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(57) Abstract: The invention relates to an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of: (a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or (b) an amino acid. The invention also relates to further compositions, kits, and the use of the aqueous composition in the treatment or prevention of a HIV infection in a subject.

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LIQUID COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 63/333,556 filed on April 22, 2022 and to European Patent Application No. EP22173922.0, 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 storage stable aqueous compositions comprising rilpivirine or a pharmaceutically acceptable salt thereof, a hyaluronidase, and one or more excipients. The present invention also relates to methods of stabilising such aqueous compositions, uses of excipients in such methods, and methods for the treatment or prevention of HIV infection.

BACKGROUND AND RELATED ART

The treatment of human immunodeficiency virus (HIV) infection, known as the cause of the acquired immunodeficiency syndrome (AIDS), remains a major medical challenge. HIV is able to evade immunological pressure, to adapt to a variety of cell types and growth conditions and to develop resistance against anti-HIV drugs. The latter include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), HIV-protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs) and HIV fusion inhibitors.

Currently available oral therapies require at least once daily dosing. Hence people living with HIV are reminded on a daily basis of their HIV-positive status and daily dosing may also lead to disclosure of their HIV-positive status. Daily dosing requires storage and transport of a large number or volume of pills and there remains the risk of patients forgetting to take their daily dose, thereby failing to comply with the prescribed dosage regimen. As well as reducing the effectiveness of the treatment, this also leads to the emergence of viral resistance.

One class of HIV drugs often used in highly active antiretroviral therapy (HAART) is the NNRTIs. Rilpivirine is an anti-retroviral of the NNRTI class that is used for the treatment of HIV infection. Rilpivirine is a second-generation NNRTI with higher potency and a reduced side effect profile compared with older NNRTIs. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase.

Rilpivirine not only shows pronounced activity against wild type HIV, but also against many of its mutated variants. Rilpivirine, its pharmacological activity, as well as a number of procedures for its preparation have been described in WO2003/016306.

Rilpivirine has been approved for the treatment of HIV infection and is commercially available as a single agent tablet (EDURANT®) containing 25 mg of rilpivirine base equivalent per tablet for once-daily oral administration as well as single tablet regimens for once-daily oral administration (COMPLERA®, ODEFSEY®, JULUCA®).

WO2007/147882 discloses intramuscular or subcutaneous injection of a therapeutically effective amount of rilpivirine in micro- or nanoparticle form, having a surface modifier adsorbed to the surface thereof; and a pharmaceutically acceptable aqueous carrier; wherein the rilpivirine active ingredient is suspended.

A prolonged release suspension for injection of rilpivirine for administration in combination with a prolonged release suspension for injection of cabotegravir has been approved as CABENUVA® in e.g. US and Canada, and as REKAMBYS® in e.g. the EU. These are the first anti-retrovirals to be provided in a long-acting injectable formulation for administration at intervals of greater than one day.

When rilpivirine is to be administered by subcutaneous or intramuscular injection it may be desirable to formulate it or to administer it with a hyaluronidase to increase dispersion and absorption of the rilpivirine. 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 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 rilpivirine and a hyaluronidase, in which the hyaluronidase is stable during storage for many weeks, months or years, in particular at refrigerated temperature, e.g. at 5°C, and without substantially affecting the particle size distribution of the rilpivirine, so that when the rilpivirine is administered after storing for a long time-period, in particular at refrigerated temperature, e.g. at 5°C, bioavailability, efficacy and prolonged release properties are maintained over the storage period.

PCT/US2021/072453 (WO2022/109555) discloses the treatment or prevention of HIV infection using rilpivirine or a pharmaceutically acceptable salt thereof in the form of micro- or nanoparticles in suspension in combination with a hyaluronidase.

SUMMARY OF THE INVENTION

The inventors have discovered new aqueous compositions of rilpivirine particles and a hyaluronidase enzyme which are surprisingly long term shelf stable, particularly in relation to maintenance of the particle size distribution of the rilpivirine particles and enzyme activity over time.

In a first aspect the invention relates to an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of:

(a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or

(b) an amino acid or a pharmaceutically acceptable salt thereof.

In a related aspect (aspect 1a), the invention relates to an aqueous composition comprising:

(i) rilpivirine or a pharmaceutically acceptable salt thereof; and

(ii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of:

(a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or

(b) an amino acid, or a pharmaceutically acceptable salt thereof.

In a related aspect (aspect 1b), the invention relates to a kit comprising:

a first product comprising an aqueous composition comprising:

(i) rilpivirine or a pharmaceutically acceptable salt thereof; and

(ii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of:

(a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or

(b) an amino acid, or a pharmaceutically acceptable salt thereof; and

a second product comprising an aqueous composition comprising a hyaluronidase.

In a related aspect (aspect 1c), the invention relates to a kit comprising:

a first product comprising an aqueous composition comprising:

(i) rilpivirine or a pharmaceutically acceptable salt thereof; and

(ii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of:

(a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or

(b) an amino acid, or a pharmaceutically acceptable salt thereof; and

a second product comprising an aqueous composition comprising:

(i) a hyaluronidase; and

(ii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of:

(a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or

(b) an amino acid, or a pharmaceutically acceptable salt thereof.

In a related aspect (aspect 1d) the invention relates to an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.1-100 mg/mL of at least one sugar or sugar alcohol, optionally wherein the pH of the aqueous composition is from about 5 to about 7, or from about 6 to 6.5, for example, about 6. The aqueous composition in this aspect (aspect 1d) may be used to prepare the aqueous compositions in the first aspect.

In a related aspect (aspect 1e), the invention relates to a kit comprising the components of the kit of aspect 1b, the components of the kit of 1c or the aqueous composition of aspect 1d, wherein the kit further comprises a composition comprising 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, such as for example an antiretroviral of the INSTI class, such as for example cabotegravir.

In a second aspect the invention relates to use of (a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or (b) an amino acid or a pharmaceutically acceptable salt thereof, in a method of stabilising an aqueous composition, wherein the method comprises the step of preparing an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and
(iii) 0.001-100 mg/mL of (a) and/or (b).

In a related aspect (aspect 2a), the invention relates to use of (a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or (b) an amino acid or a pharmaceutically acceptable salt thereof, in a method of stabilising an aqueous composition, wherein the method comprises the step of preparing an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; and
(ii) 0.001-100 mg/mL of (a) and/or (b).

In a related aspect (aspect 2b), the invention relates to use of (a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or (b) an amino acid or a pharmaceutically acceptable salt thereof, in a method of stabilising an aqueous composition, wherein the method comprises the step of preparing an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.001-100 mg/mL of (a) and/or (b).

In a related aspect (aspect 2c) the invention relates to use of at least one sugar or sugar alcohol, in a method of stabilising an aqueous composition, wherein the method comprises the step of preparing an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.1-100 mg/mL of at least one sugar or sugar alcohol, optionally wherein the pH of the aqueous composition is from about 5 to about 7, or from about 6 to 6.5, for example, about 6.

In a third aspect the invention relates to a method of stabilising an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; and (ii) a hyaluronidase;
the method comprising combining components (i) and (ii) with (iii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of: (a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or (b) an amino acid or a pharmaceutically acceptable salt thereof.

In a related aspect (aspect 3a) the invention relates to a method of stabilising an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof;
the method comprising combining component (i) with (ii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of: (a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or (b) an amino acid or a pharmaceutically acceptable salt thereof.

In a related aspect (aspect 3b) the invention relates to a method of stabilising an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; and (ii) a hyaluronidase;
the method comprising combining components (i) and (ii); and (iii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of: a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or b) an amino acid or a pharmaceutically acceptable salt thereof.

In a third aspect (aspect 3c) the invention relates to a method of stabilising an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; and (ii) a hyaluronidase; the method comprising combining components (i) and (ii) with (iii) 0.1-100 mg/mL of at least one sugar or sugar alcohol.

In a fourth aspect there is provided a method for the treatment or prevention of HIV infection in a subject, the method comprising administering to the subject an aqueous composition of the invention.

In a related aspect (aspect 4a), there is provided a method for the treatment or prevention of HIV infection in a subject, the method comprising administering to the subject the products of a kit of the invention, optionally after combining two or more of the products of the kit.

In a fifth aspect there is provided an aqueous composition of the invention, for use in the treatment or prevention of HIV infection in a subject. In a related aspect there is provided a kit of the invention, for use in the treatment or prevention of HIV infection in a subject.

In a sixth aspect there is provided the use of an aqueous composition of the invention, for the manufacture of a medicament for treating or preventing HIV infection in a subject. In a related aspect there is provided a kit of the invention, for the manufacture of a medicament for treating or preventing HIV infection in a subject.

BRIEF DESCRIPTION OF THE FIGURES

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

Figure 1: Appearance, resuspendability, and injectability studies under different storage conditions

Figure 2: Hyaluronidase melting temperature studies under different storage conditions

Figure 2A: Hyaluronidase melting temperature studies under different storage conditions

Figure 2B: Hyaluronidase melting temperature studies under different storage conditions

Figure 2C: Hyaluronidase melting temperature studies under different storage conditions – remeasured pH

Figure 3: Hyaluronidase melting temperature studies

Figure 4: Hyaluronidase melting temperature studies under different storage conditions

Figure 4A: Hyaluronidase melting temperature studies under different storage conditions – remeasured pH

Figure 5: Hyaluronidase melting temperature studies and sodium CMC concentration

These figures are explained further in the "Examples" section.

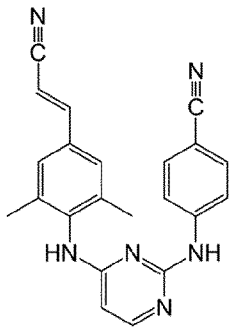
DISCLOSURE OF THE INVENTION

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. For example, embodiments refer to all aspects, unless explicitly stated otherwise.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the invention

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.

In a preferred embodiment the aqueous composition comprises rilpivirine.

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-propane-tricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

In an embodiment, the rilpivirine or a pharmaceutically acceptable salt thereof is in the form of particles suspended in the aqueous composition, for example micro- or nanoparticles suspended in the aqueous composition.

Two embodiments having preferred particle sizes are contemplated herein.

In the first preferred particle size embodiment, the rilpivirine 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. In this embodiment, the particles may have a D_v90 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. In this embodiment, the particles may have a D_v90 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 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 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 or a D_v90 of from about 500 nm to about 1,000 nm, for example from 500 nm to about 1,600 nm or from 500 nm to about 1,000 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 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 rilpivirine 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 rilpivirine 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 rilpivirine particles have a D_v90 of from about 450 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 particle size embodiment, the rilpivirine 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. The particles may have a D_v90 of about 5 µm. The particles may have a D_v90 of about 6 µm.

In the second preferred particle size embodiment, the rilpivirine 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 about 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 rilpivirine 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 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 Mastersizer™ 3000 particle size analyser from Malvern Instruments. The Malvern Mastersizer™ 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 comprises from about 100 to about 500 mg/mL rilpivirine or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 150 to about 450 mg/mL rilpivirine or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 200 to about 400 mg/mL rilpivirine or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the aqueous composition comprises from about 250 to about 350 mg/mL rilpivirine or a pharmaceutically acceptable salt thereof, e.g. about 300 mg/mL, in particular 300 mg/mL of rilpivirine.

In an embodiment, the amount of the rilpivirine or pharmaceutically acceptable salt thereof in the aqueous composition is 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 2700 mg to about 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 ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) in the aqueous composition is from about 200:1 (w/w) to about 400:1 (w/w) or

the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to (b) in the aqueous composition is from about 2:1 (w/w) to about 30:1 (w/w).

In an embodiment the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) in the aqueous composition is from about 250:1 (w/w) to about 350:1 (w/w) or the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to (b) in the aqueous composition is from about 3:1 (w/w) to about 20:1 (w/w).

In an embodiment the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) in the aqueous composition is from about 20:1 (w/w) to about 4000:1 (w/w) or the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to (b) in the aqueous composition is from about 10:1 (w/w) to about 4000:1 (w/w).

In an embodiment the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) in the aqueous composition is from about 20:1 (w/w) to about 1000:1 (w/w) or the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to (b) in the aqueous composition is from about 10:1 (w/w) to about 500:1 (w/w).

In a preferred embodiment the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) in the aqueous composition is from about 50:1 (w/w) to about 400:1 (w/w) or the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to (b) in the aqueous composition is from about 10:1 (w/w) to about 20:1 (w/w).

In some aspects of the invention (e.g. the first to sixth aspects), the aqueous composition comprises a hyaluronidase (in aspects 1a, 2a, 3a the hyaluronidase is optional). 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 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 is from about 1800 to about 2200 U/mL (e.g. about 2000 U/mL).

In an embodiment, the concentration of the hyaluronidase in the aqueous composition is from about 4.5 to about 90 µg/mL, or from about 4.5 to about 45 µg/mL, or from about 4.5 to about 22.5 µg/mL, or from about 9 to about 22.5 µg/mL, or from about 13.5 to about

22.5 µg/mL. Preferably, the concentration of the hyaluronidase in the aqueous composition is from about 16.2 to about 19.8 µg/mL, (e.g. about 18 µg/mL).

In an embodiment, the aqueous composition additionally comprises a carboxymethyl cellulose (CMC) or a derivative thereof, or a pharmaceutically acceptable salt thereof. In an embodiment, the cellulose or derivative thereof in the aqueous composition is a carboxymethyl cellulose (CMC) or a derivative thereof, or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition additionally comprises a CMC or a pharmaceutically acceptable salt thereof, preferably wherein the CMC is not cross-linked. In an embodiment, the cellulose or derivative thereof in the aqueous composition is a 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 thereof 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 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 mPas 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 mPas 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 mPa.s to about 60 mPa.s in an aqueous solution of 2% (w/v) at room temperature. In a preferred 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 90 kDa to about 110 kDa, for example about 90 kDa.

The inventors have surprisingly found that the addition of cellulose or a derivative thereof, e.g. CMC or a derivative thereof, or a pharmaceutically acceptable salt thereof, and/or an amino acid, or a pharmaceutically acceptable salt thereof, to the aqueous compositions of the invention which comprise a hyaluronidase increases the melting temperature (T_m) of the hyaluronidase (Example 6a). This is indicative of improved stability on storage.

The inventors have surprisingly found that the addition of cellulose or a derivative thereof, 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 following storage under stress test conditions (Example 9). This is indicative of improved stability on storage.

In an embodiment, the aqueous compositions of the invention may be storage stable, as defined elsewhere herein, if stored at refrigerated temperature, e.g. about 2-8 °C, for instance, 5 °C, for one of the time periods defined herein. In an embodiment, the aqueous compositions of the invention may be storage stable, as defined elsewhere herein, if stored

at about room temperature, e.g. about 25 °C, for one of the time periods defined herein. In an embodiment, the aqueous compositions of the invention may be storage stable, as defined elsewhere herein, if stored at about 30 °C, for one of the time periods defined herein.

In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of the CMC or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 75 mg/mL of the CMC or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 50 mg/mL of the CMC or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 25 mg/mL of the CMC or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 10 mg/mL of the CMC or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 7 mg/mL of the CMC or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 5 mg/mL of the CMC or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 0.5 mg/mL to about 5 mg/mL of the CMC or a pharmaceutically acceptable salt thereof. In a further preferred embodiment, the aqueous composition comprises from about 0.5 mg/mL to about 3 mg/mL of the CMC or a pharmaceutically acceptable salt thereof, e.g. about 3 mg/mL. In a preferred embodiment, the aqueous composition comprises from about 0.5 mg/mL to about 1.5 mg/mL of the CMC or a pharmaceutically acceptable salt thereof. In a more preferred embodiment, the aqueous composition comprises from about 1 mg/mL to about 1.5 mg/mL of the CMC or a pharmaceutically acceptable salt thereof, e.g. about 1 mg/mL.

In a preferred embodiment, the CMC or a pharmaceutically acceptable salt thereof is sodium CMC and the 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 comprises from about 0.002 mg to about 5 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

In an embodiment, the aqueous composition comprises from about 0.01 mg to about 2 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In an embodiment, the aqueous composition comprises from about 0.02 mg to about 1 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In an embodiment, the aqueous composition comprises from about 0.02 mg to about 0.5 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In an embodiment, the aqueous composition comprises from about 0.02 mg to about 0.1 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In a preferred embodiment, the aqueous composition comprises from about 0.03 mg to about 0.07 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase. In anotherpreferred embodiment, the aqueous composition comprises from about 0.01 mg to about 0.25 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase, e.g. about 0.05 mg to about 0.15 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase, e.g. 0.05 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase or e.g. about 0.15 mg CMC or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

In a preferred embodiment, the CMC or a pharmaceutically acceptable salt thereof is sodium CMC and the aqueous composition comprises any one of the ratios of sodium CMC to hyaluronidase specified in the paragraph directly above.

In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of the amino acid or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 1 mg/mL to about 100 mg/mL of the amino acid or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 100 mg/mL of the amino acid or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 80 mg/mL of the amino acid or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the aqueous composition comprises from about 5 mg/mL to about 60 mg/mL of the amino acid or a pharmaceutically acceptable salt thereof. In another preferred embodiment, the aqueous composition comprises from about 15 mg/mL to about 30 mg/mL or from about 15 mg/mL to about 25 mg/mL of the amino acid or a pharmaceutically acceptable salt thereof, e.g. about 20 mg/mL.

In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of glycine or a pharmaceutically acceptable salt thereof. In an embodiment, the

aqueous composition comprises from about 1 mg/mL to about 100 mg/mL of glycine or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 50 mg/mL of glycine or a pharmaceutically acceptable salt thereof. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 20 mg/mL of glycine or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the aqueous composition comprises from about 10 mg/mL to about 15 mg/mL of glycine or a pharmaceutically acceptable salt thereof.

In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of arginine or arginine hydrochloride. In an embodiment, the aqueous composition comprises from about 1 mg/mL to about 100 mg/mL of arginine or arginine hydrochloride. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 70 mg/mL of arginine or arginine hydrochloride. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 50 mg/mL of arginine or arginine hydrochloride. In a preferred embodiment, the aqueous composition comprises from about 15 mg/mL to about 25 mg/mL of arginine or arginine hydrochloride. In another preferred embodiment, the aqueous composition comprises about 20 mg/mL of arginine or arginine hydrochloride.

In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of arginine hydrochloride. In an embodiment, the aqueous composition comprises from about 1 mg/mL to about 100 mg/mL of arginine hydrochloride. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 70 mg/mL of arginine hydrochloride. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 50 mg/mL of arginine hydrochloride. In a preferred embodiment, the aqueous composition comprises from about 15 mg/mL to about 25 mg/mL of arginine hydrochloride, e.g. about 20 mg/mL of arginine hydrochloride.

In a preferred embodiment, the aqueous composition comprises arginine or arginine hydrochloride (as the amino acid) and CMC or a pharmaceutically acceptable salt thereof. In a more preferred embodiment, the aqueous composition comprises arginine hydrochloride (as the amino acid) and sodium CMC.

In an embodiment, the aqueous composition additionally comprises a sugar or sugar alcohol. Suitable sugars and sugar alcohols include mannitol, lactose, glucose, sucrose, trehalose, sorbitol, dextrose, fructose, maltose, xylitol and raffinose. Preferably, the sugar or sugar alcohol is selected from glucose and sucrose. More preferably, the sugar or

sugar alcohol is sucrose. In an embodiment, the aqueous composition additionally comprises a sugar or sugar alcohol and an amino acid or a pharmaceutically acceptable salt thereof. Pharmaceutically acceptable salts of a sugar, sugar alcohol or an amino acid 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. 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 hydrochloride). In an embodiment, the aqueous composition additionally comprises a sugar or sugar alcohol and CMC or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the aqueous composition additionally comprises sucrose (as the sugar or sugar alcohol) and CMC or a pharmaceutically acceptable salt thereof. In a more preferred embodiment, the aqueous composition additionally comprises sucrose (as the sugar or sugar alcohol) and sodium CMC.

In an embodiment the aqueous composition does not comprise glucose, e.g. it does not comprise glucose monohydrate.

In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of the sugar or sugar alcohol. In an embodiment, the aqueous composition comprises from about 1 mg/mL to about 100 mg/mL of the sugar or sugar alcohol. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 100 mg/mL of the sugar or sugar alcohol. In a preferred embodiment, the aqueous composition comprises from about 10 mg/mL to about 100 mg/mL of the sugar or sugar alcohol. In a more preferred embodiment, the aqueous composition comprises from about 45 mg/mL to about 55 mg/mL of the sugar or sugar alcohol, e.g. about 50 mg/mL of the sugar or sugar alcohol.

In an embodiment, the aqueous composition comprises glucose and/or glucose monohydrate, e.g. as the sugar or sugar alcohol.

In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of glucose monohydrate. In an embodiment, the aqueous composition

comprises from about 1 mg/mL to about 100 mg/mL of glucose monohydrate. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 50 mg/mL of glucose monohydrate. In a preferred embodiment, the aqueous composition comprises from about 10 mg/mL to about 30 mg/mL of glucose monohydrate.

In an embodiment, the aqueous composition comprises from about 0.1 mg/mL to about 100 mg/mL of sucrose. In an embodiment, the aqueous composition comprises from about 1 mg/mL to about 100 mg/mL of sucrose. In an embodiment, the aqueous composition comprises from about 10 mg/mL to about 100 mg/mL of sucrose. In a preferred embodiment, the aqueous composition comprises from about 40 mg/mL to about 70 mg/mL of sucrose. In a more preferred embodiment, the aqueous composition comprises from about 45 mg/mL to about 55 mg/mL of sucrose, e.g. about 50 mg/mL. In an embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:2 (w/w) to about 1:1000 (w/w). In an embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:2 (w/w) to about 1:500 (w/w). In an embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:2 (w/w) to about 1:200 (w/w). In an embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:2 (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 sugar or sugar alcohol is from about 1:10 (w/w) to about 1:100 (w/w). In a preferred embodiment, the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:15 (w/w) to about 1:60 (w/w), e.g. 1:16 (w/w) or 1:50 (w/w).

In an embodiment, the ratio of sodium CMC to sucrose is from about 1:2 (w/w) to about 1:1000 (w/w). In an embodiment, the ratio of sodium CMC to sucrose is from about 1:2 (w/w) to about 1:500 (w/w). In an embodiment, the ratio of sodium CMC to sucrose is from about 1:2 (w/w) to about 1:200 (w/w). In an embodiment, the ratio of sodium CMC to sucrose is from about 1:2 (w/w) to about 1:100 (w/w). In an embodiment, the ratio of sodium CMC to sucrose is from about 1:10 (w/w) to about 1:100 (w/w). In a preferred embodiment, the ratio of sodium CMC to sucrose is from about 1:15 (w/w) to about 1:60 (w/w), e.g. 1:16 (w/w) or 1:50 (w/w).

In an embodiment, the aqueous composition additionally comprises one or more surface modifiers. When the rilpivirine or a pharmaceutically acceptable salt thereof is 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 comprises from about 0.1 mg/mL to about 100 mg/mL of a poloxamer. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 100 mg/mL of a poloxamer. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 70 mg/mL of a poloxamer. In an embodiment, the aqueous composition comprises from about 5 mg/mL to about 60 mg/mL of a poloxamer.

In an embodiment, the aqueous composition comprises from about 15 mg/mL to about 35 mg/mL of a poloxamer, e.g. about 20 mg/mL to about 30 mg/mL. In an embodiment, the aqueous composition comprises from about 15 mg/mL to about 25 mg/mL of a poloxamer, e.g. about 20 mg/mL. In an embodiment, the aqueous composition comprises from about 25 mg/mL to about 35 mg/mL of a poloxamer, e.g. about 30 mg/mL.

In an embodiment, the aqueous composition comprises from about 20 mg/mL to about 60 mg/mL of a poloxamer. In an embodiment, the aqueous composition comprises from about 25 mg/mL to about 60 mg/mL of a poloxamer. In a preferred embodiment, the 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 comprises a poloxamer and rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the ratio of rilpivirine or a pharmaceutically

acceptable salt thereof to poloxamer is more than or about 10:1. In an embodiment, the aqueous composition comprises a poloxamer and rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 60:1. In an embodiment, the aqueous composition comprises a poloxamer and rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 30:1. In an embodiment, the aqueous composition comprises a poloxamer and rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 20:1. In an embodiment, the aqueous composition comprises a poloxamer and rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 15:1. In a preferred embodiment, the aqueous composition comprises a poloxamer and rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is about 15:1. In a preferred embodiment, the aqueous composition comprises a poloxamer and rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is about 10:1. The ratio is a weight by weight ratio.

In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is less than about 10:1, and the rilpivirine or a pharmaceutically acceptable salt thereof 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 comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from less than about 10:1 to about 3:1, and the rilpivirine or a pharmaceutically acceptable salt thereof 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 comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from less than about 10:1 to about 4:1, and the rilpivirine or a pharmaceutically acceptable salt thereof 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 comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from less than about 10:1 to about 6:1, and the rilpivirine or a pharmaceutically acceptable salt thereof 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 comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is about 6:1, and the rilpivirine or a pharmaceutically acceptable salt thereof 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 such as about 4 µm or about 5 µm or about 6 µm. The ratio is a weight by weight ratio.

In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is less than or about 10:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 3:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended

in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 4:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 6:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm. In a preferred embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is about 6:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm. The ratio is a weight by weight ratio.

In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is more than or about 10:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 60:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 30:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 20:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a

pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 15:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm. In a preferred embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer about 15:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm, e.g. about 500 nm to about 700 nm. In a preferred embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer about 10:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm, e.g. about 500 nm to about 700 nm. The ratio is a weight by weight ratio.

In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is less than or about 10:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 3:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 4:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm. In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is from about 10:1 to about 6:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm. In a preferred embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof in the form of particles suspended in the aqueous composition, and a poloxamer, the ratio of the rilpivirine or a

pharmaceutically acceptable salt thereof to poloxamer is about 6:1, and the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of from about 500 nm to about 1600 nm, e.g. about 500 nm to about 700 nm. The ratio is a weight by weight ratio.

In an embodiment, the relative amount (w/w) of rilpivirine or a pharmaceutically acceptable salt thereof to the surface modifier is from about 1:1 to about 40:1. In an embodiment, the relative amount (w/w) of rilpivirine or a pharmaceutically acceptable salt thereof to the surface modifier is from about 1:1 to about 30:1. In an embodiment, the relative amount (w/w) of rilpivirine or a pharmaceutically acceptable salt thereof to the surface modifier is from about 1:1 to about 20:1. In an embodiment, the relative amount (w/w) of rilpivirine or a pharmaceutically acceptable salt thereof to the surface modifier is from about 5:1 to about 15:1, e.g. about 10:1. The surface modifier is preferably a poloxamer, e.g. poloxamer 338.

In an embodiment, the relative amount (w/w) of rilpivirine or a pharmaceutically acceptable salt thereof to the surface modifier is from about 5:1 to about 25:1. In an embodiment, the relative amount (w/w) of rilpivirine or a pharmaceutically acceptable salt thereof to the surface modifier is from about 10:1 to about 20:1. In an embodiment, the relative amount (w/w) of rilpivirine or a pharmaceutically acceptable salt thereof 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, e.g. poloxamer 338.

In an embodiment, the relative amount (w/w) of rilpivirine or a pharmaceutically acceptable salt thereof 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, e.g. poloxamer 338.

In an embodiment, the aqueous composition comprises rilpivirine or a pharmaceutically acceptable salt thereof as defined herein in the form of particles suspended in the aqueous composition and one or more surface modifiers as defined herein wherein the amount of rilpivirine or a pharmaceutically acceptable salt thereof 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.

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

In an embodiment, the 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 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 pH of the aqueous composition is from about 5 to about 7. In an embodiment, the pH of the aqueous composition is from about 6 to about 7. In an embodiment, the pH of the aqueous composition is from about 6 to about 6.5. In a preferred embodiment, the pH of the aqueous composition is about 6. The pH of the 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.

In an embodiment, the 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 additionally comprises an antioxidant. In an embodiment, the antioxidant is methionine. In an embodiment, the 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 is isotonic.

In an embodiment, the aqueous composition does not comprise an isotonizing agent.

In an embodiment, the aqueous composition does not comprise a polyvinyl pyrrolidone (PVP).

In an embodiment, the aqueous composition comprises substantially no glucose, for example less than about 10% w/w glucose, or less than about 5% w/w glucose, or preferably less than about 1 % w/w glucose.

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

In a particular embodiment of the first aspect, the invention relates to an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.001-100 mg/mL of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof.

In a particular embodiment of the first aspect, the invention relates to an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.001-100 mg/mL of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and (iv) a sugar.

In a particular embodiment of the first aspect, the invention relates to an aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.001-100 mg/mL of:

(a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and
(b) an amino acid or a pharmaceutically acceptable salt thereof.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
CMC or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and

sodium hydroxidefurther optionally wherein the aqueous composition additionally comprises poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
glucose monohydrate; and
CMC or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxidefurther optionally wherein the aqueous composition additionally comprises poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide .

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
an amino acid or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from a surfactant, e.g. poloxamer, a buffering agent, e.g. sodium dihydrogen phosphate, a chelating agent, e.g. citric acid, and a pH adjusting agent, e.g. sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
glycine,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;

rilpivirine or a pharmaceutically acceptable salt thereof; and
glycine or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
arginine,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
arginine hydrochloride,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
arginine or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
sucrose; and
CMC or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
sucrose; and
sodium CMC,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
arginine or a pharmaceutically acceptable salt thereof; and
CMC or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
arginine or a pharmaceutically acceptable salt thereof; and
sodium CMC,

wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
arginine hydrochloride; and
CMC or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
a hyaluronidase;
rilpivirine or a pharmaceutically acceptable salt thereof; and
arginine hydrochloride; and
sodium CMC,
wherein the pH of the aqueous composition is from about 6 to about 7,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine; and
sodium CMC,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;

rilpivirine; and
sodium CMC,
wherein the pH of the aqueous composition is from about 6 to about 6.5, and
wherein the aqueous composition comprises from about 0.002mg sodium CMC per 100 U rHuPH20 to about 5mg sodium CMC per 100 U rHuPH20,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine; and
sodium CMC,
wherein the pH of the aqueous composition is from about 6 to about 6.5, and
wherein the aqueous composition comprises from about 0.01 mg sodium CMC per 100 U rHuPH20 to about 0.25 mg sodium CMC per 100 U rHuPH20,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine;
sodium CMC; and
a sugar or sugar alcohol,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine;

sodium CMC; and
glucose monohydrate and/or sucrose,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine;
sodium CMC; and
sucrose,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine;
sodium CMC; and
arginine or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine;
sodium CMC; and
arginine hydrochloride,
wherein the pH of the aqueous composition is from about 6 to about 6.5,

optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine;
sodium CMC; and
glucose monohydrate and/or sucrose,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
wherein the aqueous composition comprises from about 0.0025mg sodium CMC per 100 U rHuPH20 to about 5mg sodium CMC per 100 U rHuPH20,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine;
sodium CMC; and
glucose monohydrate and/or sucrose,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
wherein the aqueous composition comprises from about 0.01 mg sodium CMC per 100 U rHuPH20 to about 0.25 mg sodium CMC per 100 U rHuPH20, e.g. 0.05 mg sodium CMC per 100 U rHuPH20 or 0.15 mg sodium CMC per 100 U rHuPH20,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

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

wherein the aqueous composition comprises from about 0.01 mg sodium CMC per 100 U rHuPH20 to about 0.25 mg sodium CMC per 100 U rHuPH20, e.g. 0.05 mg sodium CMC per 100 U rHuPH20 or 0.15 mg sodium CMC per 100 U rHuPH20,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine;
sodium CMC; and
arginine or a pharmaceutically acceptable salt thereof,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
wherein the aqueous composition comprises from about 0.01 mg sodium CMC per 100 U rHuPH20 to about 0.25 mg sodium CMC per 100 U rHuPH20, e.g. 0.05 mg sodium CMC per 100 U rHuPH20 or 0.15 mg sodium CMC per 100 U rHuPH20,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine;
sodium CMC; and
arginine hydrochloride,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
wherein the aqueous composition comprises from about 0.01 mg sodium CMC per 100 U rHuPH20 to about 0.25 mg sodium CMC per 100 U rHuPH20, e.g. 0.05 mg sodium CMC per 100 U rHuPH20 or 0.15 mg sodium CMC per 100 U rHuPH20,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine; and
an amino acid or a pharmaceutically acceptable salt thereof,

wherein the pH of the aqueous composition is from about 6 to about 6.5,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine; and
arginine HCl,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine; and
an amino acid or a pharmaceutically acceptable salt thereof and a sugar or sugar alcohol,
wherein the pH of the aqueous composition is from about 6 to about 6.5,
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine; and
an amino acid or a pharmaceutically acceptable salt thereof and a sugar or sugar alcohol,
wherein the pH of the aqueous composition is from about 6 to about 6.5, and
wherein the ratio of rilpivirine to the sugar or sugar alcohol and amino acid or a pharmaceutically acceptable salt thereof is from about 2:1 (w/w) to about 30:1 (w/w),

optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine; and
an amino acid or a pharmaceutically acceptable salt thereof and a sugar or sugar alcohol and,
wherein the pH of the aqueous composition is from about 6 to about 6.5, and
wherein the ratio of rilpivirine to the sugar or sugar alcohol and amino acid or a pharmaceutically acceptable salt thereof is from about 5:1 (w/w) to about 16:1 (w/w),
optionally wherein the aqueous composition additionally comprises one or more component selected from poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide, further optionally wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine in the form of particles suspended in the aqueous composition;
sodium CMC;
sucrose; and
poloxamer 338,
optionally wherein when the rilpivirine has a Dv90 of less than or about 1600 nm the ratio of rilpivirine to poloxamer 338 is more than or about 10:1.

In a particular embodiment, the aqueous composition comprises:
from about 1800 to about 2200 U/mL rHuPH20;
from about 250 to about 350 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 0.5 mg/mL to about 5 mg/mL sodium CMC;
from about 45 mg/mL to about 55 mg/mL sucrose; and
from about 10 mg/mL to about 60 mg/mL poloxamer 338,

optionally wherein when the aqueous composition comprises about 40 mg/mL to about 60 mg/mL of poloxamer 338, e.g. about 50 mg/mL, the rilpivirine has a Dv90 of from about 3 µm to about 7 µm, e.g. about 6 µm. In another particular embodiment, the Dv90 is about 5 µm.

In a particular embodiment, the aqueous composition comprises:
from about 1800 to about 2200 U/mL rHuPH20;
from about 250 to about 350 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 0.5 mg/mL to about 5 mg/mL sodium CMC;
from about 45 mg/mL to about 55 mg/mL sucrose; and
from about 10 mg/mL to about 60 mg/mL poloxamer 338,
optionally wherein the aqueous composition comprises about 40 mg/mL to about 60 mg/mL of poloxamer 338, e.g. about 50 mg/mL, and the rilpivirine has a Dv90 of from about 500 nm to 1600 nm.

In a particular embodiment, the aqueous composition comprises:
from about 1800 to about 2200 U/mL rHuPH20;
from about 250 to about 350 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 0.5 mg/mL to about 5 mg/mL sodium CMC;
from about 45 mg/mL to about 55 mg/mL sucrose; and
from about 10 mg/mL to about 60 mg/mL poloxamer 338,
optionally wherein when the aqueous composition comprises about 20 mg/mL to about 30 mg/mL of poloxamer 338, the rilpivirine has a Dv90 of from about 500 nm to 1600 nm.

In a particular embodiment, the aqueous composition comprises:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 50 mg/mL sucrose; and
about 50 mg/mL poloxamer 338,
wherein the rilpivirine has a Dv90 of from about 4 µm to about 6 µm, e.g. about 6 µm. In another particular embodiment, the Dv90 is about 5 µm.

In a particular embodiment, the aqueous composition comprises:
about 2000 U/mL rHuPH20;

about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 50 mg/mL sucrose; and
about 50 mg/mL poloxamer 338,
wherein the rilpivirine has a Dv90 of from about 500 nm to about 1600 µm.

In a particular embodiment, the aqueous composition comprises:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 50 mg/mL sucrose; and
about 20 mg/mL to about 30 mg/mL poloxamer 338,
wherein the rilpivirine has a Dv90 of from about 500 nm to about 1600 µm.

In a particular embodiment, the aqueous composition comprises:
rHuPH20;
rilpivirine in the form of particles suspended in the aqueous composition;
sodium CMC;
arginine HCl; and
poloxamer 338,
optionally wherein when the rilpivirine has a Dv90 of less than or about 1600 nm the weight by weight ratio of rilpivirine to poloxamer 338 is more than or about 10:1.

In a particular embodiment, the aqueous composition comprises:
from about 1800 to about 2200 U/mL rHuPH20;
from about 250 to about 350 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 0.5 mg/mL to about 5 mg/mL sodium CMC;
from about 15 mg/mL to about 25 mg/mL arginine HCl; and
from about 10 mg/mL to about 60 mg/mL poloxamer 338,
optionally wherein when the rilpivirine has a Dv90 of less than or about 1600 nm the weight by weight ratio of rilpivirine to poloxamer 338 is more than or about 10:1.

In a particular embodiment, the aqueous composition comprises:
from about 1800 to about 2200 U/mL rHuPH20;
from about 250 to about 350 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;

from about 0.5 mg/mL to about 5 mg/mL sodium CMC;
from about 15 mg/mL to about 25 mg/mL arginine HCl; and
from about 10 mg/mL to about 60 mg/mL poloxamer 338,
optionally wherein when the rilpivirine has a Dv90 of less than or about 1600 nm the weight by weight ratio of rilpivirine to poloxamer 338 is equal to or less than about 10:1.

In a particular embodiment, the aqueous composition comprises:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 20 mg/mL arginine HCl; and
about 50 mg/mL poloxamer 338,
wherein the rilpivirine has a Dv90 of from about 4 µm to about 6 µm, e.g. about 6 µm. In another particular embodiment, the Dv90 is about 5 µm.

In a particular embodiment, the aqueous composition comprises:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 20 mg/mL arginine HCl; and
about 50 mg/mL poloxamer 338,
wherein the rilpivirine has a Dv90 of from about from about 500 nm to 1600 µm.

In a particular embodiment, the aqueous composition comprises:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 20 mg/mL arginine HCl; and
about 20 mg/mL to about 30 mg/mL poloxamer 338,
wherein the rilpivirine has a Dv90 of from about 500 nm to 1600 nm.

In a particular embodiment, the aqueous composition comprises:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 20 mg/mL arginine HCl; and
about 50 mg/mL poloxamer 338,

about 2 mg/mL $NaH_2PO_4.H2O$,
about 1 mg/mL citric acid.H2O,
sodium hydroxide (q.s. for pH 6), and
Water (q.s. ad 1 mL),
wherein the rilpivirine has a Dv90 of from about 4 µm to about 6 µm, e.g. about 6 µm. In another particular embodiment, the Dv90 is about 5 µm.

In a particular embodiment, the aqueous composition comprises:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 20 mg/mL arginine HCl; and
about 50 mg/mL poloxamer 338,
about 2 mg/mL $NaH_2PO_4.H2O$,
about 1 mg/mL citric acid.H2O,
sodium hydroxide (q.s. for pH 6), and
Water (q.s. ad 1 mL),
wherein the rilpivirine has a Dv90 of from about from about 500 nm to 1600 µm.

In a particular embodiment, the aqueous composition comprises:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 20 mg/mL arginine HCl; and
about 20 mg/mL to about 30 mg/mL poloxamer 338,
about 2 mg/mL $NaH_2PO_4.H2O$,
about 1 mg/mL citric acid.H2O,
sodium hydroxide (q.s. for pH 6), and
Water (q.s. ad 1 mL),
wherein the rilpivirine has a Dv90 of from about 500 nm to 1600 nm.

In any of these particular embodiments, the 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).

In a preferred embodiment, there is provided an aqueous composition having a pH of about 5 to about 7 (preferably about 6) and comprising:

(i) rilpivirine or a pharmaceutically acceptable salt thereof, in the form of particles suspended in the aqueous composition;
(ii) a hyaluronidase;
(iii) 0.1-100 mg/mL of glucose or glucose monohydrate (e.g. glucose);
(iv) a blanket of inert gas (e.g. nitrogen); and
(v) an antioxidant (e.g. methionine) e.g. about 1 mg/mL to about 2 mg/mL, e.g. 1.5 mg/mL.

In an aspect, there is provided an aqueous composition having a pH of about 6 to about 6.5, preferably 6, and comprising:
(i) rilpivirine or a pharmaceutically acceptable salt thereof, in the form of particles suspended in the aqueous composition; and
(ii) a hyaluronidase.

In an aspect, there is provided an aqueous composition having a pH of about 6 to about 6.5, preferably 6, and comprising:
(i) rilpivirine or a pharmaceutically acceptable salt thereof, in the form of particles suspended in the aqueous composition;
(ii) a hyaluronidase; and
(iii) an antioxidant (e.g. methionine) e.g. about 1 mg/mL to about 2 mg/mL, e.g. 1.5 mg/mL.

In an aspect, there is provided an aqueous composition having a pH of about 6 to about 6.5, preferably 6, and comprising:
(i) rilpivirine or a pharmaceutically acceptable salt thereof, in the form of particles suspended in the aqueous composition;
(ii) a hyaluronidase;
(iii) an antioxidant (e.g. methionine) e.g. about 1 mg/mL to about 2 mg/mL, e.g. 1.5 mg/mL.; and
(iv) 0.1-100 mg/mL of glucose or glucose monohydrate (e.g. glucose).

In preferred embodiments, the compositions of the invention reduce changes in particle size distribution of rilpivirine microparticles or nanoparticles over time. This reduction may be relative to a composition wherein excipients (a) and/or (b) have not been added to the composition.

In preferred embodiments, the compositions of the invention reduce changes in particle size distribution of rilpivirine microparticles or nanoparticles over time. This reduction may be relative to a composition wherein excipient (a) has not been added to the composition.

In preferred embodiments, the compositions of the invention reduce changes in particle size distribution of rilpivirine microparticles or nanoparticles over time. This reduction may be relative to a composition wherein excipient (b) has not been added to the composition.

In preferred embodiments, the compositions of the invention reduce changes in particle size distribution of rilpivirine microparticles or nanoparticles over time. This reduction may be relative to a composition wherein excipients (a) and (b) have not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be reducing changes in particle size distribution of rilpivirine microparticles or nanoparticles over time. This reduction may be relative to a composition wherein excipients (a) and/or (b) have not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be reducing changes in particle size distribution of rilpivirine microparticles or nanoparticles over time. This reduction may be relative to a composition wherein excipient (a) has not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be reducing changes in particle size distribution of rilpivirine microparticles or nanoparticles over time. This reduction may be relative to a composition wherein excipient (b) has not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be reducing changes in particle size distribution of rilpivirine microparticles or nanoparticles over time. This reduction may be relative to a composition wherein excipients (a) and (b) have not been added to the composition.

For example, Dv10, Dv50, and Dv90 values of the particles may remain within about 20% of the original value, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

As a further example, Dv10, Dv50, and Dv90 values of the particles may remain within about 10% of the original value, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

For example, Dv10, Dv50, and Dv90 values of the particles may remain within about 20% of the original value, after storage of the aqueous composition for about 1, about 2, about 4, about 8, about 16, or about 32 weeks at about 5 °C.

As a further example, Dv10, Dv50, and Dv90 values of the particles may remain within about 10% of the original value, after storage of the aqueous composition for about 1, about 2, about 4, about 8, about 16, or about 32 weeks at about 5 °C.

For example, Dv10, Dv50, and Dv90 values of the particles may remain within about 20% of the original value, after storage of the aqueous composition for about 1, about 2, about 4, about 8, about 16, or about 32 weeks at about 25 °C.

As a further example, Dv10, Dv50, and Dv90 values of the particles may remain within about 10% of the original value, after storage of the aqueous composition for about 1, about 2, about 4, about 8, about 16, or about 32 weeks at about 25 °C.

For example, Dv10, Dv50, and Dv90 values of the particles may remain within about 20% of the original value, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 25 °C.

As a further example, Dv10, Dv50, and Dv90 values of the particles may remain within about 30% of the original value, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 25 °C.

In preferred embodiments, the compositions of the invention maintain hyaluronidase activity over a period of time, for example, about 1, about 3, about 6, about 12, about 18, or about 24 months. This maintenance may be relative to a composition wherein excipients (a) and/or (b) have not been added to the composition.

In preferred embodiments, the compositions of the invention maintain hyaluronidase activity over a period of time, for example, about 1, about 3, about 6, about 12, about 18, or about 24 months. This maintenance may be relative to a composition wherein excipient (a) has not been added to the composition.

In preferred embodiments, the compositions of the invention maintain hyaluronidase activity over a period of time, for example, about 1, about 3, about 6, about 12, about 18, or about 24 months. This maintenance may be relative to a composition wherein excipient (b) has not been added to the composition.

In preferred embodiments, the compositions of the invention maintain hyaluronidase activity over a period of time, for example, about 1, about 3, about 6, about 12, about 18, or about 24 months. This maintenance may be relative to a composition wherein excipients (a) and (b) have not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase activity over time. This maintenance may be relative to a composition wherein excipients (a) and/or (b) have not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase activity over time. This maintenance may be relative to a composition wherein excipient (a) has not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase activity over time. This maintenance may be relative to a composition wherein excipient (b) has not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase activity over time. This maintenance may be relative to a composition wherein excipients (a) and (b) have not been added to the composition.

For example, the composition may maintain hyaluronidase activity over a period of time, for example, about 1, about 3, about 6, about 12, about 18, or about 24 months. This may be where the storage is at about 5 °C or about 25 °C.

As further example, hyaluronidase activity may remain at least 50% of the original activity, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C or about 25 °C.

As a further example, hyaluronidase activity may remain at least 50% of the original activity, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

As a further example, hyaluronidase activity may remain at least 25% of the original activity, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C or about 25 °C.

In preferred embodiments, the compositions of the invention maintain hyaluronidase concentration (for example, as determined by size exclusion chromatography) over a period of time, for example, about 1, about 3, about 6, about 12, about 18, or about 24 months.

This maintenance may be relative to a composition wherein excipients (a) and/or (b) have not been added to the composition.

This maintenance may be relative to a composition wherein excipients (a) has not been added to the composition.

This maintenance may be relative to a composition wherein excipients (b) has not been added to the composition.

This maintenance may be relative to a composition wherein excipients (a) and (b) have not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase concentration (for example, as determined by size exclusion chromatography) over time. This maintenance may be relative to a composition wherein excipients (a) and/or (b) have not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase concentration (for example, as determined by size exclusion chromatography) over time. This maintenance may be relative to a composition wherein excipient (a) has not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase concentration (for example, as determined by size exclusion chromatography) over time. This maintenance may be relative to a composition wherein excipient (b) has not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase concentration (for example, as determined by size exclusion chromatography) over time. This maintenance may be relative to a composition wherein excipients (a) and (b) have not been added to the composition.

For example, the composition may maintain hyaluronidase concentration (for example, as determined by size exclusion chromatography) over a period of time, for example, about 1 week, about 2 weeks, about 1 month, about 3 months, about 6 months, about 12 months,

about 18 months, or about 24 months. This may be where the storage is at about 5 °C or about 25 °C.

As a further example, at least 25% of the original concentration of hyaluronidase may remain, after storage of the aqueous composition for about 1 week, about 2 weeks, about 6 months, about 12 months, about 18 months, or about 24 months at about 5 °C or about 25 °C.

As a further example, at least 50% of the original concentration of hyaluronidase concentration may remain, after storage of the aqueous composition for about 6, about 12, about 18, or about 24 months at about 5 °C or about 25 °C.

As a further example, at least 95% of the original concentration of hyaluronidase concentration may remain, after storage of the aqueous composition for about 6, about 12, about 18, or about 24 months at about 5 °C or about 25 °C.

In preferred embodiments, the compositions of the invention maintain hyaluronidase purity over a period of time, for example, about 1 week, about 2 weeks, about 1 month, about 3 months, about 6 months, about 12 months, about 18 months, or about 24 months. This maintenance may be relative to a composition wherein excipients (a) and/or b) have not been added to the composition.
This maintenance may be relative to a composition wherein excipient (a) has not been added to the composition.
This maintenance may be relative to a composition wherein excipient (b) has not been added to the composition.
This maintenance may be relative to a composition wherein excipients (a) and b) have not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase purity over time. This maintenance may be relative to a composition wherein excipients (a) and/or (b) have not been added to the composition.
In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase purity over time. This maintenance may be relative to a composition wherein excipient (a) has not been added to the composition.

In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase purity over time. This maintenance may be relative to a composition wherein excipient (b) has not been added to the composition.
In uses of the invention (uses in methods of stabilising an aqueous composition), the stabilisation may be maintaining hyaluronidase purity over time. This maintenance may be relative to a composition wherein excipients (a) and (b) have not been added to the composition.

For example, the composition may maintain hyaluronidase purity over a period of time (i.e. reducing presence of degradants), for example, about 1 week, about 2 weeks, about 1 month, about 3 months, about 6 months, about 12 months, about 18 months, or about 24 months. This may be where the storage is at about 5 °C or about 25 °C.

As a further example, less than 50% of the original hyaluronidase is degraded to degradants, after storage of the aqueous composition for about 1 week, about 2 weeks, about 6 months, about 12 months, about 18 months, or about 24 months at about 5 °C or about 25 °C.

As a further example, less than 25% of the original hyaluronidase is degraded to degradants, after storage of the aqueous composition for about 6, about 12, about 18, or about 24 months at about 5 °C or about 25 °C (e.g. about 5 °C).

As a further example, less than 20% of the original hyaluronidase is degraded to degradants, after storage of the aqueous composition for about 6, about 12, about 18, or about 24 months at about 5 °C or about 25 °C (e.g. about 5 °C).

As a further example, less than 5 % of the original hyaluronidase is degraded to degradants, after storage of the aqueous composition for about 6, about 12, about 18, or about 24 months at about 5 °C or about 25 °C (e.g. about 5 °C).

In an embodiment, the degradant measured is an oxidised species of hyaluronidase. In a particular embodiment, the degradant measured is an oxidised species of hyaluronidase having reduced enzyme activity.

Uses of the compositions of the invention

The aqueous composition can be used to treat or prevent HIV infection in a subject.

Thus, in an aspect the invention relates to a method for the treatment or prevention of HIV infection in a subject, the method comprising administering to the subject the aqueous composition as defined herein. In a fifth aspect the invention relates to the aqueous composition as defined herein for use in the treatment or prevention of HIV infection in a subject. In a sixth aspect the invention relates to use of the aqueous composition as defined herein for the manufacture of a medicament for treating or preventing HIV infection in a subject.

In a preferred embodiment, the subject is a human.

In an embodiment, the 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 four months. In an embodiment, the time interval is about five months. In an embodiment, the time interval is about six months. In an embodiment, the time interval is about seven months. In an embodiment, the time interval is about eight months. In an embodiment, the time interval is about nine months. In an embodiment, the time interval is about 10 months. In an embodiment, the time interval is about 11 months.

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

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

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

mOsm/kg. In a more preferred embodiment, the aqueous composition has an osmolality of about 290 mOsm/kg.

The rilpivirine or pharmaceutically acceptable salt thereof is present in the aqueous composition (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, each administration comprises up to about 150 mL of the aqueous composition described herein. In another embodiment, each administration comprises from about 3 mL to about 150mL of the aqueous composition. In another embodiment, each administration comprises from about 3 mL to about 100mL of the aqueous composition. In another embodiment, each administration comprises from about 3 mL to about 15mL of the aqueous composition. In another embodiment, each administration comprises from about 5 mL to about 25 mL of the aqueous composition. In another embodiment, each administration comprises from about 6 mL to about 20 mL of the aqueous composition. In another embodiment, each administration comprises from about 6 mL to about 18 mL of the aqueous composition. In another embodiment, each administration comprises from about 6 mL to about 15 mL of the aqueous composition. In another embodiment, each administration comprises from about 6 mL to about 12 mL of the aqueous composition. In another embodiment, each administration comprises from about 9 mL to about 18 mL of the aqueous composition. In another embodiment, each administration comprises from about 9 mL to about 15 mL of the aqueous composition. In another embodiment, each administration comprises from about 9 mL to about 12 mL of the aqueous composition. In another embodiment, each administration comprises about 3 mL of the aqueous composition. In another embodiment, each administration comprises about 4 mL of the aqueous composition. In another embodiment, each administration comprises about 5 mL of the aqueous composition. In another embodiment, each administration comprises about 6 mL of the aqueous composition. In another embodiment, each administration comprises about 7 mL of the aqueous composition. In another embodiment, each administration comprises about 8 mL of the aqueous composition. In another embodiment, each administration comprises about 9 mL of the aqueous composition. In another embodiment, each administration comprises about 10 mL of the aqueous composition. In another embodiment, each administration comprises about 11 mL of the aqueous composition. In another embodiment, each administration comprises about 12 mL of the aqueous composition. In another embodiment, each administration comprises about 13 mL of the aqueous composition. In another embodiment, each administration

comprises about 14 mL of the aqueous composition. In another embodiment, each administration comprises about 15 mL of the aqueous composition. In another embodiment, each administration comprises about 18 mL of the aqueous composition. In a preferred embodiment, each administration comprises about 3 mL, about 7 mL, or about 15 mL of the aqueous composition.

In an embodiment, for the treatment of HIV infection, the dose of rilpivirine 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 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, for the treatment of HIV infection, the dose of rilpivirine 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 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 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 rilpivirine or pharmaceutically acceptable salt thereof in the 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 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 the instance of prevention of HIV infection, 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 aqueous composition is used in combination with 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, such as for example an antiretroviral of the INSTI class, such as for example cabotegravir. In a particular embodiment, the invention is a kit comprising a) a composition or kit of the invention and b) a second composition comprising the one or more other antiretroviral agents.

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 aqueous composition as described herein, e.g. the 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 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 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 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 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.

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 1 – Appearance studies under stress test conditions

This example compares the appearance of various compositions, each having a different combination of excipients, after storage under different conditions.

An aqueous composition, of rilpivirine nanoparticles with the following excipients were prepared:

- Rilpivirine (300 mg/mL)
- rHuPH20 (2000 U/mL)
- Sodium dihydrogen phosphate monohydrate (2 mg/mL)
- Citric acid monohydrate (1 mg/mL)
- Poloxamer 338 (50 mg/mL)
- Sodium hydroxide 5N, aq (q.s. to pH 6.0)
- Water for injection (q.s. ad 1 mL)

Compositions A-E were prepared by adding to or adjusting the components described above, as summarised in Table 1 below. In Compositions A-E the pH was adjusted to 6.0 using aqueous sodium hydroxide solution 5N.

Composition	Additional or adjusted component(s)
A	Glucose monohydrate (19.25 mg/mL)
B	Glucose monohydrate (19.25 mg/mL) Sodium CMC (1 mg/mL)
C	Glycine (13.3 mg/mL)
D	Arginine HCl (20.85 mg/mL)
E	Sucrose (56.8 mg/mL) Sodium CMC (1 mg/mL)

Table 1: Compositions A-E

Compositions A and B were prepared using rilpivirine nanoparticles (Dv10 = 95 nm, Dv50 = 220 nm, and Dv90 = 494 nm).

Compositions C-E were prepared using rilpivirine nanoparticles (having Dv10 = 102 nm, Dv50 = 234 nm, and Dv90 = 512 nm).

The results are shown in Figure 1. Injectability was tested using a 25G x 3/4" needle.

Example 2 – Particle size

This example investigates the effect of various compositions, each having a different combination of excipients, on the particle size of rilpivirine in suspension, after storage conditions of 5 °C for 1 month, 3 months, and 6 months.

Compositions A-E of rilpivirine nanoparticles (having Dv10, Dv50, and Dv90 as in Example 1) were prepared as in Example 1.

The compositions were stored under conditions of 5 °C for 1 month. The rilpivirine particle sizes were measured following the method below.

Particle size distribution measurement

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 results are shown in Table 2 and Table 2A.

Composition	Dv10 / µm		Dv50 / µm		Dv90 / µm	
	t_0	t_{1month} (5 °C)	t_0	t_{1month} (5 °C)	t_0	t_{1month} (5 °C)
A	0.115	0.118	0.254	0.262	0.556	0.581
B	0.111	0.116	0.244	0.255	0.535	0.561
C	0.118	0.123	0.259	0.267	0.563	0.573
D	0.117	0.123	0.257	0.266	0.558	0.571
E	0.114	0.119	0.251	0.260	0.548	0.566

Table 2: Particle size

Composition	Dv10 / µm		Dv50 / µm		Dv90 / µm	
	t_{3month} (5 °C)	t_{6month} (5 °C)	t_{3month} (5 °C)	t_{6month} (5 °C)	t_{3month} (5 °C)	t_{6month} (5 °C)
A	0.117	0.114	0.265	0.257	0.610	0.621
B	0.113	0.111	0.252	0.249	0.570	0.566
C	0.120	0.118	0.264	0.263	0.583	0.591
D	0.120	0.118	0.264	0.263	0.583	0.589
E	0.116	0.113	0.257	0.253	0.573	0.568

Table 2A: Particle size

Example 3 – Purity assays

This example compares the rilpivirine assay data of various compositions, each having a different combination of excipients, after storage under different conditions.

Compositions A-E of rilpivirine nanoparticles were prepared as in Example 1.

The compositions were then stored in a refrigerator at 5 °C for between 2 days and 2 weeks. The rilpivirine assay measurement of the compositions was taken straight away and after storage at 5, 25, and 40 °C for 1 month. The rilpivirine quantity was determined following the method below.

Rilpivirine assay measurement

The determination of the quantity of rilpivirine present in the compositions is based upon a gradient ultra-high performance liquid chromatographic (UHPLC) method with UV detection at 280 nm. The same method was also used to determine the quantity of a particular impurity in the compositions referred to below as Impurity 1.

The results are shown in Table 3.

Composition		Rilpivirine / %	Impurity 1/ %
A	t_0	99.8	0.09
	t_{1month} (5 °C)	99.2	0.09
	t_{1month} (25 °C)	99.1	0.09
	t_{1month} (40 °C)	100.1	0.09

Composition		Rilpivirine / %	Impurity 1/ %
B	t_0	99.5	0.09
	t_{1month} (5 °C)	98.9	0.09
	t_{1month} (25 °C)	98.5	0.09
	t_{1month} (40 °C)	99.2	0.09
C	t_0	96.5	0.09
	t_{1month} (5 °C)	96.2	0.08
	t_{1month} (25 °C)	96.8	0.09
	t_{1month} (40 °C)	96.5	0.08
D	t_0	95.9	0.09
	t_{1month} (5 °C)	95.6	0.08
	t_{1month} (25 °C)	96.0	0.09
	t_{1month} (40 °C)	96.2	0.09
E	t_0	97.5	0.09
	t_{1month} (5 °C)	97.2	0.10
	t_{1month} (25 °C)	97.3	0.09
	t_{1month} (40 °C)	97.7	0.08

Table 3: Assay data

Example 4 – pH

This example compares the pH of various rilpivirine compositions, each having a different combination of excipients, after storage under different conditions.

Compositions A-E of rilpivirine nanoparticles were prepared as in Example 1.

The compositions were stored under conditions of 5, 25, and 40 °C for 1 month. The pH was determined following the method below.

pH measurement

The pH of the compositions was measured using a benchtop pH meter. The pH meter was calibrated upfront with two points calibration to 4.0 and 7.0, and corrected for temperature. The pH was measured by submerging the probe into the aqueous composition.

The results are shown in Table 4.

Composition	t_0	t_{1month} (5 °C)	t_{1month} (25 °C)	t_{1month} (40 °C)
A	6.1	6.1	(Initial: 4.712 Re-measured: 4.441)	5.8
B	6.4	6.1	6.0	6.1
C	6.1	6.1	6.1	6.1
D	6.0	6.1	6.0	6.0
E	6.1	6.1	6.2	6.1

Table 4: pH data

The pH values measured for Composition A after 1 month storage at 25 °C was anomalous.

Example 5 – Melting temperature studies under different storage conditions

This example compares the T_m of rHuPH20 in various compositions, each having a different combination of excipients and/or pH, under different storage conditions. 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 is targeted to provide optimal thermodynamic stability of the hyaluronidase.

Compositions 1-21 were prepared by adding the component(s) shown in Table 5 below to the following composition (composition F) :

- Glucose monohydrate (19.25 mg/mL)
- rHuPH20 (2000 U/mL)
- Sodium dihydrogen phosphate monohydrate (2 mg/mL)
- Citric acid monohydrate (1 mg/mL)
- Poloxamer 338 (50 mg/mL)
- Sodium hydroxide (varied to provide target pH)
- Water for injection (q.s. ad 1 mL)

The pH of the composition was adjusted to 5.0, 6.0, 6.5, or 7.0 as necessary by varying the amount of the sodium hydroxide.

Composition	pH	Additional component 1	Additional component 2
1	5.0	-	-
2	5.0	Mannitol (50 mg/mL)	-

Composition	pH	Additional component 1	Additional component 2
3	5.0	Sucrose (50 mg/mL)	-
4	5.0	Histidine (25 mg/mL)	-
5	5.0	Glycine (25 mg/mL)	-
6	5.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)
7	5.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)
8	6.0	-	-
9	6.0	Mannitol (50 mg/mL)	-
10	6.0	Sucrose (50 mg/mL)	-
11	6.0	Histidine (25 mg/mL)	-
12	6.0	Glycine (25 mg/mL)	-
13	6.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)
14	6.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)
15	6.5	Glycine (10 mg/mL)	Sucrose (50 mg/mL)
16	7.0	Histidine (25 mg/mL)	-
17	7.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)
18	7.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)
19	7.0	Glycine (15 mg/mL)	-
20	7.0	Glycine (10 mg/mL)	-
21	7.0	Glycine (5 mg/mL)	-

Table 5: T_m studies

The T_m values in this example were measured using nano differential scanning fluorimetry (nDSF) assays. nDSF uses the intrinsic tryptophan and tyrosine fluorescence to monitor protein unfolding. The nDSF assay was 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 protein 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.

Compositions 1-21 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 was then measured straight away, and after 1 week's storage at 25 °C and 1 weeks' storage at 40 °C, at extreme storage conditions, i.e. 2 weeks' storage at 25 °C, and 2 weeks' storage at 40 °C. The pH of the aqueous compositions was remeasured immediately before the T_m values were measured. The results are shown in Figure 2, Figure 2A, Figure 2B, and Figure 2C.

Example 6a – Melting temperature studies

This example compares the T_m of rHuPH20 in various compositions, each having a different combination of excipients and/or pH.

A composition (composition G) 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 22-44 were prepared by adding the component(s) shown in Table 6 below to composition G, and the pH was adjusted to 6.0, 6.5, or 7.0 by varying the amount of the sodium hydroxide in the composition.

Composition	Additional component	pH	T_m / °C
22	-	6.5	48.44
23	-	7	47.6
24	Glycine (10 mg/mL)	6	48.79
25	Glycine (10 mg/mL)	6.5	47.83
26	Glycine (10 mg/mL)	7	46.99
27	Glycine (25 mg/mL)	6	49.74

Composition	Additional component	pH	T_m / °C
28	Glycine (25 mg/mL)	6.5	47.47
29	Glycine (25 mg/mL)	7	47.07
30	Histidine (10 mg/mL)	6	50.64
31	Histidine (10 mg/mL)	6.5	47.45
32	Histidine (10 mg/mL)	7	49.73
33	Arginine (10 mg/mL)	6	52.47
34	Arginine (10 mg/mL)	6.5	52.7
35	Arginine (10 mg/mL)	7	51.76
36	Mannitol (50 mg/mL)	6	48.87
37	Mannitol (50 mg/mL)	6.5	47.71
38	Mannitol (50 mg/mL)	7	48.23
39	Sucrose (50 mg/mL)	6	50.27
40	Sucrose (50 mg/mL)	6.5	48.41
41	Sucrose (50 mg/mL)	7	46.79
42	Sodium CMC (25 mg/mL)	6	54.1
43	Sodium CMC (25 mg/mL)	6.5	54.06
44	Sodium CMC (25 mg/mL)	7	50.41

Table 6: T_m studies

Compositions 22-44 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 rHuPH20 was then measured immediately for each composition using the method described in Example 5.

The results, which are shown in Table 6 and Figure 3.

Example 6b – Melting temperature studies 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 the enzyme (rHuPH20), and the fluorophore in the ground state is excited to a higher energy state, thereby resulting in emission. For an enzyme such as rHuPH20, the fluorescence of tryptophan may be used to measure a change in tertiary enzyme structure during or after storage under different conditions, and thus quantify the thermal stability of the rHuPH20. The maximum emission wavelengths for folded and unfolded rHuPH20 are 330 nm and 350 nm, respectively.

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 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 7, below.

Composition	**Additional component**	**pH**	**Slope 350 nm / 330 nm**
22	-	6.5	
23	-	7	
24	Glycine (10 mg/mL)	6	0.004300
25	Glycine (10 mg/mL)	6.5	0.005389
26	Glycine (10 mg/mL)	7	0.006196
27	Glycine (25 mg/mL)	6	0.001013
28	Glycine (25 mg/mL)	6.5	0.004787
29	Glycine (25 mg/mL)	7	0.002456
30	Histidine (10 mg/mL)	6	0.004556
31	Histidine (10 mg/mL)	6.5	0.005702
32	Histidine (10 mg/mL)	7	0.004277
33	Arginine (10 mg/mL)	6	0.002788
34	Arginine (10 mg/mL)	6.5	0.001392
35	Arginine (10 mg/mL)	7	0.002748

Composition	Additional component	pH	Slope 350 nm / 330 nm
36	Mannitol (50 mg/mL)	6	0.004070
37	Mannitol (50 mg/mL)	6.5	0.005511
38	Mannitol (50 mg/mL)	7	0.005598
39	Sucrose (50 mg/mL)	6	0.001455
40	Sucrose (50 mg/mL)	6.5	0.002963
41	Sucrose (50 mg/mL)	7	0.006229
42	Sodium CMC (25 mg/mL)	6	–0.00035
43	Sodium CMC (25 mg/mL)	6.5	0.001466
44	Sodium CMC (25 mg/mL)	7	0.003267

Table 7: Slope of the ratio between 350 nm / 330 nm versus time

Example 7 – Melting temperature studies under different storage conditions

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

A composition F was prepared as in Example 5. Compositions 45-57 were then prepared by omitting the glucose monohydrate (19.25 mg/mL) and adding the component(s) as shown in Table 8 to composition F, 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
45	Sucrose (100 mg/mL)	-	48.31	0.05	-	-
46	Mannitol (50 mg/mL)	-	47.65	0.26	-	-
47	Glucose (50 mg/mL)	-	47.65	0.09	-	-
48	Arginine (5 mg/mL)	-	54.99	0.06	54.93	0.01
49	Arginine (25 mg/mL)	-	52.74	0.07	52.91	0.15
50	Sucrose (100 mg/mL)	Glycine (1 mg/mL)	48.62	0.14	-	-
51	Sucrose (100 mg/mL)	Glycine (5 mg/mL)	48.86	0.05	-	-
52	Sucrose (100 mg/mL)	Arginine (5 mg/mL)	53.67	0.04	53.72	0.09
53	Sucrose (100 mg/mL)	Sodium CMC (10 mg/mL)	54.86	0.04	55.28	0.25
54	Mannitol (50 mg/mL)	Glycine (5 mg/mL)	48.13	0.15	-	-
55	Mannitol (50 mg/mL)	Arginine (5 mg/mL)	53.03	0.09	53.11	0.16
56	Mannitol (50 mg/mL)	Sodium CMC (5 mg/mL)	54.38	0.05	54.54	0.12

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
57	Mannitol (50 mg/mL)	Sodium CMC (10 mg/mL)	54.06	0.05	54.18	0.07

Table 8: T_m under different storage conditions

Compositions 45-57 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 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 pH of the aqueous compositions was remeasured immediately before the T_m values were measured.

The results are shown in Table 8 and Figure 4 and Figure 4A. Where a T_m value at t = 1 week at 40 °C is not displayed (i.e. "–" for Tm and its SD), the rHuPH20 had decomposed.

Example 8 – Sodium CMC concentration

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

A composition H 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 6.0)
- Mannitol (50 mg/mL) or sucrose (100 mg/mL)
- Water for injection (q.s. ad 1 mL)

Compositions 58-63 were then prepared by adding sodium CMC shown in Table 9 below to the above composition H, 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
58	5	Mannitol (50 mg/mL)
59	5	Sucrose (100 mg/mL)
60	10	Mannitol (50 mg/mL)
61	10	Sucrose (100 mg/mL)
62	15	Mannitol (50 mg/mL)
63	15	Sucrose (100 mg/mL)

Table 9: Sodium CMC concentration

Compositions 58-63 were prepared as set out above and then stored in a refrigerator at 5 °C for between 2 days and 2 weeks. T_m values were then measured using the method described in Example 5.

The results are shown in Figure 5.

Example 9 – Enzyme stability

This example compares the stability of rHuPH20 in various compositions under stress test conditions.

Compositions A-E including rilpivirine nanoparticles were prepared as in Example 1.

The compositions were stored under conditions of 5 °C or 25 °C/60% RH for 6 months. Enzyme 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 10.

Composition	Temperature (°C)	Activity loss (%)	SEC (µg/mL)	RP-LC Ox2* (Area%)
A	25	NA	ND	ND
	5	35	21.3	16.1
B	25	NA[2]	8.5	74.0
	5	24	21.6	12.0
C	25	85	7.9	77.9
	5	-7	24.6	27.0
D	25	80	18.4	86.6
	5	26	24.7	16.8
E	25	26	15.8	29.4
	5	NA[2]	20.7	16
NA = No reportables from the bioassay analysis ([2] = Limited number of reportables) ND = Not detectable				

*Ox2 is an oxidised form of rHuPH20. Ox2 is less active than rHuPH20.

Table 10: 6 Month Stability Data comparing Bioassay, SEC and RP (Ox2) Results

Example 10 – Enzyme stability studies under different storage conditions

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

Aqueous compositions 45-57, as described in Example 7 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 11, 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)
52	9126	6871	0.753	6091	4993	0.820	3035	1878	0.067
48	6036	4524	0.750	4084	3345	0.819	1952	1179	0.070
49	7139	5365	0.752	4927	3953	0.802	2212	1412	0.051
55	4983	3748	0.752	3563	2895	0.813	1420	853	0.060
47	5545	4226	0.762	4412	3565	0.808	1133	661	0.046
46	4997	3834	0.767	4134	3343	0.809	863	491	0.041
45	5314	4045	0.761	4333	3548	0.819	981	497	0.058
50	4615	3586	0.777	3883	3147	0.810	732	439	0.033
51	5175	3942	0.762	4334	3502	0.808	841	440	0.046
53	6991	5403	0.773	5344	4467	0.836	1647	936	0.063
54	7458	5662	0.759	5654	4589	0.812	1804	1073	0.052
56	4276	3330	0.779	3262	2728	0.836	1014	602	0.058
57	3727	2944	0.790	2947	2494	0.846	780	450	0.056

Table 11: Slope of the ratio between 350 nm / 330 nm versus time

Example 11 – 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 64-149 were then prepared by adding the component(s) as shown in Table 12, 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
64	Sucrose (100 mg/mL)	Glycine (1 mg/mL)	48.52	0.05	N/A**	N/A**
65	Sucrose (100 mg/mL)	Glycine (3 mg/mL)	48.61	0.03	N/A**	N/A**
66	Sucrose (100 mg/mL)	Glycine (5 mg/mL)	48.64	0.01	N/A**	N/A**
67	Sucrose (100 mg/mL)	Glycine (7 mg/mL)	48.75	0.07	N/A**	N/A**
68	Sucrose (100 mg/mL)	Glycine (9 mg/mL)	48.98	0.1	N/A**	N/A**
69	Sucrose (100 mg/mL)	Glycine (11 mg/mL)	48.93	0.1	N/A**	N/A**
70	Sucrose (100 mg/mL)	Glycine (13 mg/mL)	49.14	0.1	N/A**	N/A**
71	Sucrose (100 mg/mL)	Glycine (15 mg/mL)	49.25	0.07	N/A**	N/A**
72	Sucrose (100 mg/mL)	Glycine (17 mg/mL)	49.16	0.05	N/A**	N/A**
73	Sucrose (100 mg/mL)	Glycine (19 mg/mL)	49.45	0.05	N/A**	N/A**
74	Sucrose (100 mg/mL)	Glycine (21 mg/mL)	49.44	0.06	N/A**	N/A**
75	Sucrose (100 mg/mL)	Glycine (23 mg/mL)	49.71	0.08	N/A**	N/A**
76	Sucrose (100 mg/mL)	Glycine (25 mg/mL)	49.54	0.15	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
77	Mannitol (50 mg/mL)	Glycine (1 mg/mL)	48.16	0.03	N/A**	N/A**
78	Mannitol (50 mg/mL)	Glycine (3 mg/mL)	47.95	0.11	N/A**	N/A**
79	Mannitol (50 mg/mL)	Glycine (5 mg/mL)	48.12	0.05	N/A**	N/A**
80	Mannitol (50 mg/mL)	Glycine (7 mg/mL)	48.41	0.38	N/A**	N/A**
81	Mannitol (50 mg/mL)	Glycine (9 mg/mL)	48.56	0.03	N/A**	N/A**
82	Mannitol (50 mg/mL)	Glycine (11 mg/mL)	48.28	0.04	N/A**	N/A**
83	Mannitol (50 mg/mL)	Glycine (13 mg/mL)	48.37	0.08	N/A**	N/A**
84	Mannitol (50 mg/mL)	Glycine (15 mg/mL)	48.45	0.06	N/A**	N/A**
85	Mannitol (50 mg/mL)	Glycine (17 mg/mL)	48.42	0.04	N/A**	N/A**
86	Mannitol (50 mg/mL)	Glycine (19 mg/mL)	48.69	0.07	N/A**	N/A**
87	Mannitol (50 mg/mL)	Glycine (21 mg/mL)	48.83	0.02	N/A**	N/A**
88	Mannitol (50 mg/mL)	Glycine (23 mg/mL)	48.91	0.02	N/A**	N/A**
89	Mannitol (50 mg/mL)	Glycine (25 mg/mL)	48.93	0.09	N/A**	N/A**
90	Mannitol (50 mg/mL)	Sodium CMC (5 mg/mL)	53.93	0.04	54.51	0.23
91	Mannitol (50 mg/mL)	Sodium CMC (10 mg/mL)	53.64	0.07	54.39	0.42

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
92	Mannitol (50 mg/mL)	Sodium CMC (15 mg/mL)	53.4	0.02	54.19	0.29
93	Mannitol (50 mg/mL)	Sodium CMC (20 mg/mL)	N/A*	N/A*	53.49	0.26
94	Sucrose (100 mg/mL)	Sodium CMC (5 mg/mL)	54.71	0.01	55.28	0.37
95	Sucrose (100 mg/mL)	Sodium CMC (10 mg/mL)	54.25	0.04	54.94	0.31
96	Sucrose (100 mg/mL)	Sodium CMC (15 mg/mL)	54.01	0.09	54.52	0.4
97	Mannitol (50 mg/mL)	Arginine (5 mg/mL)	41.14	0.05	N/A**	N/A**
98	Mannitol (50 mg/mL)	Arginine (10 mg/mL)	40.3	0.07	N/A**	N/A**
99	Mannitol (50 mg/mL)	Arginine (15 mg/mL)	39.84	0.09	N/A**	N/A**
100	Mannitol (50 mg/mL)	Arginine (20 mg/mL)	39.51	0.09	N/A**	N/A**
101	Mannitol (50 mg/mL)	Arginine (25 mg/mL)	39.69	0.03	N/A**	N/A**
102	Sucrose (100 mg/mL)	Arginine (5 mg/mL)	41.61	0.13	N/A**	N/A**
103	Sucrose (100 mg/mL)	Arginine (10 mg/mL)	40.97	0.12	N/A**	N/A**
104	Sucrose (100 mg/mL)	Arginine (15 mg/mL)	40.53	0.06	N/A**	N/A**
105	Sucrose (100 mg/mL)	Arginine (20 mg/mL)	40.38	0.04	N/A**	N/A**
106	Sucrose (100 mg/mL)	Arginine (25 mg/mL)	40.15	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
107	Glucose (50 mg/mL)	-	47.41	0.04	N/A**	N/A**
108	Sucrose (100 mg/mL)	-	48.46	0.15	N/A**	N/A**
109	Glucose (50 mg/mL)	Sodium CMC (5 mg/mL)	53.82	0.02	54.41	0.1
110	Glucose (50 mg/mL)	Sodium CMC (10 mg/mL)	53.57	0.06	54.24	0.08
111	Glucose (50 mg/mL)	Sodium CMC (15 mg/mL)	53.27	0.23	53.88	0.13
112	Glucose (50 mg/mL)	Glycine (5 mg/mL)	48.03	0.11	N/A**	N/A**
113	Glucose (50 mg/mL)	Glycine (10 mg/mL)	47.78	0.16	N/A**	N/A**
114	Glucose (50 mg/mL)	Glycine (15 mg/mL)	48.81	0.14	N/A**	N/A**
115	Glucose (50 mg/mL)	Glycine (20 mg/mL)	48.17	0.07	N/A**	N/A**
116	Glucose (50 mg/mL)	Glycine (25 mg/mL)	48.3	0.19	N/A**	N/A**
117	Glucose (50 mg/mL)	Arginine (5 mg/mL)	41.61	0.1	N/A**	N/A**
118	Glucose (50 mg/mL)	Arginine (10 mg/mL)	41.33	0.1	N/A**	N/A**
119	Glucose (50 mg/mL)	Arginine (15 mg/mL)	41.29	0.04	N/A**	N/A**
120	Glucose (50 mg/mL)	Arginine (20 mg/mL)	41.1	0.09	N/A**	N/A**
121	Glucose (50 mg/mL)	Arginine (25 mg/mL)	41	0.13	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
122	Glucose (50 mg/mL)	Histidine (5 mg/mL)	46.72	0.06	N/A**	N/A**
123	Glucose (50 mg/mL)	Histidine (10 mg/mL)	46.18	0.03	N/A**	N/A**
124	Glucose (50 mg/mL)	Histidine (15 mg/mL)	46.15	0.05	N/A**	N/A**
125	Glucose (50 mg/mL)	Histidine (20 mg/mL)	45.57	0.08	N/A**	N/A**
126	Glucose (50 mg/mL)	Histidine (25 mg/mL)	45.48	0.03	N/A**	N/A**
127	-	Glycine (1 mg/mL)	46.94	0.07	N/A**	N/A**
128	-	Glycine (3 mg/mL)	46.91	0.08	N/A**	N/A**
129	-	Glycine (5 mg/mL)	46.99	0.09	N/A**	N/A**
130	-	Glycine (7 mg/mL)	47.17	0.09	N/A**	N/A**
131	-	Glycine (9 mg/mL)	47.2	0.09	N/A**	N/A**
132	-	Glycine (11 mg/mL)	47.18	0.05	N/A**	N/A**
133	-	Glycine (13 mg/mL)	47.72	0.11	N/A**	N/A**
134	-	Glycine (15 mg/mL)	47.28	0.03	N/A**	N/A**
135	-	Glycine (17 mg/mL)	47.34	0.11	N/A**	N/A**
136	-	Glycine (19 mg/mL)	47.58	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
137	-	Glycine (21 mg/mL)	47.41	0.04	N/A**	N/A**
138	-	Glycine (23 mg/mL)	47.52	0.07	N/A**	N/A**
139	-	Glycine (25 mg/mL)	47.61	0.14	N/A**	N/A**
140	-	Sodium CMC (1 mg/mL)	53.87	0.06	54.2	0.38
141	-	Sodium CMC (3 mg/mL)	53.34	0.03	53.96	0.35
142	-	Sodium CMC (5 mg/mL)	53.15	0.01	53.58	0.06
143	-	Sodium CMC (7 mg/mL)	53.22	0.04	53.64	0.3
144	-	Sodium CMC (9 mg/mL)	53	0.06	53.22	0.07
145	-	Sodium CMC (11 mg/mL)	52.84	0.06	53.04	0.07
146	-	Sodium CMC (13 mg/mL)	52.85	0.08	52.93	0.11
147	-	Sodium CMC (15 mg/mL)	52.45	0.05	52.76	0.18
148	-	Sodium CMC (17 mg/mL)	52.31	0.02	52.64	0.07
149	-	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 enzyme was denatured due to the applied temperature stress, or the capillaries could not be loaded to high viscosity

Table 12: T_m under different storage conditions

Compositions 64-149 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 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 12.

Also described herein are the following numbered clauses.

1. An aqueous composition comprising:
(i) rilpivirine or a pharmaceutically acceptable salt thereof;
(ii) a hyaluronidase; and
(iii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of:
(a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or
(b) an amino acid, or a pharmaceutically acceptable salt thereof.

2. The aqueous composition according to clause 1, wherein the rilpivirine is in the form of particles suspended in the aqueous composition.

3. The aqueous composition according to clause 2, wherein the rilpivirine is in the form of microparticles or nanoparticles suspended in the aqueous composition.

4. The aqueous composition according to clause 2 or 3, wherein the particles have a Dv90 of from about 100 nm to about 10 μm.

5. The aqueous composition according to clause 4, wherein the particles have a Dv90 of from about 300 nm to about 6 μm.

6. The aqueous composition according to clause 5, wherein the particles have a Dv90 of from about 300 nm to about 1,600 nm.

7. The aqueous composition according to clause 6, wherein the particles have a Dv90 of from about 450 nm to about 700 nm.

8. The aqueous composition according to clause 7, wherein the particles have a Dv90 of from about 475 nm to about 650 nm, e.g. about 525 to about 644 nm.

9. The aqueous composition according to any one of clauses 2-8, wherein the particles have a Dv10 of from about 75 nm to about 200 nm.

10. The aqueous composition according to any one of clauses 2-9, wherein the particles have a Dv50 of from about 200 nm to about 500 nm.

11. The aqueous composition according to any one of clauses 2-4, wherein the particles have a Dv90 of from about 4 µm to about 6 µm.

12. The aqueous composition according to clause 11, wherein the particles have a Dv90 of about 5 µm to about 6 µm.

13. The aqueous composition according to any one of clauses 2-5 or 11 or 12, 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.

14. The aqueous composition according to any one of the preceding clauses, wherein the aqueous composition comprises from about 200 mg/mL to about 400 mg/mL rilpivirine or a pharmaceutically acceptable salt thereof.

15. The aqueous composition according to clause 14, wherein the aqueous composition comprises from about 250 mg/mL to about 350 mg/mL rilpivirine or a pharmaceutically acceptable salt thereof, e.g. 300 mg/mL.

16. The aqueous composition according to any one of the preceding clauses, wherein the aqueous composition comprises rilpivirine.

17. The aqueous composition according to any one of the preceding clauses, wherein the hyaluronidase is recombinant human hyaluronidase.

18. The aqueous composition according to any one of the preceding clauses, wherein the hyaluronidase is rHuPH20.

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

20. The aqueous composition according to any one of the preceding clauses, wherein the aqueous composition comprises from about 1,750 U/mL to about 2,250 U/mL of the hyaluronidase.

21. The aqueous composition according to clause 20, wherein the aqueous composition comprises about 2,000 U/mL of the hyaluronidase.

22. The aqueous composition according to any one of the preceding clauses, wherein the at least one excipient comprises cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof.

23. The aqueous composition according to clause 22, wherein the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

24. The aqueous composition according to clause 23, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof is sodium carboxymethyl cellulose.

25. The aqueous composition according to clause 23 or 24, wherein the aqueous composition comprises from about 0.1 mg/mL to about 50 mg/mL carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

26. The aqueous composition according to clause 25, wherein the aqueous composition comprises from about 0.1 mg/mL to about 10 mg/mL carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

27. The aqueous composition according to clause 26, wherein the aqueous composition comprises from about 1 mg/mL to about 5 mg/mL carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

28. The aqueous composition according to clause 27, wherein the aqueous composition comprises from about 1 mg/mL to about 3 mg/mL carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

29. The aqueous composition according to clause 26, wherein the aqueous composition comprises about 1 mg/mL carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

30. The aqueous composition according to clause 28, wherein the aqueous composition comprises about 3 mg/mL carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

31. The aqueous composition according to any one of clauses 22-30, wherein the aqueous composition comprises from about 0.01 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase to about 0.25 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

32. The aqueous composition according to clause 31, wherein the aqueous composition comprises from about 0.05 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase to about 0.15 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

33. The aqueous composition according to clause 31, wherein the aqueous composition comprises from about 0.02 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase to about 0.1 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

34. The aqueous composition according to clause 33, wherein the aqueous composition comprises from about 0.03 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase to about 0.07 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

35. The aqueous composition according to any one of the preceding clauses, wherein the at least one excipient comprises an amino acid or a pharmaceutically acceptable salt thereof.

36. The aqueous composition according to clause 33, wherein the aqueous composition comprises about 5 to about 60 mg/mL amino acid or a pharmaceutically acceptable salt thereof.

37. The aqueous composition according to clause 36, wherein the aqueous composition comprises about 15 to about 25 mg/mL amino acid or a pharmaceutically acceptable salt thereof.

38. The aqueous composition according to any one of clauses 35-37, wherein the amino acid is selected from glycine and arginine, pharmaceutically acceptable salts thereof, and combinations thereof.

39. The aqueous composition according to clause 38, wherein the amino acid is glycine.

40. The aqueous composition according to any one of clause 39, wherein the aqueous composition comprises from about 5 to about 20 mg/mL glycine.

41. The aqueous composition according to clause 38, wherein the aqueous composition comprises about 10 to about 15 mg/mL glycine.

42. The aqueous composition according to clause 41, wherein the aqueous composition comprises about 13 mg/mL glycine.

43. The aqueous composition according to any one of clauses 35-38, wherein the amino acid is arginine or arginine hydrochloride.

44. The aqueous composition according to clause 43, wherein the aqueous composition comprises from about 5 to about 50 mg/mL arginine or arginine hydrochloride.

45. The aqueous composition according to clause 44, wherein the aqueous composition comprises about 15 to about 25 mg/mL arginine or arginine hydrochloride.

46. The aqueous composition according to clause 45, wherein the aqueous composition comprises about 21 mg/mL arginine or arginine hydrochloride.

47. The aqueous composition according to clause 43, wherein the amino acid is arginine hydrochloride.

48. The aqueous composition according to clause 47, wherein the aqueous composition comprises from about 5 to about 50 mg/mL arginine hydrochloride.

49. The aqueous composition according to clause 48, wherein the aqueous composition comprises about 15 to about 25 mg/mL arginine hydrochloride.

50. The aqueous composition according to clause 49, wherein the aqueous composition comprises about 20 mg/mL arginine hydrochloride.

51. The aqueous composition according to any of the preceding claims, wherein the at least one excipient additionally comprises a sugar or sugar alcohol.

52. The aqueous composition according to clause 51, wherein the aqueous composition comprises from about 10 to about 100 mg/mL sugar or sugar alcohol.

53. The aqueous composition according to clause 52, wherein the aqueous composition comprises from about 45 to about 55 mg/mL sugar or sugar alcohol.

54. The aqueous composition according to clause 53, wherein the aqueous composition comprises about 50 mg/mL sugar or sugar alcohol.

55. The aqueous composition according to any one of clauses 51-54, wherein the sugar or sugar alcohol is selected from glucose and sucrose and combinations thereof.

56. The aqueous composition according to clause 55, wherein the sugar or sugar alcohol is sucrose.

57. The aqueous composition according to clause 56, wherein the aqueous composition comprises from about 10 to about 100 mg/mL sucrose.

58. The aqueous composition according to clause 57, wherein the aqueous composition comprises from about 40 to about 70 mg/mL sucrose.

59. The aqueous composition according to clause 58, wherein the aqueous composition comprises about 57 mg/mL sucrose.

60. The aqueous composition according to clause 58, wherein the aqueous composition comprises about 50 mg/mL sucrose.

61. The aqueous composition according to clause 55, wherein the sugar or sugar alcohol is glucose.

62. The aqueous composition according to clause 61, wherein the aqueous composition comprises from about 1 to about 100 mg/mL glucose.

63. The aqueous composition according to clause 62, wherein the aqueous composition comprises from about 10 to about 30 mg/mL glucose.

64. The aqueous composition according to clause 63, wherein the aqueous composition comprises about 17 mg/mL glucose.

65. The aqueous composition according to any one of clauses 1-54 and 56-60, wherein the aqueous composition comprises substantially no glucose, for example less than 10% w/w glucose, preferably less than 1 % w/w glucose.

66. The aqueous composition according to any one of clauses 1-65, wherein the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) in the aqueous composition is from about 50:1 (w/w) to about 400:1 (w/w), or wherein the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to (b) in the aqueous composition is from about 10:1 (w/w) to about 20:1 (w/w).

67. The aqueous composition according to any one of clauses 1-65, wherein the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) in the aqueous composition is from about 200:1 (w/w) to about 400:1 (w/w) or wherein the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to (b) in the aqueous composition is from about 2:1 (w/w) to about 30:1 (w/w).

68. The aqueous composition according to clause 67, wherein the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) in the aqueous composition is from about 250:1 (w/w) to about 350:1 (w/w) or wherein the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to (b) in the aqueous composition is from about 3:1 (w/w) to about 20:1 (w/w).

69. The aqueous composition according to any one of clauses 1-65, wherein the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) or (b) in the aqueous composition is from about 5:1 (w/w) to about 16:1 (w/w).

70. The aqueous composition according to any one of clauses 1-65, wherein the ratio of rilpivirine or a pharmaceutically acceptable salt thereof to excipient (a) or (b) in the aqueous composition is from about 10:1 (w/w) to about 400:1 (w/w).

71. The aqueous composition according to any one of clauses 52-65, when dependent on any one of clauses 22-34, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:2 (w/w) to about 1:1000 (w/w).

72. The aqueous composition according to any one of clauses 52-65, when dependent on any one of clauses 22-34, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:2 (w/w) to about 1:200 (w/w).

73. The aqueous composition according to clause 72, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:2 (w/w) to about 1:100 (w/w).

74. The aqueous composition according to clause 73, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:10 (w/w) to about 1:100 (w/w).

75. The aqueous composition according to clause 74, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:15 (w/w) to about 1:60 (w/w).

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

77. The aqueous composition according to clause 76, when dependent on clause 2, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the weight by weight ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is more than or about 10:1, e.g. from about 10:1 to about 20:1.

78. The aqueous composition according to clause 76, when dependent on clause 2, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of

less than or about 1600 nm the weight by weight ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is about 15:1.

79. The aqueous composition according to clause 76, when dependent on clause 2, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the weight by weight ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is about 10:1.

80. The aqueous composition according to clause 76, when dependent on clause 2, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof has a Dv90 of less than or about 1600 nm the weight by weight ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is less than or about 10:1.

81. The aqueous composition according to clause 76, when dependent on clause 2, wherein when the rilpivirine or a pharmaceutically acceptable salt thereof 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 the weight by weight ratio of rilpivirine or a pharmaceutically acceptable salt thereof to poloxamer is less than about 10:1.

82. The aqueous composition according to any one of clauses 1-81, wherein the aqueous composition additionally comprises one or more of: a poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

83. The aqueous composition according any one of clauses 1-81, wherein the aqueous composition additionally comprises a poloxamer, sodium dihydrogen phosphate, citric acid, and sodium hydroxide.

84. The aqueous composition according to any one of clauses 1-81, wherein the aqueous composition additionally comprises poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, and sodium hydroxide.

85. The aqueous composition according to any one of the clauses 76-84, wherein the aqueous composition comprises from about 15 mg/mL to about 35 mg/mL of a poloxamer.

86. The aqueous composition according to any one of the clauses 76-84, wherein the aqueous composition comprises from about 20 mg/mL to about 30 mg/mL of a poloxamer.

87. The aqueous composition according to any one of the clauses 76-84, wherein the aqueous composition comprises from about 40 mg/mL to about 60 mg/mL of a poloxamer.

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

89. The aqueous composition according to clause 88, 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.

90. The solid composition according any one of the preceding clauses, wherein the aqueous composition does not comprise glucose, for example it does not comprise glucose monohydrate.

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

92. The aqueous composition according to clause 91, wherein the aqueous composition has a pH of from about 6 to about 7.

93. The aqueous composition according to clause 92, wherein the aqueous composition has a pH of from about 6 to about 6.5.

94. The aqueous composition according to clause 93, wherein the aqueous composition has a pH of about 6.

95. The aqueous composition according to any one of clauses 2-94, wherein the Dv10, Dv50, and Dv90 of the particles do not increase by more than about 30% after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

96. The aqueous composition according to clause 95, wherein the Dv10, Dv50, and Dv90 of the particles do not increase by more than about 20% after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

97. The aqueous composition according to clause 95, wherein the Dv10, Dv50, and Dv90 of the particles do not increase by more than about 10% after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

98. The aqueous composition according to clause 95, wherein the Dv10, Dv50, and Dv90 of the particles do not increase by more than about 50% after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 25 °C.

99. The aqueous composition according to clause 95, wherein the Dv10, Dv50, and Dv90 of the particles do not increase by more than about 20% after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 25 °C.

100. The aqueous composition according to any one of the preceding clauses, wherein hyaluronidase activity remains at least 25% of the original activity, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

101. The aqueous composition according to clause 100 wherein hyaluronidase activity remains at least 25% of the original activity, after storage of the aqueous composition for about 24 months at about 5 °C.

102. The aqueous composition according to clause 100 wherein hyaluronidase activity remains at least 25% of the original activity, after storage of the aqueous composition for about 18 months at about 5 °C.

103. The aqueous composition according to any one of the preceding clauses, wherein hyaluronidase activity remains at least 50% of the original activity, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C or about 25 °C.

104.The aqueous composition according to clause 103 wherein hyaluronidase activity remains at least 50% of the original activity, after storage of the aqueous composition for about 24 months at about 5 °C or about 25 °C.

105. The aqueous composition according to clause 104 wherein hyaluronidase activity remains at least 50% of the original activity, after storage of the aqueous composition for about 24 months at about 5 °C.

106. The aqueous composition according to clause 103 wherein hyaluronidase activity remains at least 50% of the original activity, after storage of the aqueous composition for about 18 months at about 5 °C.

107.The aqueous composition according to clause 103 wherein hyaluronidase activity remains at least 75% of the original activity, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

108.The aqueous composition according to clause 103 wherein hyaluronidase activity remains at least 75% of the original activity, after storage of the aqueous composition for about 24 months at about 5 °C.

109. The aqueous composition according to clause 103 wherein hyaluronidase activity remains at least 75% of the original activity, after storage of the aqueous composition for about 18 months at about 5 °C.

110. The aqueous composition according to any one of the preceding clauses, wherein hyaluronidase concentration remains at least 25% of the original concentration after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C, wherein the concentration is determined by size exclusion chromatography.

111. The aqueous composition according to clause 110, wherein hyaluronidase concentration remains at least 50% of the original concentration after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C, wherein the concentration is determined by size exclusion chromatography.

112.The aqueous composition according to any one of the preceding clauses, wherein less than 50% of the original hyaluronidase is degraded to degradants after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

113. The aqueous composition according to clause 112, wherein less than 20% of the original hyaluronidase is degraded to degradants after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

114.Use of:
(a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or
(b) an amino acid or a pharmaceutically acceptable salt thereof,
in a method of stabilising an aqueous composition, wherein the method comprises the step of preparing an aqueous composition comprising:
(i) rilpivirine or a pharmaceutically acceptable salt thereof;
(ii) a hyaluronidase; and
(iii) 0.001-100 mg/mL of (a) and/or (b).

115. The use of clause 114, wherein the aqueous composition is as defined in any one of clauses 1-113.

116. The use of clause 114 or clause 115, wherein the stabilisation is maintaining hyaluronidase activity over time, for example, about 6, about 12, about 18, or about 24 months.

117. The use of clause 114 or clause 115, wherein the stabilisation is maintaining hyaluronidase concentration over time, for example, about 6, about 12, about 18, or about 24 months.

118. The use of clause 114 or clause 115, wherein the stabilisation is reducing the presence of hyaluronidase degradants, for example, about 6, about 12, about 18, or about 24 months.

119. The use of one of clauses 114-118, wherein the stabilisation is reducing changes in particle size distribution of rilpivirine microparticles or nanoparticles over time, for example, about 6, about 12, about 18, or about 24 months.

120. A method of stabilising an aqueous composition comprising:
(i) rilpivirine or a pharmaceutically acceptable salt thereof; and
(ii) a hyaluronidase,
the method comprising combining components (i) and (ii) with 0.001-100 mg/mL of at least one excipient selected from the group consisting of: (a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or (b) an amino acid or a pharmaceutically acceptable salt thereof.

121. A method for the treatment or prevention of HIV infection in a subject, the method comprising administering to the subject the aqueous composition as defined in any one of clauses 1-113, in particular for the treatment of HIV infection in a subject.

122. An aqueous composition as defined in any one of clauses 1-113 for use in the treatment or prevention of HIV infection in a subject, in particular for the treatment of HIV infection in a subject.

123. Use of a aqueous composition as defined in any one of clauses 1-113 for the manufacture of a medicament for treating or preventing HIV infection in a subject, in particular for treating of HIV infection in a subject.

124. The method, the aqueous composition for use or the use according to clauses 121, 122, or 123, wherein the aqueous composition is administered to the subject by intramuscular injection or subcutaneous injection.

125. The method, the aqueous composition for use or the use according to clause 124, wherein the aqueous composition is administered to the subject by intramuscular injection.

126. The method, the aqueous composition for use or the use according to clause 124, wherein the aqueous composition is administered to the subject by subcutaneous injection.

127. The method, the aqueous composition for use or the use according to any one of clauses 121-126, wherein the aqueous composition is administered to the subject intermittently at a time interval of about three months to about two years.

128. The method, the aqueous composition for use or the use according to clause 127, wherein the time interval is about three months to about one year.

129. The method, the aqueous composition for use or the use according to clause 110, wherein the time interval is about three months to about six months.

130. The method, the aqueous composition for use or the use according to clause 113, wherein the time interval is about six months to about one year.

131. The method, the aqueous composition for use or the use according to clause 129 or 130, wherein the time interval is about six months.

132. The method, the aqueous composition for use or the use according to any one of clauses 121-131, wherein the HIV infection is HIV type 1 (HIV-1) infection.

133. The method, the aqueous composition for use or the use according to any one of clauses 121-132, wherein the subject is a human.

Claims

1. An aqueous composition comprising: (i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of:

(a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or

(b) an amino acid, or a pharmaceutically acceptable salt thereof.

2. The aqueous composition according to claim 1, wherein the rilpivirine is in the form of particles suspended in the aqueous composition.

3. The aqueous composition according to claim 2, wherein the rilpivirine is in the form of microparticles or nanoparticles suspended in the aqueous composition.

4. The aqueous composition according to any one of claims 1-3, wherein the hyaluronidase is rHuPH20.

5. The aqueous composition according to any of the preceding claims, wherein the at least one excipient comprises cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof.

6. The aqueous composition according to claim 5, wherein the cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof is carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

7. The aqueous composition according to claim 6, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof is sodium carboxymethyl cellulose.

8. The aqueous composition according to any one of claims 5-7, wherein the aqueous composition comprises from about 0.1 mg/mL to about 50 mg/mL carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

9. The aqueous composition according to claim 8, wherein the aqueous composition comprises from about 1 mg/mL to about 5 mg/mL carboxymethyl cellulose or a pharmaceutically acceptable salt thereof.

10. The aqueous composition according to any one of claims 5-9, wherein the aqueous composition comprises from about 0.01 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase to about 0.25 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

11. The aqueous composition according to claim 10, wherein the aqueous composition comprises from about 0.05 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase to about 0.15 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

12. The aqueous composition according to claim 10, wherein the aqueous composition comprises from about 0.02 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase to about 0.1 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

13. The aqueous composition according to claim 12, wherein the aqueous composition comprises from about 0.03 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase to about 0.07 mg carboxymethyl cellulose or a pharmaceutically acceptable salt thereof per 100 U hyaluronidase.

14. The aqueous composition according to any one of claims 8 to 13, wherein the carboxymethyl cellulose or a pharmaceutically acceptable salt thereof is sodium carboxymethyl cellulose.

15. The aqueous composition according to any one of the preceding claims, wherein the at least one excipient comprises an amino acid or a pharmaceutically acceptable salt thereof.

16. The aqueous composition according to claim 15, wherein the amino acid is selected from glycine, arginine, pharmaceutically acceptable salts thereof and combinations thereof.

17. The aqueous composition according to claim 16, wherein the amino acid is glycine.

18. The aqueous composition according to any of the preceding claims, wherein the aqueous composition comprises about 5 to about 60 mg/mL amino acid or a pharmaceutically acceptable salt thereof.

19. The aqueous composition according to any one of claims 15-18, wherein the aqueous composition comprises from about 5 to about 20 mg/mL glycine.

20. The aqueous composition according to claim 19, wherein the aqueous composition comprises about 10 to about 15 mg/mL glycine.

21. The aqueous composition according to claim 20, wherein the aqueous composition comprises about 13 mg/mL glycine.

22. The aqueous composition according to claim 16, wherein the amino acid is arginine or arginine hydrochloride.

23. The aqueous composition according to any of claims 16, and 22, wherein the aqueous composition comprises from about 5 to about 50 mg/mL arginine or arginine hydrochloride.

24. The aqueous composition according to claim 23, wherein the aqueous composition comprises about 15 to about 25 mg/mL arginine or arginine hydrochloride.

25. The aqueous composition according to claim 24, wherein the aqueous composition comprises about 20 mg/mL arginine or arginine hydrochloride.

26. The aqueous composition according to claim 24, wherein the aqueous composition comprises about 21 mg/mL arginine or arginine hydrochloride.

27. The aqueous composition according to any one of claims 22-26, wherein the amino acid is arginine hydrochloride.

28. The aqueous composition according to any of the preceding claims, wherein the at least one excipient additionally comprises a sugar or sugar alcohol.

29. The aqueous composition according to claim 28, wherein the sugar or sugar alcohol is selected from glucose, for example glucose monohydrate, and sucrose and combinations thereof.

30. The aqueous composition according to claim 28, wherein the sugar or sugar alcohol is sucrose.

31. The aqueous composition according to claim 30, wherein the aqueous composition comprises from about 10 to about 100 mg/mL sucrose.

32. The aqueous composition according to claim 31, wherein the aqueous composition comprises from about 40 to about 70 mg/mL sucrose.

33. The aqueous composition according to claim 32, wherein the aqueous composition comprises about 57 mg/mL sucrose.

34. The aqueous composition according to claim 32, wherein the aqueous composition comprises about 50 mg/mL sucrose.

35. The aqueous composition according to any one of claims 28-34, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:2 (w/w) to about 1:200 (w/w).

36. The aqueous composition according to claim 35, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:2 (w/w) to about 1:100 (w/w).

37. The aqueous composition according to claim 36, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:10 (w/w) to about 1:100 (w/w).

38. The aqueous composition according to claim 37, wherein the ratio of cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof to sugar or sugar alcohol is from about 1:15 (w/w) to about 1:60 (w/w).

39. The aqueous composition according any one of the preceding claims, wherein the aqueous composition additionally comprises an antioxidant.

40. The aqueous composition according to any one of the preceding claims, wherein the aqueous composition has a pH of about 6.

41. The aqueous composition according to any one of the preceding claims, wherein the Dv10, Dv50, and Dv90 values of the particles remains within about 20% of the original value, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

42. The aqueous composition according to claim 41, wherein the Dv10, Dv50, and Dv90 values of the particles remains within about 10% of the original value, after storage of the aqueous composition for about 1, about 3, about 6, about 12, about 18, or about 24 months at about 5 °C.

43. The aqueous composition according to any one of the preceding claims, which maintains hyaluronidase activity over a period of time, for example, about 1, about 3, about 6, about 12, about 18, or about 24 months.

44. The aqueous composition according to claim 43 wherein the storage is at about 5 °C or about 25 °C.

45. The aqueous composition according to claim 43 or 44 wherein hyaluronidase activity remains at least 50% of the original activity, after storage of the aqueous composition for about 6, about 12, about 18, or about 24 months at about 5 °C or about 25 °C.

46. An aqueous composition comprising: rilpivirine or a pharmaceutically acceptable salt thereof, sucrose, and sodium carboxymethyl cellulose.

47. The aqueous composition according to claim 46 further comprising a poloxamer.

48. An aqueous composition comprising: rilpivirine or a pharmaceutically acceptable salt thereof, arginine hydrochloride, and sodium carboxymethyl cellulose.

49. The aqueous composition according to claim 48 further comprising a poloxamer.

50. The aqueous composition according to any one of the preceding claims comprising:
rHuPH20;
rilpivirine in the form of particles suspended in the aqueous composition;
sodium CMC; and
sucrose.

51. The aqueous composition according to any one of the preceding claims comprising:
rHuPH20;
rilpivirine in the form of particles suspended in the aqueous composition;
sodium CMC;
sucrose; and
poloxamer 338.

52. The aqueous composition according to any one of the preceding claims comprising:
rHuPH20;
rilpivirine in the form of particles suspended in the aqueous composition;
sodium CMC; and
arginine HCl.

53. The aqueous composition according to any one of the preceding claims comprising:
rHuPH20;
rilpivirine in the form of particles suspended in the aqueous composition;
sodium CMC;
arginine HCl; and
poloxamer 338.

54. The aqueous composition according to any one of claims 1-32 or 34-53 comprising:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 50 mg/mL sucrose; and
about 50 mg/mL poloxamer 338,
wherein the rilpivirine is in the form of particles suspended in the aqueous composition and has a Dv90 of from about 4 µm to about 6 µm.

55. The aqueous composition according to any one of claims 1-32 or 34-53 comprising:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 50 mg/mL sucrose; and
about 50 mg/mL poloxamer 338,
wherein the rilpivirine is in the form of particles suspended in the aqueous composition and has a Dv90 of from about 500 nm to 1 µm.

56. The aqueous composition according to any one of claims 1-32 or 34-53 comprising:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 50 mg/mL sucrose; and
about 20 mg/mL to about 30 mg/mL poloxamer 338,
wherein the rilpivirine is in the form of particles suspended in the aqueous composition and has a Dv90 of from about 500 nm to 1 µm.

57. The aqueous composition according to any one of the claims 1-53 comprising:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 20 mg/mL arginine HCl; and
about 50 mg/mL poloxamer 338,
wherein the rilpivirine is in the form of particles suspended in the aqueous composition and has a Dv90 of from about 4 µm to about 6 µm, e.g. about 6 µm.

58. The aqueous composition according to any one of the claims 1-53 comprising:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 20 mg/mL arginine HCl; and

about 50 mg/mL poloxamer 338,
wherein the rilpivirine is in the form of particles suspended in the aqueous composition and has a Dv90 of from about from about 500 nm to 1 µm.

59. The aqueous composition according to any one of claims 1-53 comprising:
about 2000 U/mL rHuPH20;
about 300 mg/mL rilpivirine in the form of particles suspended in the aqueous composition;
from about 1 mg/mL to about 3 mg/mL sodium CMC;
about 20 mg/mL arginine HCl; and
about 20 mg/mL to about 30 mg/mL poloxamer 338,
wherein the rilpivirine is in the form of particles suspended in the aqueous composition and has a Dv90 of from about 500 nm to 1 µm.

60. Use of (a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or (b) an amino acid or a pharmaceutically acceptable salt thereof, in a method of stabilising an aqueous composition, wherein the method comprises the step of preparing an aqueous composition comprising:
(i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase; and (iii) 0.001-100 mg/mL of (a) and/or (b).

61. The use of claim 60, wherein the aqueous composition is as defined in any of claims 1-59.

62. The use of claim 60 or claim 61, wherein the stabilisation is maintaining hyaluronidase activity over time.

63. The use of claim 60 or claim 61, wherein the stabilisation is maintaining at least 10% of the original hyaluronidase concentration over time, as determined by size exclusion chromatography.

64. The use of claim 60 or claim 61, wherein the stabilisation is less than 20% of the original hyaluronidase being degraded over time.

65. The use of one of claims 60 to 63, wherein the stabilisation is reducing changes in particle size distribution of rilpivirine microparticles or nanoparticles over time.

66. A method of stabilising an aqueous composition comprising:
(i) rilpivirine or a pharmaceutically acceptable salt thereof; (ii) a hyaluronidase;
the method comprising combining components (i) and (ii) with (iii) 0.001-100 mg/mL of at least one excipient selected from the group consisting of: (a) cellulose or a derivative thereof, or a pharmaceutically acceptable salt thereof; and/or (b) an amino acid or a pharmaceutically acceptable salt thereof.

67. A method for the treatment or prevention of HIV infection in a subject, the method comprising administering to the subject the aqueous composition as defined in any one of claims 1-59.

FIG. 1

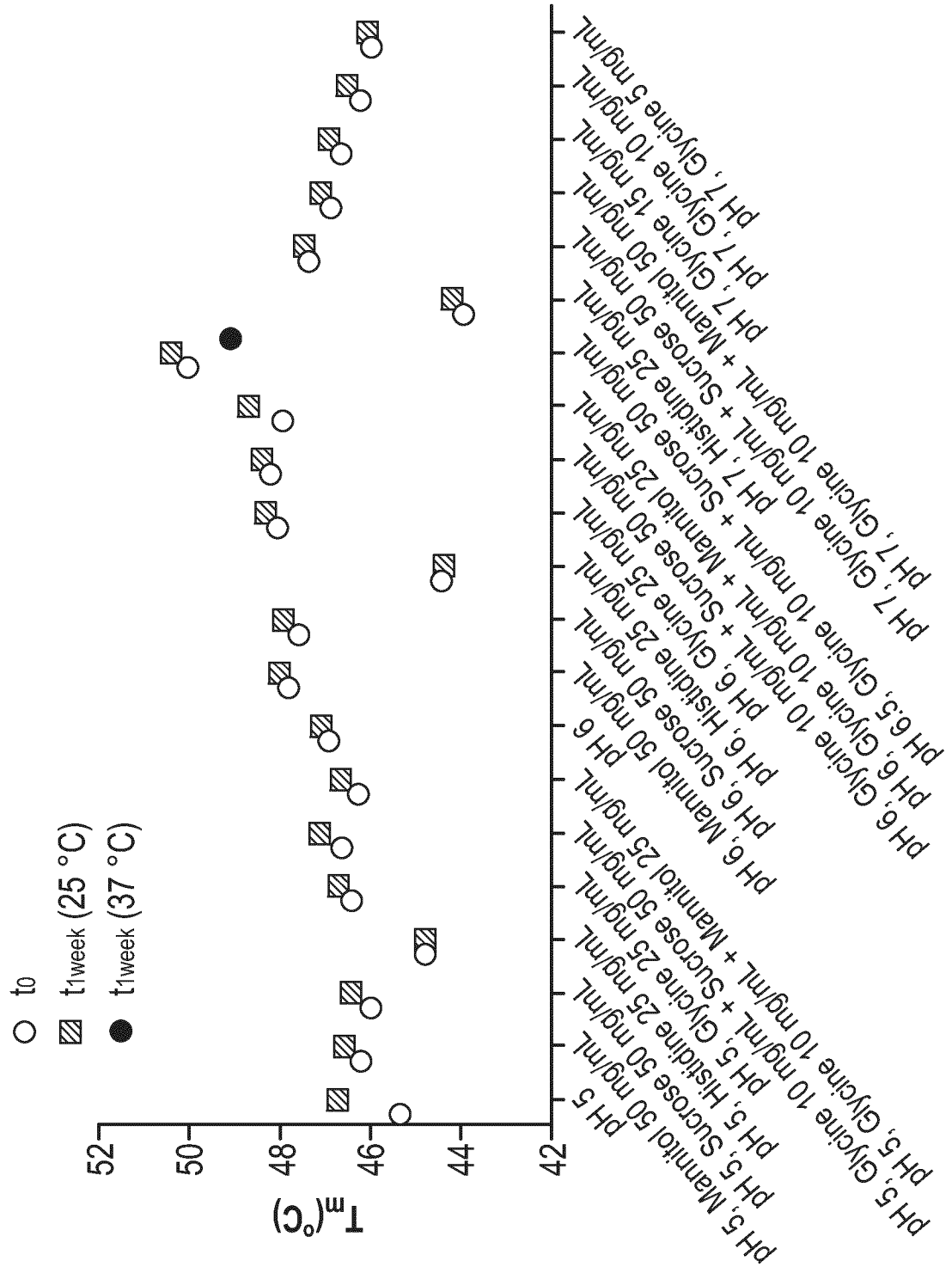
Composition	Storage conditions	Suspension appearance	Resuspendability	Injectability
A	t_0	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The composition passes smoothly through a needle, not within 15 seconds.
	t_{1month} (5 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
	t_{1month} (25 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
	t_{1month} (40 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
B	t_0	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The composition passes smoothly through a needle, not within 15 seconds.
	t_{1month} (5 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.

FIG. 1(contd.)

B(contd.)	t_{1month} (25 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
	t_{1month} (40 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
C	t_0	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The composition passes smoothly through a needle, not within 15 seconds.
	t_{1month} (5 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
	t_{1month} (25 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
	t_{1month} (40 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
D	t_0	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle, not within 15 seconds.

D(contd.)	t_{1month} (5 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
	t_{1month} (25 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
	t_{1month} (40 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
E	t_0	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The composition passes smoothly through a needle, not within 15 seconds.
	t_{1month} (5 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
	t_{1month} (25 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle.
	t_{1month} (40 °C)	White suspension, free from visible foreign material.	Homogeneous suspension after shaking. No visible agglomerates or caking on the container bottom or walls.	The product passes smoothly through a needle, not within 15 seconds.

FIG. 1(contd.)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t1week (25 °C)
t1week (37 °C)
Tm(°C)
52
50
48
46
44
42
pH 5
pH 5, Mannitol 50 mg/mL
pH 5, Sucrose 50 mg/mL
pH 5, Histidine 25 mg/mL
pH 5, Glycine 25 mg/mL
pH 5, Glycine 10 mg/mL + Sucrose 25 mg/mL
pH 5, Glycine 10 mg/mL + Mannitol 25 mg/mL
pH 6
pH 6, Mannitol 50 mg/mL
pH 6, Sucrose 50 mg/mL
pH 6, Histidine 25 mg/mL
pH 6, Glycine 25 mg/mL
pH 6, Glycine 10 mg/mL + Sucrose 25 mg/mL
pH 6, Glycine 10 mg/mL + Mannitol 25 mg/mL
pH 6,5, Glycine 10 mg/mL + Sucrose 50 mg/mL
pH 7, Histidine 50 mg/mL
pH 7, Glycine 10 mg/mL + Sucrose 25 mg/mL
pH 7, Glycine 10 mg/mL + Mannitol 25 mg/mL
pH 7, Glycine 15 mg/mL
pH 7, Glycine 10 mg/mL
pH 7, Glycine 5 mg/mL

FIG. 2

Figure 2A:

Composition	pH	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 25 °C) / °C	T_m (t = 1 week at 25 °C) SD (n = 3) / °C	T_m (t = 2 weeks at 25 °C) / °C	T_m (t = 2 weeks at 25 °C) SD (n = 3) / °C
1	5.0	-	-	45.35	0.11	46.73	0.14	46.50	0.10
2	5.0	Mannitol (50 mg/mL)	-	46.22	0.12	46.59	0.32	46.44	0.20
3	5.0	Sucrose (50 mg/mL)	-	46	0.14	46.43	0.11	46.18	0.05
4	5.0	Histidine (25 mg/mL)	-	44.8	0.06	44.78	0.05	44.70	0.10
5	5.0	Glycine (25 mg/mL)	-	46.42	0.09	46.72	0.19	46.61	0.48
6	5.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	46.64	0.1	47.13	0.31	46.56	0.05
7	5.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)	46.27	0.07	46.66	0.37	46.66	0.10
8	6.0	-	-	46.93	0.01	47.11	0.27	47.08	0.32
9	6.0	Mannitol (50 mg/mL)	-	47.82	0.05	48.36	0.06	48.08	0.26
10	6.0	Sucrose (50 mg/mL)	-	47.6	0.05	47.93	0.33	47.79	0.34
11	6.0	Histidine (25 mg/mL)	-	44.44	0.04	44.38	0.17	44.34	0.24
12	6.0	Glycine (25 mg/mL)	-	48.06	0.02	48.32	0.06	48.08	0.15
13	6.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	48.22	0.04	48.41	0.20	48.25	0.20
14	6.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)	47.95	0.04	48.7	0.14	48.04	0.31
15	6.5	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	50.05	0.03	50.41	0.46	51.02	0.33

16	7.0	Histidine (25 mg/mL)	-	43.95	0.06	44.2	0.32	43.95	0.09
17	7.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	47.36	0.15	47.47	0.19	47.23	0.03
18	7.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)	46.88	0.04	47.11	0.12	47.14	0.18
19	7.0	Glycine (15 mg/mL)	-	46.66	0.05	46.91	0.16	46.67	0.06
20	7.0	Glycine (10 mg/mL)	-	46.23	0.05	46.52	0.00	46.37	0.03
21	7.0	Glycine (5 mg/mL)	-	45.99	0.22	46.07	0.08	45.99	0.06

Fig. 2A (Contd.)

Figure 2B:

Composition	pH	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	T_m (t = 2 weeks at 40 °C) / °C	T_m (t = 2 weeks at 40 °C) SD (n = 3) / °C
1	5.0	-	-	45.35	0.11	N/A*	N/A*	N/A*	N/A*
2	5.0	Mannitol (50 mg/mL)	-	46.22	0.12	N/A*	N/A*	N/A*	N/A*
3	5.0	Sucrose (50 mg/mL)	-	46	0.14	N/A*	N/A*	N/A*	N/A*
4	5.0	Histidine (25 mg/mL)	-	44.8	0.06	N/A*	N/A*	N/A*	N/A*
5	5.0	Glycine (25 mg/mL)	-	46.42	0.09	N/A*	N/A*	N/A*	N/A*
6	5.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	46.64	0.1	N/A*	N/A*	N/A*	N/A*
7	5.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)	46.27	0.07	N/A*	N/A*	N/A*	N/A*
8	6.0	-	-	46.93	0.01	N/A*	N/A*	N/A*	N/A*
9	6.0	Mannitol (50 mg/mL)	-	47.82	0.05	N/A*	N/A*	N/A*	N/A*
10	6.0	Sucrose (50 mg/mL)	-	47.6	0.05	N/A*	N/A*	N/A*	N/A*
11	6.0	Histidine (25 mg/mL)	-	44.44	0.04	N/A*	N/A*	N/A*	N/A*
12	6.0	Glycine (25 mg/mL)	-	48.06	0.02	N/A*	N/A*	N/A*	N/A*
13	6.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	48.22	0.04	N/A*	N/A*	N/A*	N/A*
14	6.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)	47.95	0.04	N/A*	N/A*	N/A*	N/A*
15	6.5	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	50.05	0.03	49.11	0.11	49.34	0.18

16	7.0	Histidine (25 mg/mL)	-	43.95	0.06	N/A*	N/A*	N/A*
17	7.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	47.36	0.15	N/A*	N/A*	N/A*
18	7.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)	46.88	0.04	N/A*	N/A*	N/A*
19	7.0	Glycine (15 mg/mL)	-	46.66	0.05	N/A*	N/A*	N/A*
20	7.0	Glycine (10 mg/mL)	-	46.23	0.05	N/A*	N/A*	N/A*
21	7.0	Glycine (5 mg/mL)	-	45.99	0.22	N/A*	N/A*	N/A*

N/A* = note that no transition in the fluorescence ratio was observed.

Fig. 2B (Contd.)

Figure 2C:

Composition	pH	Additional component 1	Additional component 2	Remeasured pH
1	5.0	-	-	5.41
2	5.0	Mannitol (50 mg/mL)	-	5.36
3	5.0	Sucrose (50 mg/mL)	-	5.38
4	5.0	Histidine (25 mg/mL)	-	7.29
5	5.0	Glycine (25 mg/mL)	-	5.42
6	5.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	5.44
7	5.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)	5.41
8	6.0	-	-	6.21
9	6.0	Mannitol (50 mg/mL)	-	6.17
10	6.0	Sucrose (50 mg/mL)	-	6.15
11	6.0	Histidine (25 mg/mL)	-	7.38
12	6.0	Glycine (25 mg/mL)	-	6.06
13	6.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	6.10
14	6.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)	6.10
15	6.5	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	6.52
16	7.0	Histidine (25 mg/mL)	-	7.48
17	7.0	Glycine (10 mg/mL)	Sucrose (50 mg/mL)	6.59
18	7.0	Glycine (10 mg/mL)	Mannitol (25 mg/mL)	6.62
19	7.0	Glycine (15 mg/mL)	-	6.62
20	7.0	Glycine (10 mg/mL)	-	6.65
21	7.0	Glycine (5 mg/mL)	-	6.68

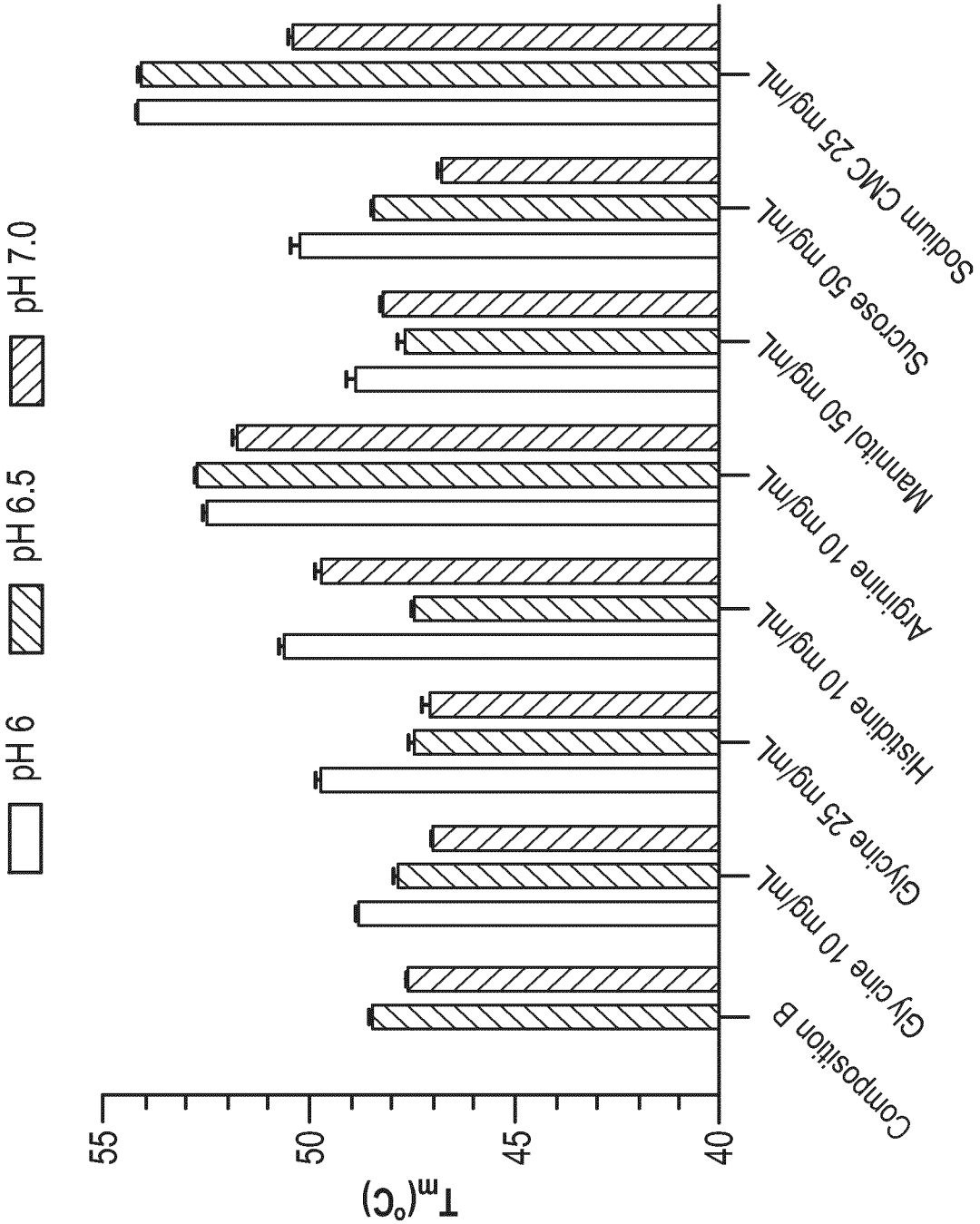
pH 6
pH 6.5
pH 7.0
T_m(°C)
55
50
45
40
Composition B
Gly cine 10 mg/mL
Glycine 25 mg/mL
Histidine 10 mg/mL
Arginine 10 mg/mL
Mannitol 50 mg/mL
Sucrose 50 mg/mL
Sodium CMC 25 mg/mL

FIG. 3

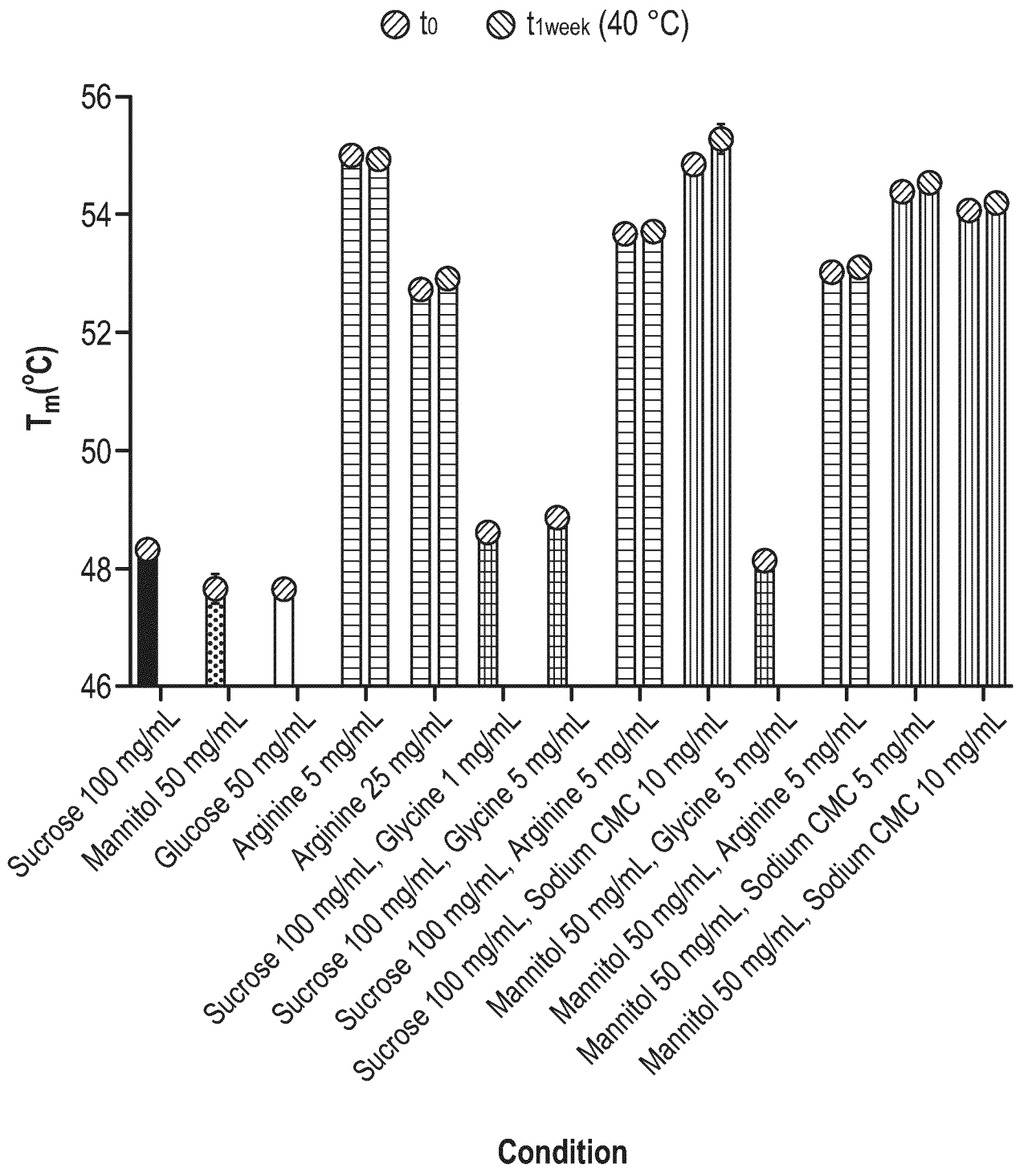
t0
t1week (40 °C)
56
54
52
50
48
46
Tm(°C)
Sucrose 100 mg/mL
Mannitol 50 mg/mL
Glucose 50 mg/mL
Arginine 5 mg/mL
Arginine 25 mg/mL
Sucrose 100 mg/mL, Glycine 1 mg/mL
Sucrose 100 mg/mL, Glycine 5 mg/mL
Sucrose 100 mg/mL, Arginine 5 mg/mL
Sucrose 100 mg/mL, Sodium CMC 10 mg/mL
Mannitol 50 mg/mL, Glycine 5 mg/mL
Mannitol 50 mg/mL, Arginine 5 mg/mL
Mannitol 50 mg/mL, Sodium CMC 5 mg/mL
Mannitol 50 mg/mL, Sodium CMC 10 mg/mL
Condition

FIG. 4

Figure 4A:

Composition	Additional component 1	Additional component 2	Re-measured pH
45	Sucrose (100 mg/mL)	-	6.00
46	Mannitol (50 mg/mL)	-	5.99
47	Glucose (50 mg/mL)	-	6.01
48	Arginine (5 mg/mL)	-	5.77
49	Arginine (25 mg/mL)	-	5.86
50	Sucrose (100 mg/mL)	Glycine (1 mg/mL)	5.99
51	Sucrose (100 mg/mL)	Glycine (5 mg/mL)	5.96
52	Sucrose (100 mg/mL)	Arginine (5 mg/mL)	6.03
53	Sucrose (100 mg/mL)	Sodium CMC (10 mg/mL)	5.93
54	Mannitol (50 mg/mL)	Glycine (5 mg/mL)	5.96
55	Mannitol (50 mg/mL)	Arginine (5 mg/mL)	6.07
56	Mannitol (50 mg/mL)	Sodium CMC (5 mg/mL)	5.96
57	Mannitol (50 mg/mL)	Sodium CMC (10 mg/mL)	5.92

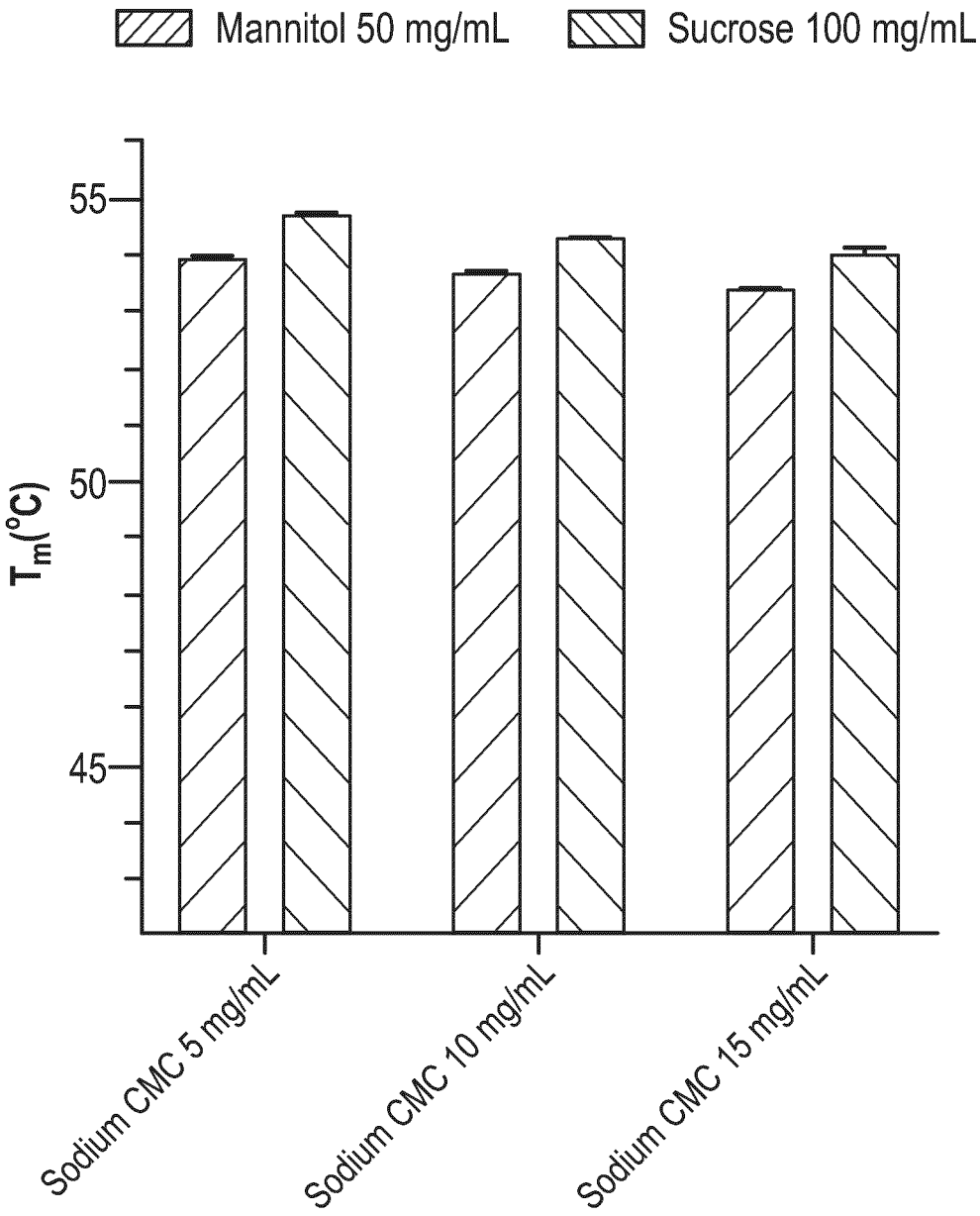
Mannitol 50 mg/mL
Sucrose 100 mg/mL
55
50
45
T_m(°C)
Sodium CMC 5 mg/mL
Sodium CMC 10 mg/mL
Sodium CMC 15 mg/mL

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2023/060689

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/EP2023/060689

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/10 A61K9/00 A61K47/18 A61K47/26 A61K47/38
A61K31/00 A61P31/00
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 A61P

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/147882 A2 (TIBOTEC PHARM LTD [IE]; BAERT LIEVEN ELVIRE COLETTE [BE] ET AL.) 27 December 2007 (2007-12-27) page 1, lines 4-8 page 3, line 32 - page 4, line 2 page 15, lines 36-37 page 16, lines 1-9, 31 page 23; example 1 -----	1-67
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[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
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"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
1 August 2023	09/08/2023

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	Raposo, Antonio

1

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/060689

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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