature was determined. The results are shown in Table 9.

Composition	Rilpivirine particle size	Poloxamer 338 / mg/mL	Additional component 1	Additional component 2	T_c / °C
23	Nano	50	Arginine HCl (50 mg/mL)	-	-
24	Nano	50	Arginine HCl (35 mg/mL)	-	-17.0
25	Nano	20	Arginine HCl (35 mg/mL)	Sodium CMC (1 mg/mL)	-
26	Micro	10	Arginine HCl (35 mg/mL)	Sodium CMC (1 mg/mL)	-26.6
27	Nano	50	Arginine HCl (35 mg/mL)	Sodium CMC (3 mg/mL)	-
28	Micro	50	Arginine HCl (35 mg/mL)	Sodium CMC (3 mg/mL)	-
29	Nano	20	Arginine HCl (30 mg/mL)	Sodium CMC (3 mg/mL)	-
30	Micro	10	Arginine HCl (30 mg/mL)	Sodium CMC (3 mg/mL)	-26.8

Composition	Rilpivirine particle size	Poloxamer 338 / mg/mL	Additional component 1	Additional component 2	T_c / °C
21	Nano	50	Sucrose (100 mg/mL)	Sodium CMC (10 mg/mL)	-
31	Nano	50	Sucrose (100 mg/mL)	Sodium CMC (3 mg/mL)	-29.5
32	Micro	50	Sucrose (100 mg/mL)	Sodium CMC (3 mg/mL)	-23.0
33	Nano	20	Sucrose (100 mg/mL)	Sodium CMC (3 mg/mL)	-30.6
34	Micro	10	Sucrose (100 mg/mL)	Sodium CMC (3 mg/mL)	-27.0
35	Nano	20	Sucrose (100 mg/mL)	Sodium CMC (1 mg/mL)	-27.0
36	Micro	10	Sucrose (100 mg/mL)	Sodium CMC (1 mg/mL)	-27.0
37	Nano	50	Arginine HCl (30 mg/mL)	Sodium CMC (3 mg/mL)	-19.0
38	Micro	50	Arginine HCl (30 mg/mL)	Sodium CMC (3 mg/mL)	-20.4

"-" in T_c column means not tested

Table 9: Compositions and T_c

The freeze dried compositions all had a relatively low water content (<1% as determined by Karl Fisher). The appearance of all compositions was acceptable.

The compositions were then reconstituted with water to provide 9 mL of the reconstituted aqueous composition after being stored under the following conditions:

- 2 weeks: 50 °C/75% RH
- 1 month: 30 °C/75% RH and 40 °C/75% RH
- 3 months: 30 °C/75% RH and 40 °C/75% RH

Hyaluronidase stability was evaluated through one or more of the following: (i) activity (bioassay method); (ii) quantification/aggregation (size-exclusion chromatography/SEC) and (iii) purity (reversed-phase liquid chromatography/RP-LC).

The rilpivirine particle sizes were measured as follows. The volume-based particle size distribution of the rilpivirine suspensions was determined by means of wet dispersion laser diffraction, using a Malvern Mastersizer 3000 laser diffraction (Malvern Instruments) and Hydro MV wet dispersion module.

The viscosity of the compositions was measured using a HAAKE Mars 60 rheometer. 1.5 mL of the aqueous reconstituted composition was withdrawn from the vial using a 2 mL syringe equipped with an 18G needle. The sample was added dropwise to the plate (no air bubbles were present). The shear rate sweep was performed from 0.1 till 1000 sec-1 with a cone 60/1° and plate.

The injection force was measured using a 20 mL Luer Lock syringe equipped with 23 G x ¾ inch winged infusion set.

The results are shown in Figure 3, 4, and 5 (Ox1 and Ox2 are oxidised forms of rHuPH20. Ox1 retains more enzymatic activity than Ox2. Ox1 and Ox2 are less active than rHuPH20).

Example 8 – Hyaluronidase stability studies under different storage conditions

This example compares the fluorescence emission spectra of rHuPH20 compositions after storage under different conditions.

Aqueous compositions 11-13, as described in Example 2 above, were prepared. The spectra of the compositions were collected immediately after storage at 5 °C and after storage at 50 °C for one day. In addition to peak maximum and minimum, the intensity ratio 350/330 nm was calculated at each time point and plotted as a function of storage

time. The slope of this curve was used to have a semi-quantitative thermal stability assessment and comparison among compositions.

Composition preparation

200 µl of each composition was dispensed manually into an UV-STAR®, COC, 96-well flat-bottom microplate.

The fluorescence emission spectrum of the samples was measured before and after stressing via a Tecan plate reader (Infinite 200). The following method parameters were used:

Temperature:

- Parameter (on), temperature = 25.0 °C

Wait for temperature:

- Parameter minimum = 24.5 °C; maximum = 25.5 °C
-

Fluorescence intensity scan:

- Scan selection (emission scan)
- Mode (top)
- Excitation wavelengths: from = 280 nm; bandwidth: 230…315: 5 nm; 316…850: 9 nm
- Emission wavelengths: from = 310 nm; to = 420 nm; step = 1 nm; bandwidth: 280…850: 20 nm; 111 measurements
- Integration: lag time = 0 µs; integration time = 20 µs
- Read: number of flashes = 25; settle time = 0 ms
- Gain (manual = 95)
- Label: name = Label1

The results are shown in Table 10, below.

Composition	t_0			t_1 = day 1 at 50 °C			Difference t_1 - t_0		
	330 nm	350 nm	350/330	330 nm	350 nm	350/330	Δ330 nm	Δ350 nm	Δ (Ratio 350/330)
11	6991	5403	0.773	5344	4467	0.836	1647	936	0.063
12	4276	3330	0.779	3262	2728	0.836	1014	602	0.058
13	3727	2944	0.790	2947	2494	0.846	780	450	0.056

Table 10: Slope of the ratio between 350 nm / 330 nm versus time

Example 9 – Melting temperature studies under different storage conditions

This example compares the melting temperatures of rHuPH20 in various compositions under different storage conditions.

Aqueous compositions of rilpivirine nanoparticles (having Dv10 of 75-200 nm, Dv50 of 200-500 nm, and Dv90 of 500-1600 nm) with the following excipients were prepared:

- rHuPH20 (2000 U/mL)
- Sodium dihydrogen phosphate monohydrate (2 mg/mL)
- Citric acid monohydrate (1 mg/mL)
- Poloxamer 338 (50 mg/mL)
- Sodium hydroxide (q.s. for pH 6)
- Water for injection (q.s. ad 1 mL)

Compositions 39-124 were then prepared by adding the component(s) as shown in Table 11, and the pH was adjusted to 6.0 by varying the amount of sodium hydroxide in the composition.

Composition	Additional component 1	Additional component 2	T_m (t = 0) / °C	T_m (t = 0) SD (n = 3) / °C	T_m (t = 1 week at 40 °C) / °C	T_m (t = 1 week at 40 °C) SD (n = 3) / °C
39	Sucrose (100 mg/mL)	Glycine (1 mg/mL)	48.52	0.05	N/A**	N/A**
40	Sucrose (100 mg/mL)	Glycine (3 mg/mL)	48.61	0.03	N/A**	N/A**
41	Sucrose (100 mg/mL)	Glycine (5 mg/mL)	48.64	0.01	N/A**	N/A**
42	Sucrose (100 mg/mL)	Glycine (7 mg/mL)	48.75	0.07	N/A**	N/A**
43	Sucrose (100 mg/mL)	Glycine (9 mg/mL)	48.98	0.1	N/A**	N/A**
44	Sucrose (100 mg/mL)	Glycine (11 mg/mL)	48.93	0.1	N/A**	N/A**

Composition	Additional component 1	Additional component 2	T_m (t = 0) / °C	T_m (t = 0) SD (n = 3) / °C	T_m (t = 1 week at 40 °C) / °C	T_m (t = 1 week at 40 °C) SD (n = 3) / °C
45	Sucrose (100 mg/mL)	Glycine (13 mg/mL)	49.14	0.1	N/A**	N/A**
46	Sucrose (100 mg/mL)	Glycine (15 mg/mL)	49.25	0.07	N/A**	N/A**
47	Sucrose (100 mg/mL)	Glycine (17 mg/mL)	49.16	0.05	N/A**	N/A**
48	Sucrose (100 mg/mL)	Glycine (19 mg/mL)	49.45	0.05	N/A**	N/A**
49	Sucrose (100 mg/mL)	Glycine (21 mg/mL)	49.44	0.06	N/A**	N/A**
50	Sucrose (100 mg/mL)	Glycine (23 mg/mL)	49.71	0.08	N/A**	N/A**
51	Sucrose (100 mg/mL)	Glycine (25 mg/mL)	49.54	0.15	N/A**	N/A**
52	Mannitol (50 mg/mL)	Glycine (1 mg/mL)	48.16	0.03	N/A**	N/A**
53	Mannitol (50 mg/mL)	Glycine (3 mg/mL)	47.95	0.11	N/A**	N/A**
54	Mannitol (50 mg/mL)	Glycine (5 mg/mL)	48.12	0.05	N/A**	N/A**
55	Mannitol (50 mg/mL)	Glycine (7 mg/mL)	48.41	0.38	N/A**	N/A**
56	Mannitol (50 mg/mL)	Glycine (9 mg/mL)	48.56	0.03	N/A**	N/A**
57	Mannitol (50 mg/mL)	Glycine (11 mg/mL)	48.28	0.04	N/A**	N/A**
58	Mannitol (50 mg/mL)	Glycine (13 mg/mL)	48.37	0.08	N/A**	N/A**
59	Mannitol (50 mg/mL)	Glycine (15 mg/mL)	48.45	0.06	N/A**	N/A**

Composition	Additional component 1	Additional component 2	T_m (t = 0) / °C	T_m (t = 0) SD (n = 3) / °C	T_m (t = 1 week at 40 °C) / °C	T_m (t = 1 week at 40 °C) SD (n = 3) / °C
60	Mannitol (50 mg/mL)	Glycine (17 mg/mL)	48.42	0.04	N/A**	N/A**
61	Mannitol (50 mg/mL)	Glycine (19 mg/mL)	48.69	0.07	N/A**	N/A**
62	Mannitol (50 mg/mL)	Glycine (21 mg/mL)	48.83	0.02	N/A**	N/A**
63	Mannitol (50 mg/mL)	Glycine (23 mg/mL)	48.91	0.02	N/A**	N/A**
64	Mannitol (50 mg/mL)	Glycine (25 mg/mL)	48.93	0.09	N/A**	N/A**
65	Mannitol (50 mg/mL)	Sodium CMC (5 mg/mL)	53.93	0.04	54.51	0.23
66	Mannitol (50 mg/mL)	Sodium CMC (10 mg/mL)	53.64	0.07	54.39	0.42
67	Mannitol (50 mg/mL)	Sodium CMC (15 mg/mL)	53.4	0.02	54.19	0.29
68	Mannitol (50 mg/mL)	Sodium CMC (20 mg/mL)	N/A*	N/A*	53.49	0.26
69	Sucrose (100 mg/mL)	Sodium CMC (5 mg/mL)	54.71	0.01	55.28	0.37
70	Sucrose (100 mg/mL)	Sodium CMC (10 mg/mL)	54.25	0.04	54.94	0.31
71	Sucrose (100 mg/mL)	Sodium CMC (15 mg/mL)	54.01	0.09	54.52	0.4
72	Mannitol (50 mg/mL)	Arginine (5 mg/mL)	41.14	0.05	N/A**	N/A**
73	Mannitol (50 mg/mL)	Arginine (10 mg/mL)	40.3	0.07	N/A**	N/A**
74	Mannitol (50 mg/mL)	Arginine (15 mg/mL)	39.84	0.09	N/A**	N/A**

Composition	Additional component 1	Additional component 2	T_m (t = 0) / °C	T_m (t = 0) SD (n = 3) / °C	T_m (t = 1 week at 40 °C) / °C	T_m (t = 1 week at 40 °C) SD (n = 3) / °C
75	Mannitol (50 mg/mL)	Arginine (20 mg/mL)	39.51	0.09	N/A**	N/A**
76	Mannitol (50 mg/mL)	Arginine (25 mg/mL)	39.69	0.03	N/A**	N/A**
77	Sucrose (100 mg/mL)	Arginine (5 mg/mL)	41.61	0.13	N/A**	N/A**
78	Sucrose (100 mg/mL)	Arginine (10 mg/mL)	40.97	0.12	N/A**	N/A**
79	Sucrose (100 mg/mL)	Arginine (15 mg/mL)	40.53	0.06	N/A**	N/A**
80	Sucrose (100 mg/mL)	Arginine (20 mg/mL)	40.38	0.04	N/A**	N/A**
81	Sucrose (100 mg/mL)	Arginine (25 mg/mL)	40.15	0.1	N/A**	N/A**
82	Glucose (50 mg/mL)	-	47.41	0.04	N/A**	N/A**
83	Sucrose (100 mg/mL)	-	48.46	0.15	N/A**	N/A**
84	Glucose (50 mg/mL)	Sodium CMC (5 mg/mL)	53.82	0.02	54.41	0.1
85	Glucose (50 mg/mL)	Sodium CMC (10 mg/mL)	53.57	0.06	54.24	0.08
86	Glucose (50 mg/mL)	Sodium CMC (15 mg/mL)	53.27	0.23	53.88	0.13
87	Glucose (50 mg/mL)	Glycine (5 mg/mL)	48.03	0.11	N/A**	N/A**
88	Glucose (50 mg/mL)	Glycine (10 mg/mL)	47.78	0.16	N/A**	N/A**
89	Glucose (50 mg/mL)	Glycine (15 mg/mL)	48.81	0.14	N/A**	N/A**

Composition	Additional component 1	Additional component 2	T_m (t = 0) / °C	T_m (t = 0) SD (n = 3) / °C	T_m (t = 1 week at 40 °C) / °C	T_m (t = 1 week at 40 °C) SD (n = 3) / °C
90	Glucose (50 mg/mL)	Glycine (20 mg/mL)	48.17	0.07	N/A**	N/A**
91	Glucose (50 mg/mL)	Glycine (25 mg/mL)	48.3	0.19	N/A**	N/A**
92	Glucose (50 mg/mL)	Arginine (5 mg/mL)	41.61	0.1	N/A**	N/A**
93	Glucose (50 mg/mL)	Arginine (10 mg/mL)	41.33	0.1	N/A**	N/A**
94	Glucose (50 mg/mL)	Arginine (15 mg/mL)	41.29	0.04	N/A**	N/A**
95	Glucose (50 mg/mL)	Arginine (20 mg/mL)	41.1	0.09	N/A**	N/A**
96	Glucose (50 mg/mL)	Arginine (25 mg/mL)	41	0.13	N/A**	N/A**
97	Glucose (50 mg/mL)	Histidine (5 mg/mL)	46.72	0.06	N/A**	N/A**
98	Glucose (50 mg/mL)	Histidine (10 mg/mL)	46.18	0.03	N/A**	N/A**
99	Glucose (50 mg/mL)	Histidine (15 mg/mL)	46.15	0.05	N/A**	N/A**
100	Glucose (50 mg/mL)	Histidine (20 mg/mL)	45.57	0.08	N/A**	N/A**
101	Glucose (50 mg/mL)	Histidine (25 mg/mL)	45.48	0.03	N/A**	N/A**
102	-	Glycine (1 mg/mL)	46.94	0.07	N/A**	N/A**
103	-	Glycine (3 mg/mL)	46.91	0.08	N/A**	N/A**
104	-	Glycine (5 mg/mL)	46.99	0.09	N/A**	N/A**

Composition	Additional component 1	Additional component 2	T_m (t = 0) / °C	T_m (t = 0) SD (n = 3) / °C	T_m (t = 1 week at 40 °C) / °C	T_m (t = 1 week at 40 °C) SD (n = 3) / °C
105	-	Glycine (7 mg/mL)	47.17	0.09	N/A**	N/A**
106	-	Glycine (9 mg/mL)	47.2	0.09	N/A**	N/A**
107	-	Glycine (11 mg/mL)	47.18	0.05	N/A**	N/A**
108	-	Glycine (13 mg/mL)	47.72	0.11	N/A**	N/A**
109	-	Glycine (15 mg/mL)	47.28	0.03	N/A**	N/A**
110	-	Glycine (17 mg/mL)	47.34	0.11	N/A**	N/A**
111	-	Glycine (19 mg/mL)	47.58	0.09	N/A**	N/A**
112	-	Glycine (21 mg/mL)	47.41	0.04	N/A**	N/A**
113	-	Glycine (23 mg/mL)	47.52	0.07	N/A**	N/A**
114	-	Glycine (25 mg/mL)	47.61	0.14	N/A**	N/A**
115	-	Sodium CMC (1 mg/mL)	53.87	0.06	54.2	0.38
116	-	Sodium CMC (3 mg/mL)	53.34	0.03	53.96	0.35
117	-	Sodium CMC (5 mg/mL)	53.15	0.01	53.58	0.06
118	-	Sodium CMC (7 mg/mL)	53.22	0.04	53.64	0.3
119	-	Sodium CMC (9 mg/mL)	53	0.06	53.22	0.07

Composition	Additional component 1	Additional component 2	T_m (t = 0) / °C	T_m (t = 0) SD (n = 3) / °C	T_m (t = 1 week at 40 °C) / °C	T_m (t = 1 week at 40 °C) SD (n = 3) / °C
120	-	Sodium CMC (11 mg/mL)	52.84	0.06	53.04	0.07
121	-	Sodium CMC (13 mg/mL)	52.85	0.08	52.93	0.11
122	-	Sodium CMC (15 mg/mL)	52.45	0.05	52.76	0.18
123	-	Sodium CMC (17 mg/mL)	52.31	0.02	52.64	0.07
124	-	Sodium CMC (19 mg/mL)	N/A*	N/A*	52.61	0.09

N/A* = Note that for high sodium CMC concentrations (>17 mg/mL) the capillary chips of the nanoDSF instrument could not be loaded, presumably due to high solution viscosity.

N/A** = Note that for these conditions either the hyaluronidase was denatured due to the applied temperature stress, or the capillaries could not be loaded to high viscosity

Table 11: T_m under different storage conditions

Compositions 39-124 were prepared as set out above and then stored in a refrigerator at 5 °C between 2 days and 2 weeks. The T_m values were measured straight away (i.e. “t=0”) and after storage for 1 week at 40 °C using the method as described in Example 5.

The results are shown in Table 11.

Also described herein are the following numbered clauses.

1. A solid composition obtainable by freeze drying an aqueous composition comprising (i) a hyaluronidase, (ii) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and (iii) a drug.

2. The solid composition according to clause 1, wherein the hyaluronidase is recombinant human hyaluronidase.

3. The solid composition according to clause 2, wherein the recombinant human hyaluronidase is rHuPH20.

4. The solid composition according to any one of the preceding clauses, wherein aqueous composition comprises from about 1,500 U/mL to about 2,500 U/mL hyaluronidase.

5. The solid composition according to clause 4, wherein aqueous composition comprises from about 1,800 U/mL to about 2,200 U/mL hyaluronidase.

6. The solid composition according to clause 5, wherein aqueous composition comprises about 2,000 U/mL hyaluronidase.

7. The solid composition according to any one of the preceding clauses, wherein the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

8. The solid composition according to clause 7, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof is sodium carboxymethyl cellulose.

9. The solid composition according to clause 7 or 8, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof is not cross-linked.

10. The solid composition according to any one of clauses 7-9, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof has a degree of substitution (carboxymethyl to cellulose) of from about 0.5 to about 1.

11. The solid composition according to any one of clauses 7-10, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof has a molecular weight of from about 90 kDa to about 750 kDa, and/or wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof has a viscosity of from about 30 mPas to about 50 mPa.s.

12. The solid composition according to any one of the preceding clauses, wherein the aqueous composition comprises from about 1 to about 100 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof.

13. The solid composition according to clause 12, wherein the aqueous composition comprises from about 1 to about 50 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof.

14. The solid composition according to clause 13, wherein the aqueous composition comprises from about 10 to about 25 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof.

15. The solid composition according to clause 13, wherein the aqueous composition comprises from about 1 to about 5 mg/mL of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, for example about 3 mg/mL.

16. The solid composition according to any one of clauses 1-15, wherein the aqueous composition comprises from about 0.01 mg to about 5 mg of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

17. The solid composition according to clause 16, wherein the aqueous composition comprises from about 0.05 mg to about 2.5 mg of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

18. The solid composition according to clause 17, wherein the aqueous composition comprises from about 0.05 mg to about 0.25 mg of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase, for example about 0.15 mg of the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

19. The solid composition according to any one of the preceding clauses, wherein the aqueous composition additionally comprises a cryoprotectant.

20. The solid composition according to clause 1921 wherein the cryoprotectant is a sugar or a sugar alcohol.

21. The solid composition according to clause 20, wherein the sugar or sugar alcohol is selected from mannitol and sucrose.

22. The solid composition according to clause 21, wherein the sugar or sugar alcohol is sucrose.

23. The solid composition according to clause 19, wherein the cryoprotectant is an amino acid or a pharmaceutically acceptable salt thereof.

24. The solid composition according to clause 23, wherein the amino acid or a pharmaceutically acceptable salt thereof is arginine, for example arginine HCl.

25. The solid composition according to any one of clauses 19-24, wherein the aqueous composition comprises from about 1 mg/mL to about 200 mg/mL of the cryoprotectant.

26. The solid composition according to clause 25, wherein the aqueous composition comprises from about 1 mg/mL to about 150 mg/mL of the cryoprotectant.

27. The solid composition according to clause 26, wherein the aqueous composition comprises from about 25 mg/mL to about 125 mg/mL of the cryoprotectant.

28. The solid composition according to clause 27, wherein the aqueous composition comprises from about 50 mg/mL to about 100 mg/mL of the cryoprotectant.

29. The solid composition according to clause 27, wherein the aqueous composition comprises from about 75 mg/mL to about 125 mg/mL of the cryoprotectant, for example about 100 mg/mL of the cryoprotectant.

30. The solid composition according to clause 27, wherein the aqueous composition comprises from about 25 mg/mL to about 35 mg/mL of the cryoprotectant, for example about 30 mg/mL of the cryoprotectant.

31. The solid composition according to any one of clauses 19-30, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant is from about 1:1 (w/w) to about 1:100 (w/w), optionally from about 1:1 (w/w) to about 1:50 (w/w).

32. The solid composition according to clause 31, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant is from about 1:8 (w/w) to about 1:40 (w/w).

33. The solid composition according to clause 31, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant is from about 1:2 (w/w) to about 1:15 (w/w).

34. The solid composition according to clause 33, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant is from about 1:4 (w/w) to about 1:11 (w/w).

35. The solid composition according to clause 34, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant is from about 1:5 (w/w) to about 1:10 (w/w).

36. The solid composition according to clause 34, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant is from about 1:9 (w/w) to about 1:11 (w/w).

37. The solid composition according to clause 32, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant is from about 1:30 (w/w) to about 1:35 (w/w).

38. The solid composition according to any one of the preceding clauses, wherein the aqueous composition has a pH of from about 5 to about 7.

39. The solid composition according to clause 38, wherein the aqueous composition has a pH of from about 6 to about 7.

40. The solid composition according to clause 39, wherein the aqueous composition has a pH of from about 6 to about 6.5.

41. The solid composition according to clause 40, wherein the aqueous composition has a pH of about 6.

42. The solid composition according to any one of the preceding clauses, wherein the drug is in the form of particles suspended in the aqueous composition.

43. The solid composition according to clause 42, wherein the drug is in the form of micro- or nanoparticles suspended in the aqueous composition.

44. The solid composition according to clause 42 or 43, wherein the particles have a Dv90 of from about 100 nm to about 10 µm.

45. The solid composition according to clause 44, wherein the particles have a Dv90 of from about 500 nm to about 6 µm.

46. The solid composition according to clause 45, wherein the particles have a Dv90 of from about 500 nm to about 1600 nm.

47. The solid composition according to clause 46, wherein the particles have a Dv90 of about 500 nm to about 700 nm.

48. The solid composition according to any one of clauses 42-47, wherein the particles have a Dv10 of from about 75 nm to about 200 nm.

49. The solid composition according to according to any one of clauses 42-48, wherein the particles have a Dv50 of from about 200 nm to about 500 nm.

50. The solid composition according to any one of clauses 42-44, wherein the particles have a Dv90 of from about 4 µm to about 6 µm.

51. The solid composition according to clause 50, wherein the particles have a Dv90 of about 5 μm to about 6 μm.

52. The solid composition according to any one of clauses 42-44, 50 or 51, wherein the particles have a Dv10 of from about 300 nm to about 500 nm, and/or wherein the particles have a Dv50 of from about 1.5 μm to about 2 μm.

53. The solid composition according to any one of clauses 42-52, when dependent on any of clauses 19-52, wherein the ratio of drug:cryoprotectant in the aqueous composition is from about 1:1 (w/w) to about 20:1 (w/w).

54. The solid composition according to clause 53, wherein the ratio of drug:cryoprotectant in the aqueous composition is from about 2:1 (w/w) to about 10:1 (w/w).

55. The solid composition according to clause 54, wherein the ratio of drug:cryoprotectant in the aqueous composition is from about 3:1 (w/w) to about 10:1 (w/w).

56. The solid composition according to clause 54, wherein the ratio of drug:cryoprotectant in the aqueous composition is from about 2:1 (w/w) to about 7:1 (w/w).

57. The solid composition according to clause 56, wherein the ratio of drug:cryoprotectant in the aqueous composition is from about 2:1 (w/w) to about 6:1 (w/w).

58. The solid composition according to any one of the preceding clauses, wherein the drug is selected from: drugs for treatment of chronic and long-term diseases and disorders, for example for treatment of chronic viral infection (such as chronic infection with varicella-zoster virus, measles virus, HIV, hepatitis B virus, hepatitis C virus, hepatitis D virus or human cytomegalovirus), cancer, psychiatric diseases and disorders, mood disorders (such as bipolar, cyclothymic or depression), diabetes, hypertension, abnormal cholesterol and triglyceride levels, inflammatory disorders (such as allergy, asthma, autoimmune diseases, coeliac disease, hepatitis, inflammatory bowel disease, Crohn disease, gout, myositis, scleroderma, rheumatoid arthritis, lupus vasculitis, ankylosing spondylitis or chronic obstructive pulmonary disease), cystic fibrosis, multiple sclerosis, autoimmune disorders, neurodegenerative disorders (such as Parkinson Disease or Alzheimer's disease), chronic pain, inherited metabolic disorders or epilepsy.

59. The solid composition according to clause 58, wherein the drug is rilpivirine or a pharmaceutically acceptable salt thereof.

60. The solid composition according to clause 59, wherein the drug is rilpivirine, i.e. rilpivirine free base.

61. The solid composition according to any one of clauses 1 to 58, wherein the drug is not an antibody.

62. The solid composition according to any one of clauses 1 to 58, wherein the drug is not a biologic.

63. The solid composition according to any one of clauses 1 to 58, wherein the drug has a molecular weight of less than 1000 Da.

64. The solid composition according to any one of the preceding clauses, wherein the aqueous composition additionally comprises a surface modifying agent, a buffering agent and/or a pH adjusting agent, and/or a chelating agent.

65. The solid composition according to any one of the preceding clauses, wherein the aqueous composition additionally comprises one or more of a poloxamer, sodium dihydrogen phosphate, citric acid and sodium hydroxide, optionally wherein the aqueous composition additionally comprises a poloxamer, sodium dihydrogen phosphate, citric acid and sodium hydroxide.

66. The solid composition according to any one of the preceding clauses, wherein the aqueous composition additionally comprises a poloxamer, for example poloxamer 338.

67. The solid composition according to clause 66, when dependent on clause 42, wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer is from about 3:1 (w/w) to about 15:1 (w/w).

68. The solid composition according to clause 67, wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer is from about 6:1 (w/w) to about 15:1 (w/w).

69. The solid composition according to clause 68, wherein when the drug has a Dv90 of less than about 1600 nm the ratio of drug to poloxamer is about 6:1 (w/w).

70. The solid composition according to clause 68, wherein the relative amount (w/w) of drug to poloxamer is less than about 12:1 (w/w).

71. The solid composition according to clause 1-70, wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate and sodium hydroxide.

72. The solid composition according to any one of clauses 66-71, wherein the aqueous composition comprises from about 5 mg/mL to about 15 mg/mL of the poloxamer.

73. The solid composition according to any one of clauses 66-71, wherein the aqueous composition comprises from about 40 mg/mL to about 60 mg/mL of the poloxamer.

74. The solid composition according any one of the preceding clauses, wherein the aqueous composition additionally comprises an antioxidant, optionally wherein the antioxidant is methionine.

75. The solid composition according to clause 74, wherein the aqueous composition comprises from about 1.0 mg/mL to about 2.0 mg/mL of the antioxidant, for example about 1.5 mg/mL.

76. The solid composition according any one of the preceding clauses, wherein the aqueous composition does not comprise glucose.

77. A reconstituted aqueous composition obtainable by reconstituting the solid composition as defined in any one of clauses 1-76.

78. The reconstituted aqueous composition according to clause 77, wherein the reconstituting comprises adding an aqueous dispersion medium to the solid composition.

79. The reconstituted aqueous composition according to clause 78, wherein the aqueous dispersion medium is water.

80. A method for the treatment or prevention of a disease or disorder in a subject, the method comprising administering to the subject a reconstituted aqueous composition as defined in any one of clauses 77-79.

81. A reconstituted aqueous composition as defined in any one of clauses 77-79 for use in the treatment or prevention of a disease or disorder in a subject.

82. Use of a reconstituted aqueous composition as defined in any one of clauses 77-79 for the manufacture of a medicament for treating or preventing a disease or disorder in a subject.

83. The method, the reconstituted aqueous composition for use or the use according to clauses 80, 81 or 83, wherein the disease or disorder is HIV infection.

84. The method, the reconstituted aqueous composition for use or the use according to clause 83, wherein the HIV infection is type 1 (HIV-1) infection.

85. The method, the reconstituted aqueous composition for use or the use according to any one of clauses 80-84, wherein the reconstituted aqueous composition is administered to the subject by intramuscular injection or subcutaneous injection.

86. The method, the aqueous composition for use or the use according to clause 85, wherein the aqueous composition is administered to the subject by intramuscular injection.

87. The method, the aqueous composition for use or the use according to clause 85, wherein the aqueous composition is administered to the subject by subcutaneous injection.

88. The method, the reconstituted aqueous composition for use or the use according to any one of clauses 80-87, wherein the reconstituted aqueous composition is administered to the subject intermittently at a time interval of about three months to about two years.

89. The method, the reconstituted aqueous composition for use or the use according to clause 88, wherein the time interval is about three months to about one year.

90. The method, the reconstituted aqueous composition for use or the use according to clause 89, wherein the time interval is about three months to about six months.

91. The method, the reconstituted aqueous composition for use or the use according to clause 89, wherein the time interval is about six months to about one year.

92. The method, the reconstituted aqueous composition for use or the use according to clause 90 or 91, wherein the time interval is about six months.

93. The method, the reconstituted aqueous composition for use or the use according to any one of clauses 80-92, wherein the subject is a human.

94. A solid composition according to any one of clauses 1-76 for use in the treatment or prevention of a disease or disorder in a subject.

95. Use of the solid composition according to any one of clauses 1-76 for the manufacture of a medicament for treating or preventing a disease or disorder in a subject.

96. Use of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof for stabilising a hyaluronidase in a solid composition comprising a drug.

97. The use according to clause 96, wherein the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is as defined in any one of clauses 7-11.

98. The use according to any one of clauses 96 or 97, wherein the solid composition is as defined in any one of clauses 1-76.

99. The use according to any one of clauses 96-98, wherein the hyaluronidase is as defined in any one of clauses 2 or 3.

100. The use according to any one of clauses 96-99, wherein the drug is as defined in any one of clauses 42-52.

101. A method for stabilising a hyaluronidase in a solid composition, the method comprising freeze drying an aqueous composition comprising the hyaluronidase and cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and a drug.

102. The method according to clause 101, wherein the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is as defined in any one of clauses 7-11.

103. The method according to clause 101 or 102, wherein the hyaluronidase is as defined in any one of clauses 2 or 3.

104. The method according to clause 101-103, wherein the solid composition is as defined in any one of clauses 1-76.

105. The method according to clause 101-104, wherein the drug is as defined in any one of clauses 42-52.

Also described herein are the following numbered embodiments.

1. A solid composition obtainable by freeze drying an aqueous composition comprising (i) a hyaluronidase, (ii) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and (iii) a drug.

2. The solid composition according to embodiment 1, wherein the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

3. The solid composition according to embodiment 2, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof is sodium carboxymethyl cellulose.

4. The solid composition according to any one of embodiments 2 or 3, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof is not cross linked.

5. The solid composition according to any one of the preceding embodiments, wherein the hyaluronidase is rHuPH20.

6. The solid composition according to any one of the preceding embodiments, wherein the aqueous composition comprises from about 0.01 mg to about 5 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

7. The solid composition according to any one of the preceding embodiments, wherein the aqueous composition additionally comprises a cryoprotectant.

8. The solid composition according to embodiment 7, wherein the cryoprotectant is a sugar, optionally wherein the sugar is mannitol or sucrose.

9. The solid composition according to embodiment 7 or 8, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant is from about 1:4 (w/w) to about 1:11 (w/w).

10. The solid composition according to any one of the preceding embodiments, wherein the aqueous composition has a pH of about 6-7, optionally about 6.

11. The solid composition according to any one of the preceding embodiments , wherein the drug is rilpivirine and the rilpivirine is in the form of particles suspended in the aqueous composition, optionally wherein the particles are micro- or nanoparticles suspended in the aqueous composition.

12. A reconstituted aqueous composition obtainable by reconstituting the solid composition as defined in any one of embodiments 1-11 with an aqueous dispersion medium.

13. A method for the treatment or prevention of a disease or disorder in a subject, the method comprising administering to the subject a reconstituted aqueous composition as defined in embodiment 12.

Claims

1. A solid composition obtainable by freeze drying an aqueous composition comprising (i) a hyaluronidase, (ii) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof, and (iii) a drug.

2. The solid composition according to claim 1, wherein the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

3. The solid composition according to claim 2, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof is sodium carboxymethyl cellulose.

4. The solid composition according to any one of claims 2 or 3, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof is not cross linked.

5. The solid composition according to any one of the preceding claims, wherein the hyaluronidase is rHuPH20.

6. The solid composition according to any one of the preceding claims, wherein the aqueous composition comprises from about 0.01 mg to about 5 mg cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

7. The solid composition according to any one of the preceding claims, wherein the aqueous composition additionally comprises a cryoprotectant.

8. The solid composition according to claim 7, wherein the cryoprotectant is a sugar, optionally wherein the sugar is sucrose.

9. The solid composition according to claim 7, wherein the cryoprotectant is an amino acid or a pharmaceutically acceptable salt thereof, optionally wherein the amino acid or a pharmaceutically acceptable salt thereof is arginine, further optionally wherein the amino acid or a pharmaceutically acceptable salt thereof is arginine HCl.

10. The solid composition according to any one of claims 7-9, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to cryoprotectant is from about 1:8 (w/w) to about 1:40 (w/w).

11. The solid composition according to any one of the preceding claims, wherein the aqueous composition has a pH of about 6-7, optionally about 6.

12. The solid composition according to any one of the preceding claims, wherein the drug is rilpivirine and the rilpivirine is in the form of particles suspended in the aqueous composition, optionally wherein the particles are micro- or nanoparticles suspended in the aqueous composition.

13. A reconstituted aqueous composition obtainable by reconstituting the solid composition as defined in any one of claims 1-12 with an aqueous dispersion medium.

14. A method for the treatment or prevention of a disease or disorder in a subject, the method comprising administering to the subject a reconstituted aqueous composition as defined in claim 13.

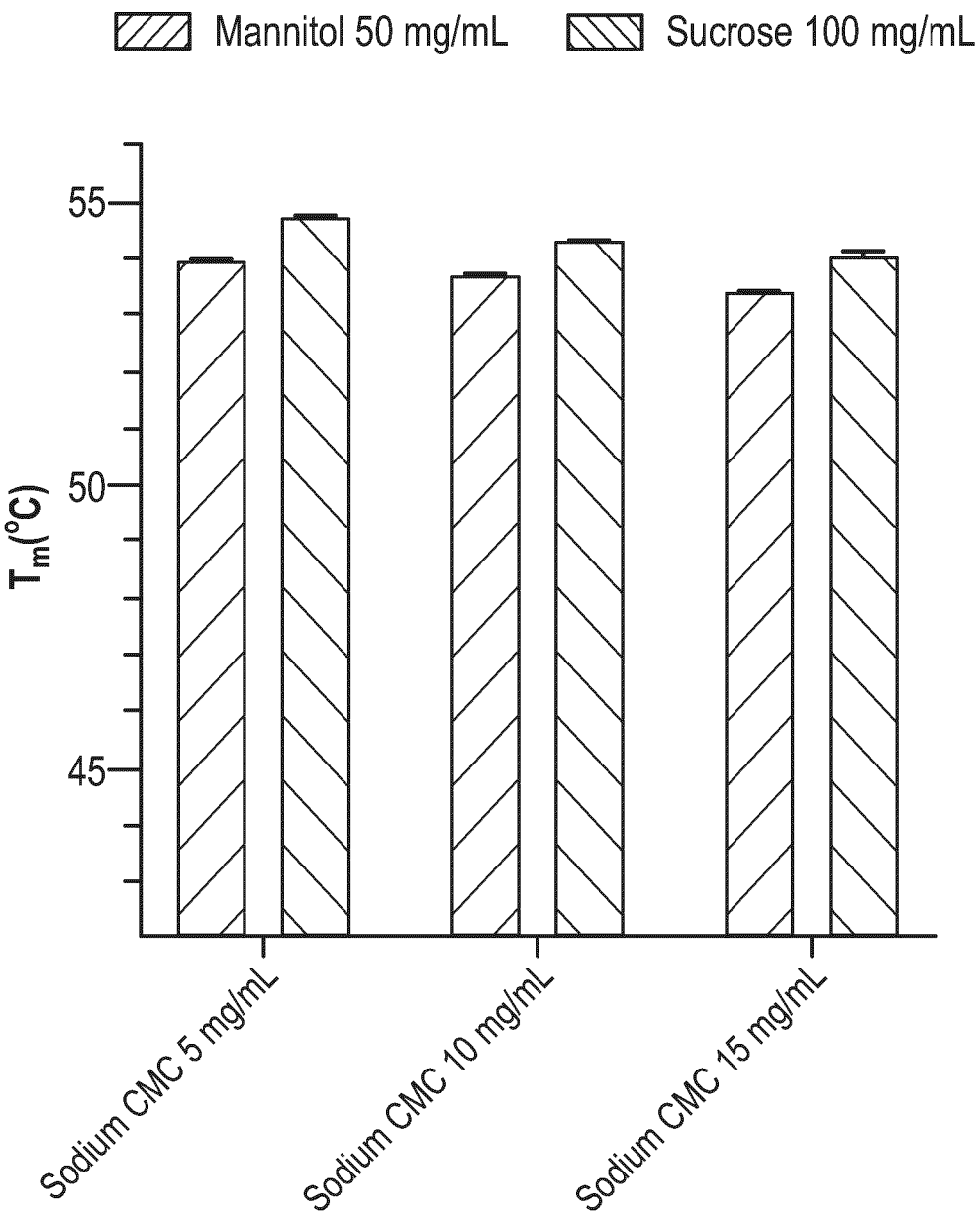

Mannitol 50 mg/mL
Sucrose 100 mg/mL
55
50
45
T_m(°C)
Sodium CMC 5 mg/mL
Sodium CMC 10 mg/mL
Sodium CMC 15 mg/mL

FIG. 1

FIG. 2

Composition		Dv10 / µm				Dv50 / µm				Dv90 / µm			
		t_0	t_{1month}, 25 °C/60% RH	t_{1month}, 40 °C/75% RH	t_{6month}, 25 °C/60% RH	t_0	t_{1month}, 25 °C/60% RH	t_{1month}, 40 °C/75% RH	t_{6month}, 25 °C/60% RH	t_0	t_{1month}, 25 °C/60% RH	t_{1month}, 40 °C/75% RH	t_{6month}, 25 °C/60% RH
21 (100mg/mL sucrose + 10 mg/mL sodium CMC)	Front	0.120	0.126	0.130	0.119	0.276	0.281	0.293	0.271	0.637	0.63	0.665	0.612
	Middle	0.120	0.125	0.130	0.121	0.276	0.279	0.293	0.275	0.638	0.622	0.661	0.622
22 (50 mg/mL mannitol + 10 mg/mL sodium CMC)	Front	0.121	0.127	0.129	0.123	0.281	0.287	0.301	0.286	0.67	0.66	0.745	0.679
	Middle	0.120	0.128	0.128	0.123	0.277	0.292	0.299	0.286	0.649	0.673	0.751	0.674

FIG. 3

Composition	Storage conditions	Dv90 / µm	D_v90 increase vs t = 0/ %	SEC (µg/mL)	RP-LC / area %			% Enzyme activity loss
					Main peak	Ox1	Ox2	
23	t = 0, 5°C	0.651	-	22.56	79.94	19.47	0.59	-
23	t = 1 month, 30°C/75% RH	0.738	13.36	22.23	70.55	27.56	1.89	8.28
23	t = 3 months, 30°C/75% RH	0.738	13.36	22.84	62.55	34.49	2.96	11.03
23	t = 1 month, 40°C/75% RH	0.896	37.63	20.23	59.21	36.76	4.03	24.76
23	t = 3 months, 40°C/75% RH	1.286	97.54	20.24	45.16	46.23	8.62	21.10
23	t = 2 weeks, 50°C/75% RH	1.683	158.53	-	-	-	-	37.95
24	t = 0, 5°C	0.691	-	22.57	77.85	21.23	0.77	-
24	t = 1 month, 30°C/75% RH	0.703	1.74	20.11	66.94	30.53	2.53	11.16
24	t = 3 months, 30°C/75% RH	0.759	9.84	22.03	58.31	37.39	4.3	34.62
24	t = 1 month, 40°C/75% RH	0.892	29.09	19.99	53.26	41.07	5.67	21.13
24	t = 3 months, 40°C/75% RH	1.070	54.85	20.09	39.59	49.32	11.09	29.02
24	t = 2 weeks, 50°C/75% RH	0.892	29.09	-	-	-	-	34.87
25	t = 0, 5°C	1.642	-	21.70	70.77	27.71	1.52	-
25	t = 1 month, 30°C/75% RH	6.698	307.92	21.11	65.05	32.06	2.90	-
25	t = 3 months, 30°C/75% RH	-	-	-	-	-	-	-
25	t = 1 month, 40°C/75% RH	-	-	-	-	-	-	-

25	t = 3 months, 40°C/75% RH	-	-	-	-	-	-	-
25	t = 2 weeks, 50°C/75% RH	182.301	11002.38	-	-	-	-	-
26	t = 0, 5°C	4.355	NA	21.81	80.2	19.18	0.62	NA
26	t = 1 month, 30°C/75% RH	4.124	-5.30	21.25	68.9	28.91	2.19	0.70
26	t = 3 months, 30°C/75% RH	4.307	-1.10	23.22	57.09	38.25	4.65	8.65
26	t = 1 month, 40°C/75% RH	4.906	12.65	20.3	47.72	44.68	7.61	7.73
26	t = 3 months, 40°C/75% RH	6.120	40.53	20.28	29.56	52.64	17.8	31.98
26	t = 2 weeks, 50°C/75% RH	14.486	232.63	-	-	-	-	48.44
29	t = 0, 5°C	1.724	-	22.09	73.63	25.37	1.00	-
29	t = 1 month, 30°C/75% RH	6.773	292.87	21.28	66.45	30.86	2.69	-
29	t = 3 months, 30°C/75% RH	-	-	-	-	-	-	-
29	t = 1 month, 40°C/75% RH	154.098	-	19.89	53.21	40.53	6.25	-
29	t = 3 months, 40°C/75% RH	-	-	-	-	-	-	-
29	t = 2 weeks, 50°C/75% RH	158.857	9114.44	-	-	-	-	-
30	t = 0, 5°C	4.266	-	22.73	79.41	19.87	0.72	-
30	t = 1 month, 30°C/75% RH	4.181	-1.99	21.83	68.66	29.09	2.24	2.13
30	t = 3 months, 30°C/75% RH	4.327	1.43	22.44	62.11	33.93	3.96	17.12
30	t = 1 month, 40°C/75% RH	4.980	16.74	20.49	50.9	41.69	7.41	16.16
30	t = 3 months, 40°C/75% RH	6.403	50.09	19.6	33.54	49.66	16.8	38.27
30	t = 2 weeks, 50°C/75% RH	30.467	614.18	-	-	-	-	-

37	t = 0, 5°C	0.875	-	21.07	89.68	10.09	0.24	-
37	t = 1 month, 30°C/75% RH	0.794	-9.26	20.17	83.29	16.04	0.68	4.44
37	t = 3 months, 30°C/75% RH	0.972	11.09	21.19	77.18	21.49	1.34	12.82
37	t = 1 month, 40°C/75% RH	1.029	17.60	18.79	70.14	27.77	2.09	13.50
37	t = 3 months, 40°C/75% RH	1.188	35.77	13.14	50.99	41.35	7.66	24.57
37	t = 2 weeks, 50°C/75% RH	1.169	33.60	-	-	-	-	47.48
38	t = 0, 5°C	3.947	-	21.68	90.49	9.26	0.25	-
38	t = 1 month, 30°C/75% RH	3.953	0.15	21.46	84.32	15.12	0.56	-5.83
38	t = 3 months, 30°C/75% RH	3.989	1.06	23.04	79.1	19.68	1.22	25.90
38	t = 1 month, 40°C/75% RH	4.150	5.14	19.65	72.97	25.29	1.73	15.86
38	t = 3 months, 40°C/75% RH	4.335	9.83	20.34	56.14	38.18	5.68	-
38	t = 2 weeks, 50°C/75% RH	4.490	13.76	-	-	-	-	38.89
21	t = 0, 5°C	0.599	-	16.36	76.56	22.67	0.77	-
21	t = 1 month, 30°C/75% RH	0.616	2.84	16.47	65.79	32.13	2.09	-
21	t = 3 months, 30°C/75% RH	0.615	2.67	16.64	60.83	36.34	2.83	-
21	t = 1 month, 40°C/75% RH	0.673	12.35	15.84	56.26	40.27	3.47	-
21	t = 3 months, 40°C/75% RH	0.700	16.86	15.26	48.76	47.23	4.00	-
21	t = 2 weeks, 50°C/75% RH	0.742	23.87	-	-	-	-	-
31	t = 0, 5°C	0.615	-	16.02	77.77	21.24	0.99	-
31	t = 1 month, 30°C/75% RH	0.627	1.95	18.1	66.12	31.93	1.95	-41.62

31	t = 3 months, 30°C/75% RH	0.665	8.13	17.51	58.45	38.34	3.21	8.44
31	t = 1 month, 40°C/75% RH	0.736	19.67	17.77	55.24	41.02	3.74	4.70
31	t = 3 months, 40°C/75% RH	0.789	28.29	17.17	42.46	51.55	5.99	9.71
31	t = 2 weeks, 50°C/75% RH	0.900	46.34	-	-	-	-	-
32	t = 0, 5°C	3.745	NA	19.78	87.91	11.65	0.45	-
32	t = 1 month, 30°C/75% RH	3.758	0.35	20.01	83.3	16.06	0.64	4.52
32	t = 3 months, 30°C/75% RH	3.767	0.59	19.93	81.19	17.8	1.02	15.94
32	t = 1 month, 40°C/75% RH	3.868	3.28	19.4	79.15	19.86	0.99	13.99
32	t = 3 months, 40°C/75% RH	3.992	6.60	19.29	73.98	24.69	1.33	17.73
32	t = 2 weeks, 50°C/75% RH	4.262	13.81	-	-	-	-	33.56
33	t = 0, 5°C	1.465	-	21.06	7.59	82.7	9.71	-
33	t = 1 month, 30°C/75% RH	1.246	Initial particle size not on target, hence not relevant	20.22	68.74	29.52	1.74	-
33	t = 3 months, 30°C/75% RH	-	-	-	-	-	-	-
33	t = 1 month, 40°C/75% RH	3.382	Initial particle size not on target, hence not relevant	19.83	58.45	38.59	2.96	-
33	t = 3 months, 40°C/75% RH	-	-	-	-	-	-	-
33	t = 2 weeks, 50°C/75% RH	30.288	-	-	-	-	-	-
34	t = 0, 5°C	3.825	-	21.05	78.44	20.59	0.97	-

34	t = 1 month, 30°C/75% RH	3.946	3.16	20.34	63.5	34.23	2.26	7.27
34	t = 3 months, 30°C/75% RH	3.887	1.62	22.3	55.8	40.75	3.45	15.51
34	t = 1 month, 40°C/75% RH	4.024	5.20	19.68	43.12	51.67	5.22	11.67
34	t = 3 months, 40°C/75% RH	4.181	9.31	21.39	30.79	60.73	8.48	21.56
34	t = 2 weeks, 50°C/75% RH	4.496	17.54	-	-	-	-	30.14
35	t = 0, 5°C	2.909	Initial particle size not on target, hence not relevant	22.28	58.39	38.9	2.72	-
35	t = 1 month, 30°C/75% RH	5.153		20.91	66.83	31.29	1.88	-
35	t = 3 months, 30°C/75% RH	-	-	-	-	-	-	-
35	t = 1 month, 40°C/75% RH	24.507	Initial particle size not on target, hence not relevant	20.85	55.85	40.58	3.57	-
35	t = 3 months, 40°C/75% RH	-	-	-	-	-	-	-
35	t = 2 weeks, 50°C/75% RH	27.955	-	-	-	-	-	-
36	t = 0, 5°C	4.292	NA	22.46	80.25	19.13	0.62	NA
36	t = 1 month, 30°C/75% RH	4.295	0.07	20.7	64.81	33.04	2.15	10.68
36	t = 3 months, 30°C/75% RH	4.016	-6.43	22.84	52.27	43.66	4.07	23.03
36	t = 1 month, 40°C/75% RH	4.466	4.05	21.27	44.77	49.88	5.34	13.83
36	t = 3 months, 40°C/75% RH	5.022	17.01	22.8	17.03	67.36	15.61	9.78
36	t = 2 weeks, 50°C/75% RH	5.471	27.47	-	-	-	-	-

"-" = not tested

FIG. 4

Composition	Viscosity / mPa·s									
	t = 0	SD	t = 1 month, 40°C/75% RH	SD	t = 1 month, 30°C/75% RH	SD	t = 3 months, 40°C/75% RH	SD	t = 3 month, 30°C/75% RH	SD
23	2.479	0.02155	2.336	0.02213	2.17	0.02018	1.979	0.02076	2.236	0.01948
24	2.459	0.01872	2.162	0.0221	2.141	0.01862	1.805	0.01934	1.952	0.01809
25	0.215	0.01347	-	-	0.153	0.01312	-	-	0.11	0.01292
26	0.12	0.00603	0.12	0.0067	0.13	0.00609	0.16	0.007069	0.115	0.005995
29	3.602	0.02709	-	-	2.992	0.02664	-	-	1.848	0.02376
30	0.636	0.01042	0.629	0.01061	0.638	0.01017	1.132	0.01179	0.515	0.009528
21	8.732	0.13	5.208	0.08944	7.813	0.119	9.247	0.135	7.069	0.106
31	4.723	0.04767	5.333	0.05368	4.648	0.04861	5.428	0.05888	5.628	0.05453
32	1.257	0.03621	1.041	0.02914	1.263	0.03448	1.441	0.03297	1.314	0.03746
33	2.069	0.03862	1.433	0.03425	1.574	0.0311	1.649	0.03175	1.798	0.02715
34	0.45	0.01418	0.479	0.01472	0.47	0.0154	0.487	0.01372	0.43	0.01292
35	0.152	0.01853	0.153	0.02184	0.14	0.01893	0.127	0.02044	0.15	0.01767
36	0.142	0.00862	0.123	0.00906	0.124	0.00862	0.12	0.0089	0.156	0.00847
37	4.45	0.03699	6.858	0.05576	6.111	0.04502	4.478	0.0429	4.662	0.04255
38	0.156	0.02528	1.705	0.02846	1.657	0.02689	1.454	0.02646	1.523	0.02505

“-“ = not tested.

FIG. 5

Composition	Injection force / N				
	t = 0	t = 1 month, 40°C/75% RH	t = 1 month, 30°C/75% RH	t = 3 months, 40°C/75% RH	t = 3 months, 30°C/75% RH
23	16.0	17.3	16.3	16.8	17.9
24	15.8	16.2	15.4	16.3	17.6
25	12.7	-	12.2	-	16.2
26	10.1	8.7	9.4	10.7	14.1
29	20.9	-	18.3	-	19.9
30	12.3	12.6	12.9	14.2	14.0
21	51.9	43.7	52.6	51.6	50.3
31	26.8	28.2	25.6	30.1	31.9
32	24.8	24.8	24.6	25.5	30.7
33	21.2	21.3	21.9	22.3	26.1
34	12.8	15.1	12.9	14.2	18.1
35	15.8	17.5	15.0	15.6	19.7
36	12.0	9.8	11.2	10.5	14.1
37	23.2	23.8	22.6	23.4	26.1
38	21.3	19.8	19.2	21.7	22.3

“-“ = not tested.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2023/060688

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed.

   b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      ☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/060688

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/19
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2022/109555 A1 (JANSSEN SCIENCES IRELAND UNLIMITED CO [IE]) 27 May 2022 (2022-05-27) claims	13,14
Y	WO 2008/110619 A1 (TIBOTEC PHARM LTD [IE]; BAERT LIEVEN ELVIRE COLETTE [BE] ET AL.) 18 September 2008 (2008-09-18) page 2, line 33 - line 35; claims	1-12
A	EP 3 799 860 A1 (JANSSEN PHARMACEUTICA NV [BE]) 7 April 2021 (2021-04-07) paragraph [0049]; claims	1-14

-/--

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2023	02/10/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Couckuyt, Philippe

3

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/060688

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/078140 A2 (DELIATROPH PHARMACEUTICALS INC [US]; BOOKBINDER LOUIS H [US] ET AL.) 16 September 2004 (2004-09-16) cited in the application [0002],[0355][0382],[0384],[0406-0417]; claims	1-12
A	JAMES J. HOBSON ET AL: "Semi-solid prodrug nanoparticles for long-acting delivery of water-soluble antiretroviral drugs within combination HIV therapies", NATURE COMMUNICATIONS, vol. 10, no. 1, 29 March 2019 (2019-03-29), XP055683254, DOI: 10.1038/s41467-019-09354-z page 2, first Column, 2nd paragraph, pages 6-7 paragraph "discussion", Figures 1 and 3, 4	1-14
A	Izutsu Ken-Ichi: "Physical stability and protein stability of freeze-dried cakes during storage at elevated temperatures", , 7 February 1994 (1994-02-07), XP055978663, Retrieved from the Internet: URL:https://link.springer.com/content/pdf/10.1023/A:1018931319772.pdf [retrieved on 2022-11-07] the whole document	1-14
A	WO 2018/013673 A1 (REFORM BIOLOGICS LLC [US]) 18 January 2018 (2018-01-18) [0028],[0044]; claims 1, 27-28, 49-51	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/060688

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022109555 A1	27-05-2022	TW 202233192 A	01-09-2022
		UY 39520 A	31-05-2022
		WO 2022109555 A1	27-05-2022
WO 2008110619 A1	18-09-2008	AP 2964 A	30-09-2014
		AR 065720 A1	24-06-2009
		AR 114086 A2	22-07-2020
		AU 2008225774 A1	18-09-2008
		BR PI0808897 A2	02-09-2014
		CA 2676981 A1	18-09-2008
		CL 2008000746 A1	22-09-2008
		CN 101636149 A	27-01-2010
		EP 2043608 A1	08-04-2009
		ES 2535162 T3	05-05-2015
		IL 199874 A	29-02-2016
		JP 5554571 B2	23-07-2014
		JP 2010520918 A	17-06-2010
		KR 20090119964 A	23-11-2009
		RU 2009137911 A	20-04-2011
		TW 200911303 A	16-03-2009
		US 2010120795 A1	13-05-2010
		WO 2008110619 A1	18-09-2008
		ZA 200906344 B	29-04-2015
EP 3799860 A1	07-04-2021	AU 2012241726 A1	24-10-2013
		BR 112013026363 A2	27-12-2016
		CA 2832410 A1	18-10-2012
		CN 103764117 A	30-04-2014
		CN 108210469 A	29-06-2018
		DK 2696848 T3	12-10-2020
		EP 2696848 A1	19-02-2014
		EP 3799860 A1	07-04-2021
		ES 2823805 T3	10-05-2021
		HK 1257447 A1	18-10-2019
		HR P20201241 T1	27-11-2020
		HU E050970 T2	28-01-2021
		JP 6161593 B2	12-07-2017
		JP 2014515021 A	26-06-2014
		LT 2696848 T	10-09-2020
		MX 362344 B	11-01-2019
		PL 2696848 T3	28-12-2020
		PT 2696848 T	03-09-2020
		RU 2013150803 A	20-05-2015
		SI 2696848 T1	30-10-2020
		US 2014038996 A1	06-02-2014
		US 2016317534 A1	03-11-2016
		US 2019076428 A1	14-03-2019
		US 2022409616 A1	29-12-2022
		WO 2012140220 A1	18-10-2012
WO 2004078140 A2	16-09-2004	AT 448323 T	15-11-2009
		AU 2004218354 A1	16-09-2004
		AU 2009245838 A1	07-01-2010
		BR PI0408116 A	01-03-2006
		CA 2517145 A1	16-09-2004
		CN 1942588 A	04-04-2007
		CN 102943067 A	27-02-2013
		CY 1109750 T1	10-09-2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/060688

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		CY 1116110 T1	08-02-2017
		CY 1116370 T1	22-06-2016
		CY 1117358 T1	26-04-2017
		DK 1603541 T3	29-03-2010
		DK 2163643 T3	23-03-2015
		DK 2177620 T3	26-01-2015
		DK 2405015 T3	21-03-2016
		EA 200501384 A1	30-06-2006
		EP 1603541 A2	14-12-2005
		EP 2163643 A1	17-03-2010
		EP 2177620 A1	21-04-2010
		EP 2311973 A1	20-04-2011
		EP 2330213 A1	08-06-2011
		EP 2405015 A2	11-01-2012
		EP 3009517 A1	20-04-2016
		ES 2335005 T3	18-03-2010
		ES 2526536 T3	13-01-2015
		ES 2532399 T3	26-03-2015
		ES 2564103 T3	17-03-2016
		HK 1086746 A1	29-09-2006
		HK 1138883 A1	03-09-2010
		HK 1138885 A1	03-09-2010
		HK 1165834 A1	12-10-2012
		HU E027661 T2	28-10-2016
		HU S1600031 I1	29-08-2016
		IL 170300 A	30-06-2016
		IL 227867 A	24-09-2015
		JP 4464395 B2	19-05-2010
		JP 5538770 B2	02-07-2014
		JP 5756785 B2	29-07-2015
		JP 2006524507 A	02-11-2006
		JP 2010029190 A	12-02-2010
		JP 2013031446 A	14-02-2013
		KR 20050118273 A	16-12-2005
		KR 20110114692 A	19-10-2011
		KR 20120094493 A	24-08-2012
		KR 20130135986 A	11-12-2013
		LU 92780 I2	21-09-2015
		LU 93138 I2	05-09-2016
		MX PA05009429 A	12-12-2005
		NZ 542873 A	31-07-2008
		PL 1603541 T3	30-04-2010
		PL 2163643 T3	30-06-2015
		PL 2177620 T3	29-05-2015
		PL 2405015 T3	30-09-2016
		PT 1603541 E	19-02-2010
		PT 2163643 E	18-05-2015
		PT 2177620 E	16-02-2015
		SG 177008 A1	30-01-2012
		SG 2012041067 A	28-08-2014
		SI 1603541 T1	31-03-2010
		SI 2163643 T1	31-03-2015
		SI 2177620 T1	27-02-2015
		SI 2405015 T1	29-04-2016
		US 2004268425 A1	30-12-2004
		US 2009181013 A1	16-07-2009
		US 2009181032 A1	16-07-2009
		US 2009214505 A1	27-08-2009

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/060688

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2009253175 A1	08-10-2009
		US 2011152359 A1	23-06-2011
		US 2012148555 A1	14-06-2012
		US 2012251620 A1	04-10-2012
		US 2013058893 A1	07-03-2013
		US 2014199282 A1	17-07-2014
		US 2017246264 A1	31-08-2017
		US 2019224286 A1	25-07-2019
		US 2021023184 A1	28-01-2021
		WO 2004078140 A2	16-09-2004
		ZA 200507978 B	28-03-2007
WO 2018013673 A1	18-01-2018	CA 3030422 A1	18-01-2018
		EP 3484520 A1	22-05-2019
		JP 2019527729 A	03-10-2019
		KR 20190027878 A	15-03-2019
		US 2018015168 A1	18-01-2018
		US 2018015169 A1	18-01-2018
		US 2019275159 A1	12-09-2019
		US 2020282065 A1	10-09-2020
		WO 2018013673 A1	18-01-2018