(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
03 April 2025 (03.04.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/068743 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 9/14* (2006.01)
A61K 9/10 (2006.01) *A61K 47/26* (2006.01)

(21) International Application Number:
PCT/IB2023/059640

(22) International Filing Date:
27 September 2023 (27.09.2023)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: PHARMACEUTICAL COMPOSITION OF CABOTEGRAVIR

(57) **Abstract:** The present invention relates to Human Immunodeficiency Virus (HIV) prevention and treatment. In particular, the invention relates to a pharmaceutical composition comprising: cabotegravir; a wetting agent; a stabilizer; and a tonicity adjuster; wherein cabotegravir is present in the form of particles having a mass median diameter (X50) of between (and including) 2.5 μm and 10 μm.

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PHARMACEUTICAL COMPOSITION OF CABOTEGRAVIR

SEQUENCE LISTING

The instant application contains a Sequence Listing, which has been submitted electronically in computer readable form in XML file format and is hereby incorporated by reference in its entirety. Said XML file, created on 25 September 2023, is named "70392WO01P" and is 7,779 bytes in size.

FIELD OF THE INVENTION

The invention relates to Human Immunodeficiency Virus (HIV) treatment or prevention. In particular, the invention relates to long-acting treatment or prevention of HIV.

BACKGROUND TO THE INVENTION

Patients with HIV infection commonly undergo complex treatment regimens which involve taking multiple pills at regular intervals each day. Patient non-compliance is a known problem accompanying these complex HIV treatment regimens and can lead to the emergence of multiple drug resistant strains of HIV.

The application of long-acting parenteral pharmaceuticals has been established in clinical practice for decades, notably in the areas of contraception, anti-psychotics, and opiate addiction. More recently, long-acting parenteral pharmaceuticals have been proposed as a way of overcoming the non-compliance problem with HIV treatment regimens. Long-acting injectable formulations, some of which are approved and marketed, such as CABENUVA®, have demonstrated prolonged exposures (≥ 30 days) following injection, enabling dosing at once-monthly and bimonthly intervals.

Achieving an injectable suspension with a high concentration of anti-HIV drug in order to dose less frequently and overcome the non-compliance problem with HIV treatment regimens, whilst keeping the same or similar injection volume as previous HIV treatment regimens in order to maintain patient experience, is desirable. Similarly, where an anti-HIV drug may be used for prevention of HIV (*e.g.*, pre-exposure prophylaxis, or PrEP), achieving an injectable suspension with a high concentration of anti-HIV drug that provides a longer-acting effect could increase adherence due to less frequent dosing. Yet high concentration suspensions typically suffer from difficulty in resuspension and particle size growth. Moreover, high concentration suspensions with larger particle sizes (*e.g.*, on micron scale) are more difficult to stabilize in ready-to-use suspensions.

Lyophilized formulations offer several advantages over ready-to-use suspensions – namely, avoiding resuspension difficulties or failures, maintaining product stability, and overcoming scale-up issues.

There is a need in the art for a long-acting injectable to treat or prevent HIV that can be dosed at longer intervals whilst still achieving the same patient experience, minimizing injection-site reactions, and overcoming known difficulties with high-concentration and/or ready-to-use suspensions.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a pharmaceutical composition comprising:

cabotegravir;

a wetting agent;

a stabilizer; and

a tonicity adjuster;

wherein cabotegravir is present in the form of particles having a mass median diameter (X50) of between (and including) 2.5 µm and 10 µm.

According to a second aspect of the invention, there are provided methods for (a) treating HIV in a human in need thereof comprising administering to said human a therapeutically effective amount of the pharmaceutical composition as defined herein; and (b) preventing HIV in a human comprising administering to said human an effective amount of the pharmaceutical composition as defined herein.

According to a third aspect of the invention, there is provided a pharmaceutical composition as defined herein for use in the treatment or prevention of HIV.

According to a further aspect of the invention, there is provided a kit comprising cabotegravir, wherein cabotegravir is present in the form of particles having a mass median diameter (X50) between (and including) 2.5 µm and 10 µm; a wetting agent; a stabilizer; and a tonicity adjuster.

The pharmaceutical compositions of the invention may be advantageous in a number of respects. The pharmaceutical compositions of the invention allow a high concentration of larger-sized cabotegravir particles to be present in the composition. The larger-size particles of the invention, in turn, favorably modify absorption kinetics, thus permitting ultra long-acting therapy, which allows for longer time intervals between dosing compared to existing therapies. This may improve patient compliance, reducing likelihood of drug-resistant HIV strains. Compositions of the invention may also lower injection site reactions therefore improving patient experience. Finally, lyophilized compositions of the invention minimize resuspension failures and maintain product stability and syringeability.

DESCRIPTION OF DRAWINGS/FIGURES

FIGs. 1 and 2 are flowcharts for exemplary processes for manufacturing a lyophilized composition as described herein.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

The term "**alkyl**" refers to a saturated hydrocarbon radical, straight or branched, having the specified number of carbon atoms. For example, the term "C_{1-6} alkyl" refers to an alkyl group having 1 to 6 carbon atoms. Exemplary groups include, but are not limited to, methyl, ethyl, propyl (*n*-propyl and isopropyl), butyl (*n*-butyl, *sec*-butyl, isobutyl and *tert*-butyl), pentyl, and hexyl.

When the term "**alkyl**" is used in combination with other substituent groups, such as "**halo(C_{1-4})alkyl**" and "**hydroxy(C_{1-4})alkyl**" the term "alkyl" is intended to encompass a divalent straight or branched chain hydrocarbon radical, wherein the point of attachment is through the alkyl moiety.

The term "**alkylene**" refers to a divalent radical derived from a straight or branched, saturated hydrocarbon group of, for example, 1 to 3 carbon atoms (C_{1-3} alkylene). Exemplary groups include, but are not limited to, -CH_2-, -CH_2CH_2-, and -$CH_2CH_2CH_2$-.

The term "**cycloalkyl**" refers to a non-aromatic, saturated, monocyclic, hydrocarbon ring containing the specified number of carbon atoms. For example, "cycloalkyl" may contain 3 to 8 carbon atoms, *i.e.*, C_{3-8} cycloalkyl. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

The term "**heteroaryl**" refers to a group or moiety comprising an aromatic monovalent monocyclic or bicyclic radical, containing 5 to 10 ring atoms, including at least one heteroatom independently selected from nitrogen, oxygen and sulfur. This term also encompasses bicyclic heterocyclic-aryl compounds containing an aryl ring moiety fused to a heterocycloalkyl ring moiety, containing 5 to 10 ring atoms, including at least one heteroatom independently selected from nitrogen, oxygen and sulfur. Exemplary groups include, but are not limited to furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, benzofuranyl, isobenzofuryl, 2,3-dihydrobenzofuryl, 1,3-benzodioxolyl, dihydrobenzodioxinyl, benzothienyl, indolizinyl, indolyl, isoindolyl, dihydroindolyl, benzimidazolyl, dihydrobenzimidazolyl, benzoxazolyl, dihydrobenzoxazolyl, benzthiazolyl, benzoisothiazolyl, dihydrobenzoisothiazolyl, indazolyl, imidazopyridinyl, pyrazolopyridinyl, benzotriazolyl, triazolopyridinyl, purinyl, quinolinyl,

tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, and pteridinyl. Examples of 5-membered "heteroaryl" groups include furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, and isothiazolyl. Examples of 6-membered "heteroaryl" groups include oxo-pyridyl, pyridinyl, pyridazinyl, pyrazinyl, and pyrimidinyl. Examples of 6,6-fused "heteroaryl" groups include quinolinyl, isoquinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, and pteridinyl. Examples of 6,5-fused "heteroaryl" groups include benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, indolizinyl, indolyl, isoindolyl, and indazolyl.

The terms "**halogen**" and "**halo**" represent chloro, fluoro, bromo, or iodo substituents.

The term "**optionally substituted**" indicates that a group may be unsubstituted or substituted with one or more substituents as defined herein. The term "substituted" in reference to a group indicates that a hydrogen atom attached to a member atom within a group is replaced by one of the defined substituents. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

The term "**member atoms**" refers to the atom or atoms that form a chain or ring. Where more than one member atom is present in a chain and within a ring, each member atom is covalently bound to an adjacent member atom in the chain or ring. Atoms that make up a substituent group attached to a chain or ring are not member atoms in the chain or ring.

As used herein, the term "**aqueous solution**" refers to any solution comprising water or in which the solvent is water. Additionally, "aqueous solution" is used to describe solutions displaying commonalities to water or watery solutions, not limited to characteristics such as appearance, smell, color, taste, viscosity, pH, absorbance, or physical state under particular temperatures.

As used herein, the term "**lyophilization**," also known as freeze-drying or cryodesiccation, is a dehydration process which involves freezing the product without destroying the physical structure of the matter.

As used herein, the terms "**lyophilized**" and "**freeze-dried**" can be used interchangeably herein and refer to a condition and/or state of a sample, formulation, or product obtained by means of lyophilization.

As used interchangeably herein, the terms "**lyophilized pharmaceutical composition**" and "**lyophilized composition**" refer to a pharmaceutical composition in lyophilized form, as taught herein.

As used herein, the term "**pharmaceutically acceptable salts**" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively.

Pharmaceutically acceptable salts include, amongst others, those described in Berge, J. Pharm. Sci., 1977, 66, 1-19, or those listed in P H Stahl and C G Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Second Edition Stahl/Wermuth: Wiley-VCH/VHCA, 2011 (see www(dot)wiley(dot)com/WileyCDA/WileyTitle/productCd-3906390519.html). Suitable pharmaceutically acceptable salts can include acid or base addition salts. Suitable pharmaceutically acceptable salts of the invention include base addition salts.

Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS, tromethamine), arginine, benethamine (*N*-benzylphenethylamine), benzathine (*N,N'*-dibenzylethylenediamine), *bis*-(2-hydroxyethyl)amine, bismuth, calcium, chloroprocaine, choline, clemizole (1-*p* chlorobenzyl-2-pyrrolidine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidine, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, and zinc.

As used herein, the term "**pharmaceutical composition**" means a composition that is suitable for pharmaceutical use.

As used herein, the term "**prevention**" or "**preventing**" refers to avoidance of the stated disease in a subject who is not suffering from the stated disease.

As used herein, "**reconstitution**" refers to the process of restoring a dried, lyophilized, dehydrated, or concentrated matter to its original or liquid state by adding a solvent to the lyophilized matter, allowing the lyophilized matter to rehydrate, followed by agitating the mixture of the solvent and lyophilized matter. The reconstituted matter may be part of a product, formulation, sample, raw material, or any biological material but is certainly not limited to matter falling under the common definition of these terms. Reconstitution can be assessed visually with the naked eye. The lyophilized matter is

deemed reconstituted when a homogeneous suspension is observed. In particular, a suspension with a cloudy appearance is considered suitably reconstituted.

As used herein, the term "**self-administered**" means administration by someone other than a healthcare professional, for example, a patient may administer the pharmaceutical composition to their self or someone else, other than a healthcare professional administering the pharmaceutical composition to the patient.

As used herein, the term "**subject**" or "**patient**" refers to a human.

As used herein, the term "**treatment**" or "**treating**" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, slowing or eliminating the progression, invasion, or spread of the condition, and reducing or delaying the recurrence of the condition in a previously afflicted subject.

As used herein, the term "**diameter**" refers to a spherical volume equivalent diameter.

As used herein, the term "**CD4 binding site (CD4bs) binding protein**" refers to antibodies and other protein constructs, such as domains, that are capable of binding to the CD4 binding site of the HIV envelope glycoprotein, gp120. The terms "**CD4bs binding protein**," "**CD4bs binding domain**" and "**antigen binding protein**" are used interchangeably herein. This does not include the natural cognate ligand or receptor. In some embodiments, monoclonal antibodies and antigen binding fragments thereof that bind to the CD4 binding site on gp120 and neutralize HIV-1 are provided herein. In some embodiments, the CD4bs binding protein includes N6 and N6LS, or an antigen binding fragment thereof.

As used herein, the term "**antibody**" in the broadest sense refers to molecules with an immunoglobulin-like domain (for example IgG, IgM, IgA, IgD or IgE) and includes monoclonal, recombinant, polyclonal, chimeric, human, humanized, multispecific antibodies, including bispecific antibodies, and heteroconjugate antibodies; a single variable domain (*e.g.*, a domain antibody (DAB)), antigen binding antibody fragments, Fab, F(ab')2, Fv, disulfide linked Fv, single chain Fv, disulfide-linked scFv, diabodies, TANDABS, etc. and modified versions of any of the foregoing (for a summary of alternative "antibody" formats see Holliger and Hudson, Nature Biotechnology, 2005, Vol 23, No. 9, 1126-1136).

As used interchangeably herein, the terms "**full antibody or immunoglobulin**," "**whole antibody or immunoglobulin**," and "**intact antibody or immunoglobulin**" refer to a heterotetrameric glycoprotein with an approximate molecular weight of 150,000 Daltons. An intact antibody is composed of two identical heavy chains (HCs) and two identical light chains (LCs) linked by covalent disulfide bonds. This H2L2 structure folds to form three functional domains comprising two antigen-binding fragments, known as 'Fab'

fragments, and a 'Fc' crystallizable fragment. The Fab fragment is composed of the variable domain at the amino-terminus, variable heavy (VH) or variable light (VL), and the constant domain at the carboxyl terminus, CH1 (heavy) and CL (light). The Fc fragment is composed of two domains formed by dimerization of paired CH2 and CH3 regions. The Fc may elicit effector functions by binding to receptors on immune cells or by binding C1q, the first component of the classical complement pathway. The five classes of antibodies IgM, IgA, IgG, IgE and IgD are defined by distinct heavy chain amino acid sequences, which are called μ, α, γ, ε and δ respectively, each heavy chain can pair with either a K or λ light chain. The majority of antibodies in the serum belong to the IgG class, there are four isotypes of human IgG (IgG1, IgG2, IgG3 and IgG4), the sequences of which differ mainly in their hinge region.

Fully human antibodies can be obtained using a variety of methods, for example using yeast-based libraries or transgenic animals (*e.g.*, mice) that are capable of producing repertoires of human antibodies. Yeast presenting human antibodies on their surface that bind to an antigen of interest can be selected using FACS (Fluorescence-Activated Cell Sorting) based methods or by capture on beads using labeled antigens. Transgenic animals that have been modified to express human immunoglobulin genes can be immunized with an antigen of interest and antigen-specific human antibodies isolated using B-cell sorting techniques. Human antibodies produced using these techniques can then be characterized for desired properties such as affinity, developability and selectivity.

Alternative antibody formats include alternative scaffolds in which the one or more CDRs of the antigen binding protein can be arranged onto a suitable non-immunoglobulin protein scaffold or skeleton, such as an affibody, a SpA scaffold, an LDL receptor class A domain, an Avimer (see, *e.g.*, U.S. Patent Application Publication Nos. 2005/0053973, 2005/0089932, 2005/0164301) or an EGF domain.

As used herein, the term "**broadly neutralizing antibody**" (**bnAb**) is defined as an antibody which inhibits viral attachment and cell entry via binding to the HIV envelope glycoprotein (Env) (e.g., gp160, gp120, gp41), as a non-limiting example, by a 50% inhibition of infection in vitro, in more than 50%, 60%, 70%, 80%, 90%, 95%, 99% or greater, of a large panel of (greater than 100) HIV-1 envelope pseudotyped viruses and viral isolates. See, *e.g.*, US Published Patent Application No. 20120121597; Burton *et al.*, Broadly Neutralizing Antibodies to HIV and Their Role in Vaccine Design. Annu Rev Immunol. 2016 May 20; 34:635-59.

As used herein, "**CDRs**" are defined as the complementarity determining region amino acid sequences of an antigen binding protein. These are the hypervariable regions of immunoglobulin heavy and light chains. There are three heavy chain and three light

chain CDRs (or CDR regions) in the variable portion of an immunoglobulin. Thus, "CDRs" as used herein refers to all three heavy chain CDRs, all three light chain CDRs, all heavy and light chain CDRs, or at least two CDRs.

Throughout this specification, amino acid residues in variable domain sequences and variable domain regions within full-length antigen binding sequences, *e.g.*, within an antibody heavy chain sequence or antibody light chain sequence, are numbered according to the Kabat numbering convention. Similarly, the terms “CDR”, “CDRL1”, “CDRL2”, “CDRL3”, “CDRH1”, “CDRH2”, “CDRH3” used in the Examples follow the Kabat numbering convention. For further information, see Kabat *et al.*, Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987).

It will be apparent to those skilled in the art that there are alternative numbering conventions for amino acid residues in variable domain sequences and full-length antibody sequences. There are also alternative numbering conventions for CDR sequences, for example, those set out in Chothia *et al.* (1989) Nature 342: 877-883. The structure and protein folding of the antigen binding protein may mean that other residues are considered part of the CDR sequence and would be understood to be so by a skilled person.

Other numbering conventions for CDR sequences available to a skilled person include “AbM” (University of Bath) and “contact” (University College London) methods.

Table 1 below represents one definition using each numbering convention for each CDR or binding unit. The Kabat numbering scheme is used in Table 1 to number the variable domain amino acid sequence. It should be noted that some of the CDR definitions may vary depending on the individual publication used.

Table 1

	Kabat CDR	Chothia CDR	AbM CDR	Contact CDR
H1	31-35/35A/ 35B	26-32/33/34	26-35/35A/35B	30-35/35A/35B
H2	50-65	52-56	50-58	47-58
H3	95-102	95-102	95-102	93-101
L1	24-34	24-34	24-34	30-36
L2	50-56	50-56	50-56	46-55
L3	89-97	89-97	89-97	89-96

As used herein, "**antibody half-life**" (or "**serum half-life**") refers to the time required for the serum concentration of an antigen binding protein to reach half of its original value. The serum half-life of proteins can be measured by pharmacokinetic studies according to the method described by Kim *et al.*, 1994, Eur. J. of Immuno. 24: 542-548. According to this method, radio-labelled protein is injected intravenously into mice and its plasma concentration is periodically measured as a function of time, for example, at about 3 minutes to about 72 hours after the injection. Other methods for pharmacokinetic analysis and determination of the serum half-life of a molecule will be familiar to those skilled in the art.

Antigen binding proteins of the present invention may have amino acid modifications that increase the affinity of the constant domain or fragment thereof for FcRn. Increasing the serum half-life of therapeutic and diagnostic IgG antibodies and other bioactive molecules has many benefits including reducing the amount and/or frequency of dosing of these molecules. In one embodiment, an antigen binding protein of the invention comprises all or a portion (an FcRn binding portion) of an IgG constant domain having one or more of the following amino acid modifications.

For example, with reference to IgG1, M252Y/S254T/T256E (commonly referred to as "YTE" mutations) and M428L/N434S (commonly referred to as "LS" mutations) increase FcRn binding at pH 6.0 (Wang *et al.* 2018). Serum half-life can also be enhanced by T250Q/M428L, V259I/V308F/M428L, N434A, and T307A/E380A/N434A mutations (with reference to IgG1 and Kabat numbering) (Monnet *et al.*). Serum half-life and FcRn binding can also be extended by introducing H433K and N434F mutations (commonly referred to as "HN" or "NHance" mutations) (with reference to IgG1) (WO2006/130834).

STATEMENT OF THE INVENTION

The present invention provides a pharmaceutical composition comprising:
cabotegravir;
a wetting agent;
a stabilizer; and
a tonicity adjuster;
wherein cabotegravir is present in the form of particles having a mass median diameter (X50) of between (and including) 2.5 µm and 10 µm.

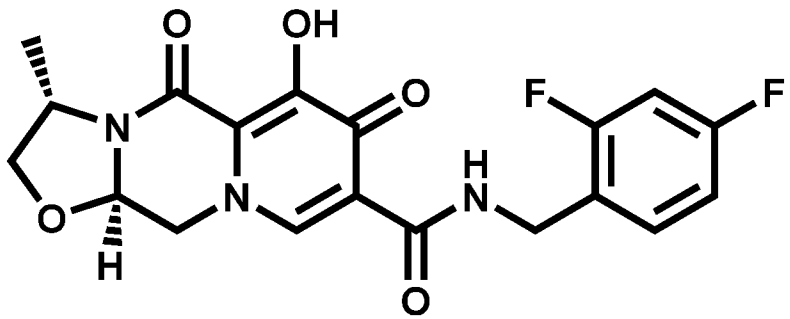
For example, an embodiment of the present invention provides a pharmaceutical composition comprising cabotegravir having a mass median diameter (X50) of between (and including) 2.5 µm and 10 µm; polysorbate 80; sodium CMC; and mannitol.

The pharmaceutical compositions described herein may be administered by any appropriate route. In a preferred embodiment, the compositions are administered parenterally (including subcutaneously, intramuscularly, intravenously, or intradermally). In one embodiment the composition is administered intramuscularly. In another embodiment the composition is administered subcutaneously.

Cabotegravir

Cabotegravir (*N*-((2,4-difluorophenyl)methyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,1,11,11a hexahydro(1,3)oxazolo(3,2-a)pyrido(1,2-d)pyrazine-8-carboxamide) is described in US 8,129,385 in example Z-1, which example is incorporated herein by reference. Cabotegravir is an integrase strand transfer inhibitor (INSTI) that exhibits subnanomolar potency and antiviral activity against a broad range of HIV-1 strains. Oral administration of cabotegravir has exhibited acceptable safety and tolerability profiles, a long half-life, and few drug-drug interactions. Cabotegravir has been demonstrated to be efficacious in treatment and prevention of HIV both in oral and parenteral dosage forms, see for instance, Margolis DA, Brinson CC, Eron JJ, et al. 744 and Rilpivirine as Two Drug Oral Maintenance Therapy: LAI116482 (LATTE) Week 48 Results. 21st Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2014; Boston, MA, Margolis DA, Podzamczer D, Stellbrink H-J, et al. Cabotegravir + Rilpivirine as Long-Acting Maintenance Therapy: LATTE-2 Week 48 Results, 21st International AIDS Conference; July 18-22, 2016; Durban, South Africa, Abstract THAB0206LB. Levin: Conference reports for National AIDS Treatment Advocacy Project (NATAP); 2016, and Markowitz M, Frank I, Grant R, et al. ÉCLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men. Abstract presented at 23rd CROI; February 22-25, 2016; Boston, MA.

Cabotegravir is represented by formula (I):



(I).

In an embodiment of the invention, cabotegravir is present in the pharmaceutical composition as the free acid.

The pharmaceutical composition of the present invention comprises particles of crystalline cabotegravir. In an embodiment, cabotegravir particles of the pharmaceutical composition have an X50 value greater than or equal to 2.5 μm and less than or equal to

10 μm (*i.e.*, 2.5 μm ≤ X50 ≤ 10 μm). Particle size distribution may be measured by any suitable method, for example, by laser diffraction as described in the Examples section herein.

Without wishing to be bound by theory, it is thought that the larger drug particle size favorably modifies absorption kinetics, thus permitting ultra long-acting therapy. Without wishing to be bound by theory, it is also thought that the larger drug particle size favorably reduces injection site reactions, therefore improving patient experience.

It is further believed that an injectable microsuspension formulation may provide an additional sustained therapeutic effect over commercial nanosuspension formulations due to a reduced drug substance specific surface area resulting in a slower drug depot dissolution. The prolonged dissolution may enable further enhancement to patient compliance and treatment effectiveness when compared to commercial nanosuspension formulations.

Highly potent hydrophobic compounds like cabotegravir may benefit from an increased specific surface area via size reduction to increase drug dissolution *in vivo*. However, optimization of particle size of these compounds may influence resultant pharmacokinetic performance—smaller crystal sizes of active substances may dissolve more rapidly than larger crystal sizes due to the increased relative surface area. As such, suspensions of larger average particle sizes may exhibit an extended and more controlled release profile from the injected depot when compared to suspensions of smaller average particle sizes.

In an embodiment, the pharmaceutical composition contains about 100 to about 800 mg/mL of cabotegravir. In a further embodiment, the pharmaceutical composition contains about 200 mg/mL to about 700 mg/mL, from about 300 mg/mL to about 650 mg/mL, from about 400 mg/mL to about 600 mg/mL, about 400, about 500, or about 533 mg/mL of cabotegravir. In an embodiment the pharmaceutical composition contains about 400 mg/mL of cabotegravir. In a further embodiment, the pharmaceutical composition contains about 533 mg/mL of cabotegravir.

In another embodiment, the pharmaceutical composition contains cabotegravir in an amount between about 300 mg and about 4800 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount between about 350 mg and about 4000 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount between about 375 mg and about 3200 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount between about 400 mg and about 2000 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount of about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about

500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, about 2625 mg, about 2650 mg, about 2675 mg, about 2700 mg, about 2725 mg, about 2750 mg, about 2775 mg, about 2800 mg, about 2825 mg, about 2850 mg, about 2875 mg, about 2900 mg, about 2925 mg, about 2950 mg, about 2975 mg, about 3000 mg, about 3025 mg, about 3050 mg, about 3075 mg, about 3100 mg, about 3125 mg, about 3150 mg, about 3175 mg, or about 3200 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount of about 800 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount of about 1600 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount of about 2665 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount of about 3200 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount of about 4000 mg. In an embodiment, the pharmaceutical composition contains cabotegravir in an amount of about 4800 mg.

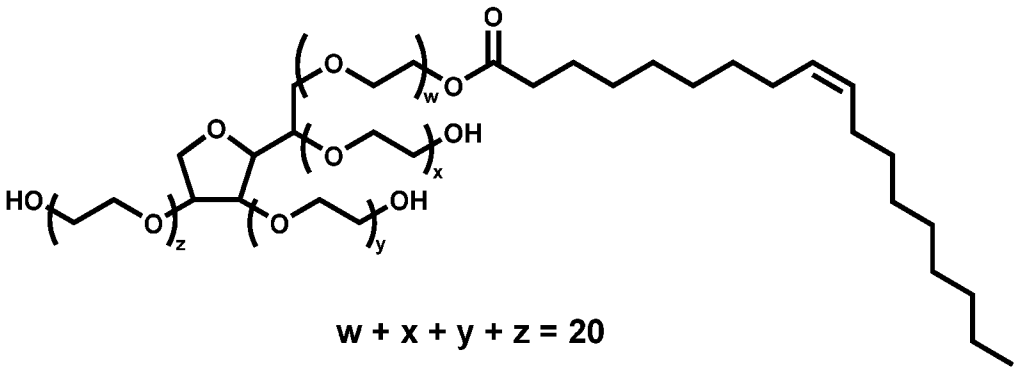
Wetting agents

Wetting agents or surfactants are compounds that, when dissolved in a liquid, can reduce the surface tension of a gas, liquid, or solid surface in that liquid. They are often amphiphilic and may aid in wetting and enhance manufacturability of the drug product. In addition, a surfactant may additionally impart long-term product stability by steric or electrostatic repulsion. Non-ionic surfactants are preferred over ionic surfactants as they are generally non-toxic, non-irritating, and inert. Examples of surfactants include, but are not limited to, polysorbate 20 (Tween-20), polysorbate 80 (Tween-80), sorbitan

monolaurate (Span-20), sorbitan monooleate (Span-80), poloxamer 188 (Kolliphor P188), poloxamer 338 (Kolliphor P338), and poloxamer 407 (Kolliphor P407).

In an embodiment, the pharmaceutical composition of the invention comprises polysorbate 80 (PS80) as the wetting agent.

PS80 (IUPAC name: polyoxyethylene (20) sorbitan monooleate; CAS No. 9005-65-6) is a nonionic surfactant and emulsifier derived from polyethoxylated sorbitan and oleic acid. The hydrophilic groups in PS80 are polyethers also known as polyoxyethylene groups, which are polymers of ethylene oxide. In the nomenclature of polysorbates, the numeric designation following "polysorbate" (e.g., "polysorbate **80**") refers to the lipophilic group, in this case, the oleic acid. The structure of PS80 is provided by formula (II):



w + x + y + z = 20

(II).

The inventors have surprisingly found that the use of PS80 in a lyophilized microsuspension resulted in superior *in vivo* performance, tolerability, and increased flexibility in manufacturability.

In an embodiment, the pharmaceutical composition contains from about 0.1 mg/mL to about 150 mg/mL of the wetting agent. In a further embodiment, the pharmaceutical composition contains from about 1 mg/mL to about 80 mg/mL, from about 2 mg/mL to about 40 mg/mL, or from about 2.5 mg/mL to about 5 mg/mL of the wetting agent.

In an embodiment, the pharmaceutical composition contains about, in mg/mL, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0 of the wetting agent. In another embodiment, the pharmaceutical composition contains about 3.0 mg/mL of the wetting agent. In another embodiment, the pharmaceutical composition contains about 4.0 mg/mL of the wetting agent.

In an embodiment, the pharmaceutical composition contains about 0.1 mg to about 900 mg of the wetting agent. In another embodiment, the pharmaceutical composition contains about 0.5 mg to about 200 mg of the wetting agent. In another embodiment, the

pharmaceutical composition comprises about 1.0 mg to about 100 mg of the wetting agent. In another embodiment, the pharmaceutical composition contains about 2.0 mg to about 50 mg of the wetting agent. In another embodiment, the pharmaceutical composition contains about, in mg, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, 20.0, 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, 21.0, 21.1, 21.2, 21.3, 21.4, 21.5, 21.6, 21.7, 21.8, 21.9, 22.0, 22.1, 22.2, 22.3, 22.4, 22.5, 22.6, 22.7, 22.8, 22.9, 23.0, 23.1, 23.2, 23.3, 23.4, 23.5, 23.6, 23.7, 23.8, 23.9, 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, 28.0, 28.1, 28.2, 28.3, 28.4, 28.5, 28.6, 28.7, 28.8, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 30.0, 30.1, 30.2, 30.3, 30.4, 30.5, 30.6, 30.7, 30.8, 30.9, 31.0, 31.1, 31.2, 31.3, 31.4, 31.5, 31.6, 31.7, 31.8, 31.9, 32.0, 32.1, 32.2, 32.3, 32.4, 32.5, 32.6, 32.7, 32.8, 32.9, 33.0, 33.1, 33.2, 33.3, 33.4, 33.5, 33.6, 33.7, 33.8, 33.9, 34.0, 34.1, 34.2, 34.3, 34.4, 34.5, 34.6, 34.7, 34.8, 34.9, 35.0, 35.1, 35.2, 35.3, 35.4, 35.5, 35.6, 35.7, 35.8, 35.9, 36.0, 36.1, 36.2, 36.3, 36.4, 36.5, 36.6, 36.7, 36.8, 36.9, 37.0, 37.1, 37.2, 37.3, 37.4, 37.5, 37.6, 37.7, 37.8, 37.9, 38.0, 38.1, 38.2, 38.3, 38.4, 38.5, 38.6, 38.7, 38.8, 38.9, 39.0, 39.1, 39.2, 39.3, 39.4, 39.5, 39.6, 39.7, 39.8, 39.9, 40.0, 40.1, 40.2, 40.3, 40.4, 40.5, 40.6, 40.7, 40.8, 40.9, 41.0, 41.2, 41.3, 41.4, 41.5, 41.6, 41.7, 41.8, 41.9, 42.0, 42.1, 42.2, 42.3, 42.4, 42.5, 42.6, 42.7, 42.8, 42.9, 43.0, 43.1, 43.2, 43.3, 43.4, 43.5, 43.6, 43.7, 43.8, 43.9, 44.0, 44.1, 44.2, 44.3, 44.4, 44.5, 44.6, 44.7, 44.8, 44.9, 45.0, 45.1, 45.2, 45.3, 45.4, 45.5, 45.6, 45.7, 45.8, 45.9, 46.0, 46.1, 46.2, 46.3, 46.4, 46.5, 46.6, 46.7, 46.8, 46.9, 47.0, 47.1, 47.2, 47.3, 47.4, 47.5, 47.6, 47.7, 47.8, 47.9, 48.0, 48.1, 48.2, 48.3, 48.4, 48.5, 48.6, 48.7, 48.8, 48.9, 49.0, 49.1, 49.2, 49.3, 49.4, 49.5, 49.6, 49.7, 49.8, 49.9, or 50.0 of the wetting agent. In an embodiment, the pharmaceutical composition comprises about 5.9 mg of the wetting agent. In an embodiment, the pharmaceutical composition comprises about 8.0 mg of the wetting agent.

In an embodiment, a weight ratio of the wetting agent to cabotegravir is in a range of from 1:10 to 1:400. In another embodiment, the weight ratio of the wetting agent to cabotegravir is in a range of from 1:50 to 1:200. In another embodiment, the weight ratio of the wetting agent to cabotegravir is in a range of from 1:100 to 1:150. In another embodiment, the weight ratio of the wetting agent to cabotegravir is about 1:100, about 1:101, about 1:102, about 1:103, about 1:104, about 1:105, about 1:106, about 1:107, about 1:108, about 1:109, about 1:110, about 1:111, about 1:112, about 1:113, about 1:114, about 1:115, about 1:116, about 1:117, about 1:118, about 1:119, about 1:120, about 1:121, about 1:122, about 1:123, about 1:124, about 1:125, about 1:126, about 1:127, about 1:128, about 1:129, about 1:130, about 1:131, about 1:132, about 1:133, about 1:134, about 1:135, about 1:136, about 1:137, about 1:138, about 1:139, about 1:140, about 1:141, about 1:142, about 1:143, about 1:144, about 1:145, about 1:146, about 1:147, about 1:148, about 1:149, or about 1:150. In another embodiment, the weight ratio of the wetting agent to cabotegravir is about 1:100. In another embodiment, the weight ratio of the wetting agent to cabotegravir is about 1:136.

Stabilizers

Stabilizers are components added to help preserve critical product attributes throughout shelf life. In the case of suspensions, stabilizers can be used to induce charge effects, add steric stabilization, increase viscosity of the vehicle, etc. These factors can preserve particle size, product resuspendability, and/or improve manufacturability. Examples of stabilizers include, but are not limited to, sodium carboxymethylcellulose (CMC), polyethylene glycol 3350, polyethylene glycol 4000, povidone K12, and povidone K17.

In an embodiment, the pharmaceutical composition of the invention comprises sodium CMC as the stabilizer.

In an embodiment, the pharmaceutical composition contains about 0.1 to about 150 mg/mL of the stabilizer. In a further embodiment, the pharmaceutical composition contains about 1 mg/mL to about 25 mg/mL, from about 2 mg/mL to about 15 mg/mL, or from about 3 mg/mL to about 10 mg/mL of the stabilizer.

In an embodiment, the pharmaceutical composition contains about, in mg/mL, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10.0 of the stabilizer. In another embodiment, the pharmaceutical composition contains about 3.7 mg/mL of the stabilizer. In another embodiment, the pharmaceutical composition contains about 5.0 mg/mL of the stabilizer.

In an embodiment, the pharmaceutical composition contains about 0.1 mg to about 300 mg of the stabilizer. In another embodiment, the pharmaceutical composition contains about 1.0 mg to about 200 mg of the stabilizer. In another embodiment, the pharmaceutical composition comprises about 2.0 mg to about 100 mg of the stabilizer. In another embodiment, the pharmaceutical composition contains about 4.0 mg to about 50 mg of the stabilizer. In another embodiment, the pharmaceutical composition contains about, in mg, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, 20.0, 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, 21.0, 21.1, 21.2, 21.3, 21.4, 21.5, 21.6, 21.7, 21.8, 21.9, 22.0, 22.1, 22.2, 22.3, 22.4, 22.5, 22.6, 22.7, 22.8, 22.9, 23.0, 23.1, 23.2, 23.3, 23.4, 23.5, 23.6, 23.7, 23.8, 23.9, 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, 28.0, 28.1, 28.2, 28.3, 28.4, 28.5, 28.6, 28.7, 28.8, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 30.0, 30.1, 30.2, 30.3, 30.4, 30.5, 30.6, 30.7, 30.8, 30.9, 31.0, 31.1, 31.2, 31.3, 31.4, 31.5, 31.6, 31.7, 31.8, 31.9, 32.0, 32.1, 32.2, 32.3, 32.4, 32.5, 32.6, 32.7, 32.8, 32.9, 33.0, 33.1, 33.2, 33.3, 33.4, 33.5, 33.6, 33.7, 33.8, 33.9, 34.0, 34.1, 34.2, 34.3, 34.4, 34.5, 34.6, 34.7, 34.8, 34.9, 35.0, 35.1, 35.2, 35.3, 35.4, 35.5, 35.6, 35.7, 35.8, 35.9, 36.0, 36.1, 36.2, 36.3, 36.4, 36.5, 36.6, 36.7, 36.8, 36.9, 37.0, 37.1, 37.2, 37.3, 37.4, 37.5, 37.6, 37.7, 37.8, 37.9, 38.0, 38.1, 38.2, 38.3, 38.4, 38.5, 38.6, 38.7, 38.8, 38.9, 39.0, 39.1, 39.2, 39.3, 39.4, 39.5, 39.6, 39.7, 39.8, 39.9, 40.0, 40.1, 40.2, 40.3, 40.4, 40.5, 40.6, 40.7, 40.8, 40.9, 41.0, 41.2, 41.3, 41.4, 41.5, 41.6, 41.7, 41.8, 41.9, 42.0, 42.1, 42.2, 42.3, 42.4, 42.5, 42.6, 42.7, 42.8, 42.9, 43.0, 43.1, 43.2, 43.3, 43.4, 43.5, 43.6, 43.7, 43.8, 43.9, 44.0, 44.1, 44.2, 44.3, 44.4, 44.5, 44.6, 44.7, 44.8, 44.9, 45.0, 45.1, 45.2, 45.3, 45.4, 45.5, 45.6, 45.7, 45.8, 45.9, 46.0, 46.1, 46.2, 46.3, 46.4, 46.5, 46.6, 46.7, 46.8, 46.9, 47.0, 47.1, 47.2, 47.3, 47.4, 47.5, 47.6, 47.7, 47.8, 47.9, 48.0, 48.1, 48.2, 48.3, 48.4, 48.5, 48.6, 48.7, 48.8, 48.9, 49.0, 49.1, 49.2, 49.3, 49.4, 49.5, 49.6, 49.7, 49.8, 49.9, or 50.0 of the stabilizer. In an embodiment, the pharmaceutical composition comprises about 7.4 mg of the stabilizer. In an embodiment, the pharmaceutical composition comprises about 10.0 mg of the stabilizer.

In an embodiment, a weight ratio of the stabilizer to cabotegravir is in a range of from 1:10 to 1:400. In another embodiment, the weight ratio of the stabilizer to cabotegravir is in a range of from 1:40 to 1:200. In another embodiment, the weight ratio of the stabilizer to cabotegravir is in a range of from 1:70 to 1:120. In another embodiment, the weight ratio of the stabilizer to cabotegravir is about 1:70, about 1:71, about 1:72, about 1:73, about 1:74, about 1:75, about 1:76, about 1:77, about 1:78, about 1:79, about 1:80, about 1:81, about 1:82, about 1:83, about 1:84, about 1:85, about 1:86, about 1:87, about 1:88, about 1:89, about 1:90, about 1:91, about 1:92, about 1:93, about 1:94, about 1:95, about 1:96, about 1:97, about 1:98, about 1:99, about 1:100, about 1:101, about 1:102, about 1:103, about 1:104, about 1:105, about 1:106, about 1:107, about 1:108, about 1:109, about 1:110, about 1:111, about 1:112, about 1:113, about 1:114, about 1:115, about 1:116, about 1:117, about 1:118, about 1:119, or about 1:120. In another embodiment, the weight ratio of the stabilizer to cabotegravir is about 1:80. In another embodiment, the weight ratio of the stabilizer to cabotegravir is about 1:108.

Tonicity adjusters

Tonicity adjusters act to provide and maintain a stable tonicity for the pharmaceutical composition disclosed herein. In some embodiments, tonicity adjusters also function as a non-aqueous solvent, a solubilizer, and/or a stabilizer. In such instances, tonicity adjusters may be used at concentrations higher than needed for tonicity if their primary purpose is stabilization or may be used at concentrations higher than needed for stabilization if their primary purpose is tonicity adjustment.

In some embodiments, the tonicity adjuster is a pharmaceutically acceptable inorganic chloride, *e.g.*, potassium chloride, sodium chloride, magnesium chloride or calcium chloride. In yet other embodiments, the tonicity adjuster is a saccharide such as mannitol, sorbitol, lactose, trehalose, raffinose, dextrose, maltose, galactose, sucrose, or polysucrose. In still further aspects, the tonicity adjuster is mannitol. In other aspects, the tonicity adjuster is a non-aqueous polar aprotic or protic materials such as polyethylene glycol, N,N-dimethylacetamide, N-methyl pyrrolidone, glycerol, propylene glycol, ethanol, t-butyl alcohol, benzyl alcohol, benzyl benzoate, dimethyl sulfoxide, or glycerol. In further aspects, the tonicity adjuster is a polymer such as polyethylene glycol, polygalacturonic acid, galacturonic acid, polyvinylpyrrolidine (PVP), for example, PEG 300, PEG 400, PEG 3350, PEG 6000, or PEG 8000. In still other aspects, the tonicity adjuster is an amino acid such as lysine, arginine, glycine, methionine, or other amino acids. In yet further aspects, the tonicity adjuster is a cyclodextrin such as dextran, Ficoll, and polyvinylpyrrolidone, and other similar excipients and combinations of these agents.

In an embodiment, the pharmaceutical composition of the invention comprises mannitol as the tonicity adjuster.

In an embodiment, the pharmaceutical composition contains about 0.1 to about 250 mg/mL of the tonicity adjuster. In a further embodiment, the pharmaceutical composition contains about 1 mg/mL to about 150 mg/mL, from about 10 mg/mL to about 125 mg/mL, from about 15 mg/mL to about 50 mg/mL, or from about 20 mg/mL to about 40 mg/mL of the tonicity adjuster.

In an embodiment, the pharmaceutical composition contains about, in mg/mL, 20.0, 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, 21.0, 21.1, 21.2, 21.3, 21.4, 21.5, 21.6, 21.7, 21.8, 21.9, 22.0, 22.1, 22.2, 22.3, 22.4, 22.5, 22.6, 22.7, 22.8, 22.9, 23.0, 23.1, 23.2, 23.3, 23.4, 23.5, 23.6, 23.7, 23.8, 23.9, 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, 28.0, 28.1, 28.2, 28.3, 28.4, 28.5, 28.6, 28.7, 28.8, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 30.0, 30.1, 30.2, 30.3, 30.4, 30.5, 30.6, 30.7, 30.8, 30.9, 31.0, 31.1, 31.2, 31.3, 31.4, 31.5, 31.6, 31.7, 31.8, 31.9, 32.0, 32.1, 32.2, 32.3, 32.4, 32.5, 32.6, 32.7, 32.8, 32.9, 33.0, 33.1, 33.2, 33.3, 33.4, 33.5, 33.6, 33.7, 33.8, 33.9, 34.0, 34.1, 34.2, 34.3, 34.4, 34.5, 34.6, 34.7, 34.8, 34.9, 35.0, 35.1, 35.2, 35.3, 35.4, 35.5, 35.6, 35.7, 35.8, 35.9, 36.0, 36.1, 36.2, 36.3, 36.4, 36.5, 36.6, 36.7, 36.8, 36.9, 37.0, 37.1, 37.2, 37.3, 37.4, 37.5, 37.6, 37.7, 37.8, 37.9, 38.0, 38.1, 38.2, 38.3, 38.4, 38.5, 38.6, 38.7, 38.8, 38.9, 39.0, 39.1, 39.2, 39.3, 39.4, 39.5, 39.6, 39.7, 39.8, 39.9, or 40.0 of the tonicity adjuster. In another embodiment, the pharmaceutical composition contains about 25.9 mg/mL of the tonicity adjuster. In another embodiment, the pharmaceutical composition contains about 35.0 mg/mL of the tonicity adjuster.

In an embodiment, the pharmaceutical composition contains about 0.1 mg to about 400 mg of the tonicity adjuster. In another embodiment, the pharmaceutical composition contains about 1.0 mg to about 300 mg of the tonicity adjuster. In another embodiment, the pharmaceutical composition comprises about 10 mg to about 100 mg of the tonicity adjuster. In another embodiment, the pharmaceutical composition contains about 35 mg to about 80 mg of the tonicity adjuster. In another embodiment, the pharmaceutical composition contains about, in mg, 35.0, 35.1, 35.2, 35.3, 35.4, 35.5, 35.6, 35.7, 35.8, 35.9, 36.0, 36.1, 36.2, 36.3, 36.4, 36.5, 36.6, 36.7, 36.8, 36.9, 37.0, 37.1, 37.2, 37.3, 37.4, 37.5, 37.6, 37.7, 37.8, 37.9, 38.0, 38.1, 38.2, 38.3, 38.4, 38.5, 38.6, 38.7, 38.8, 38.9, 39.0, 39.1, 39.2, 39.3, 39.4, 39.5, 39.6, 39.7, 39.8, 39.9, 40.0, 40.1, 40.2, 40.3, 40.4, 40.5, 40.6, 40.7, 40.8, 40.9, 41.0, 41.1, 41.2, 41.3, 41.4, 41.5, 41.6, 41.7, 41.8, 41.9, 42.0, 42.1, 42.2, 42.3, 42.4, 42.5, 42.6, 42.7, 42.8, 42.9, 43.0, 43.1, 43.2, 43.3, 43.4, 43.5, 43.6, 43.7, 43.8, 43.9, 44.0, 44.1, 44.2, 44.3, 44.4, 44.5, 44.6, 44.7, 44.8, 44.9, 45.0, 45.1, 45.2, 45.3, 45.4,

45.5, 45.6, 45.7, 45.8, 45.9, 46.0, 46.1, 46.2, 46.3, 46.4, 46.5, 46.6, 46.7, 46.8, 46.9, 47.0, 47.1, 47.2, 47.3, 47.4, 47.5, 47.6, 47.7, 47.8, 47.9, 48.0, 48.1, 48.2, 48.3, 48.4, 48.5, 48.6, 48.7, 48.8, 48.9, 49.0, 49.1, 49.2, 49.3, 49.4, 49.5, 49.6, 49.7, 49.8, 49.9, 50.0, 50.1, 50.2, 50.3, 50.4, 50.5, 50.6, 50.7, 50.8, 50.9, 51.0, 51.1, 51.2, 51.3, 51.4, 51.5, 51.6, 51.7, 51.8, 51.9, 52.0, 52.1, 52.2, 52.3, 52.4, 52.5, 52.6, 52.7, 52.8, 52.9, 53.0, 53.1, 53.2, 53.3, 53.4, 53.5, 53.6, 53.7, 53.8, 53.9, 54.0, 54.1, 54.2, 54.3, 54.4, 54.5, 54.6, 54.7, 54.8, 54.9, 55.0, 55.1, 55.2, 55.3, 55.4, 55.5, 55.6, 55.7, 55.8, 55.9, 56.0, 56.1, 56.2, 56.3, 56.4, 56.5, 56.6, 56.7, 56.8, 56.9, 57.0, 57.1, 57.2, 57.3, 57.4, 57.5, 57.6, 57.7, 57.8, 57.9, 58.0, 58.1, 58.2, 58.3, 58.4, 58.5, 58.6, 58.7, 58.8, 58.9, 59.0, 59.1, 59.2, 59.3, 59.4, 59.5, 59.6, 59.7, 59.8, 59.9, 60.0, 60.1, 60.2, 60.3, 60.4, 60.5, 60.6, 60.7, 60.8, 60.9, 61.0, 61.1, 61.2, 61.3, 61.4, 61.5, 61.6, 61.7, 61.8, 61.9, 62.0, 62.1, 62.2, 62.3, 62.4, 62.5, 62.6, 62.7, 62.8, 62.9, 63.0, 63.1, 63.2, 63.3, 63.4, 63.5, 63.6, 63.7, 63.8, 63.9, 64.0, 64.1, 64.2, 64.3, 64.4, 64.5, 64.6, 64.7, 64.8, 64.9, 65.0, 65.1, 65.2, 65.3, 65.4, 65.5, 65.6, 65.7, 65.8, 65.9, 66.0, 66.1, 66.2, 66.3, 66.4, 66.5, 66.6, 66.7, 66.8, 66.9, 67.0, 67.1, 67.2, 67.3, 67.4, 67.5, 67.6, 67.7, 67.8, 67.9, 68.0, 68.1, 68.2, 68.3, 68.4, 68.5, 68.6, 68.7, 68.8, 68.9, 69.0, 69.1, 69.2, 69.3, 69.4, 69.5, 69.6, 69.7, 69.8, 69.9, 70.0, 70.1, 70.2, 70.3, 70.4, 70.5, 70.6, 70.7, 70.8, 70.9, 71.0, 71.1, 71.2, 71.3, 71.4, 71.5, 71.6, 71.7, 71.8, 71.9, 72.0, 72.1, 72.2, 72.3, 72.4, 72.5, 72.6, 72.7, 72.8, 72.9, 73.0, 73.1, 73.2, 73.3, 73.4, 73.5, 73.6, 73.7, 73.8, 73.9, 74.0, 74.1, 74.2, 74.3, 74.4, 74.5, 74.6, 74.7, 74.8, 74.9, 75.0, 75.1, 75.2, 75.3, 75.4, 75.5, 75.6, 75.7, 75.8, 75.9, 76.0, 76.1, 76.2, 76.3, 76.4, 76.5, 76.6, 76.7, 76.8, 76.9, 77.0, 77.1, 77.2, 77.3, 77.4, 77.5, 77.6, 77.7, 77.8, 77.9, 78.0, 78.1, 78.2, 78.3, 78.4, 78.5, 78.6, 78.7, 78.8, 78.9, 79.0, 79.1, 79.2, 79.3, 79.4, 79.5, 79.6, 79.7, 79.8, 79.9, or 80.0 of the tonicity adjuster. In an embodiment, the pharmaceutical composition comprises about 51.8 mg of the tonicity adjuster. In an embodiment, the pharmaceutical composition comprises about 70 mg of the tonicity adjuster. In an embodiment, the pharmaceutical composition comprises about 105 mg of the tonicity adjuster. In an embodiment, the pharmaceutical composition comprises about 140 mg of the tonicity adjuster. In an embodiment, the pharmaceutical composition comprises about 175 mg of the tonicity adjuster. In an embodiment, the pharmaceutical composition comprises about 210 mg of the tonicity adjuster. In an embodiment, the pharmaceutical composition comprises about 245 mg of the tonicity adjuster. In an embodiment, the pharmaceutical composition comprises about 280 mg of the tonicity adjuster.

In an embodiment, a weight ratio of the tonicity adjuster to cabotegravir is in a range of from 1:1 to 1:100. In another embodiment, the weight ratio of the tonicity adjuster to cabotegravir is in a range of from 1:5 to 1:50. In another embodiment, the weight ratio of the tonicity adjuster to cabotegravir is in a range of from 1:8 to 1:25. In another embodiment, the weight ratio of the tonicity adjuster to cabotegravir is about 1:8, about

1:9, about 1:10, about 1:11, about 1:12, about 1:13, about 1:14, about 1:15, about 1:16, about 1:17, about 1:18, about 1:19, about 1:20, about 1:21, about 1:22, about 1:23, about 1:24, or about 1:25. In another embodiment, the weight ratio of the tonicity adjuster to cabotegravir is about 1:11. In another embodiment, the weight ratio of the tonicity adjuster to cabotegravir is about 1:15.

Cabotegravir particle size

Dissolution properties of the pharmaceutical composition are affected, *inter alia*, by particle size and particle size distribution of the active pharmaceutical ingredient (*i.e.*, cabotegravir).

As used herein, X50 (or "the X50 value") is the cabotegravir particle diameter, in microns, at which 50% by volume of the particles of cabotegravir have a smaller diameter and 50% by volume have a larger diameter, also known as the mass median diameter (MMD) or the median of the particle size distribution by volume.

As used herein, X90 (or "the X90 value") is the cabotegravir particle diameter, in microns, at which 90% by volume of the cabotegravir particles have a smaller diameter and 10% by volume have a larger diameter.

As used herein, X10 (or "the X10 value") is the cabotegravir particle diameter, in microns, at which 10% by volume of the cabotegravir particles have a smaller diameter and 90% by volume have a larger diameter.

In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 90% of the cabotegravir particles have a particle diameter less than or equal to 25 µm (*i.e.*, X90 is 25 µm). In an embodiment, cabotegravir particles of the pharmaceutical composition have an X90 value greater than or equal to 5 µm and less than or equal to 25 µm (*i.e.*, 5 µm ≤ X90 ≤ 25 µm). In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 90% of the cabotegravir particles have a particle diameter less than or equal to 20 µm (*i.e.*, X90 is 20 µm). In an embodiment, cabotegravir particles of the pharmaceutical composition have an X90 value greater than or equal to 6 µm and less than or equal to 20 µm (*i.e.*, 6 µm ≤ X90 ≤ 20 µm). In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 90% of the cabotegravir particles have a particle diameter less than or equal to 18 µm (*i.e.*, X90 is 18 µm). In an embodiment, cabotegravir particles of the pharmaceutical composition have an X90 value greater than or equal to 7 µm and less than or equal to 18 µm (*i.e.*, 7 µm ≤ X90 ≤ 18 µm).

In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 90% of the cabotegravir particles (X90) have a particle diameter smaller than or equal to 7.0 µm, 7.1 µm, 7.2 µm, 7.3 µm, 7.4 µm, 7.5 µm, 7.6 µm, 7.7 µm,

7.8 µm, 7.9 µm, 8.0 µm, 8.1 µm, 8.2 µm, 8.3 µm, 8.4 µm, 8.5 µm, 8.6 µm, 8.7 µm, 8.8 µm, 8.9 µm, 9.0 µm, 9.1 µm, 9.2 µm, 9.3 µm, 9.4 µm, 9.5 µm, 9.6 µm, 9.7 µm, 9.8 µm, 9.9 µm, 10.0 µm, 10.1 µm, 10.2 µm, 10.3 µm, 10.4 µm, 10.5 µm, 10.6 µm, 10.7 µm, 10.8 µm, 10.9 µm, 11.0 µm, 11.1 µm, 11.2 µm, 11.3 µm, 11.4 µm, 11.5 µm, 11.6 µm, 11.7 µm, 11.8 µm, 11.9 µm, 12.0 µm, 12.1 µm, 12.2 µm, 12.3 µm, 12.4 µm, 12.5 µm, 12.6 µm, 12.7 µm, 12.8 µm, 12.9 µm, 13.0 µm, 13.1 µm, 13.2 µm, 13.3 µm, 13.4 µm, 13.5 µm, 13.6 µm, 13.7 µm, 13.8 µm, 13.9 µm, 14.0 µm, 14.1 µm, 14.2 µm, 14.3 µm, 14.4 µm, 14.5 µm, 14.6 µm, 14.7 µm, 14.8 µm, 14.9 µm, 15.0 µm, 15.1 µm, 15.2 µm, 15.3 µm, 15.4 µm, 15.5 µm, 15.6 µm, 15.7 µm, 15.8 µm, 15.9 µm, 16.0 µm, 16.1 µm, 16.2 µm, 16.3 µm, 16.4 µm, 16.5 µm, 16.6 µm, 16.7 µm, 16.8 µm, 16.9 µm, 17.0 µm, 17.1 µm, 17.2 µm, 17.3 µm, 17.4 µm, 17.5 µm, 17.6 µm, 17.7 µm, 17.8 µm, 17.9 µm, or 18.0 µm. In another embodiment, the pharmaceutical composition has a particle size distribution by volume such that 90% of the cabotegravir particles (X90) have a particle diameter smaller than or equal to 9 µm (*i.e.*, X90 is 9 µm). In another embodiment, the pharmaceutical composition has a particle size distribution by volume such that 90% of the cabotegravir particles (X90) have a particle diameter smaller than or equal to 14 µm (*i.e.*, X90 is 14 µm). In another embodiment, the pharmaceutical composition has a particle size distribution by volume such that 90% of the cabotegravir particles (X90) have a particle diameter smaller than or equal to 17 µm (*i.e.*, X90 is 17 µm).

In an aspect, the pharmaceutical composition has a particle size distribution by volume such that 50% of the cabotegravir particles have a particle diameter less than or equal to 10 µm (*i.e.*, X50 is 10 µm). In an embodiment, cabotegravir particles of the pharmaceutical composition have an X50 value greater than or equal to 2.5 µm and less than or equal to 10 µm (*i.e.*, 2.5 µm ≤ X50 ≤ 10 µm). In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 50% of the cabotegravir particles have a particle diameter less than or equal to 8.5 µm (*i.e.*, X50 is 8.5 µm). In an embodiment, cabotegravir particles of the pharmaceutical composition have an X50 value greater than or equal to 3 µm and less than or equal to 8.5 µm (*i.e.*, 3 µm ≤ X50 ≤ 8.5 µm). In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 50% of the cabotegravir particles have a particle diameter less than or equal to 8 µm (*i.e.*, X50 is 8 µm). In an embodiment, cabotegravir particles of the pharmaceutical composition have an X50 value greater than or equal to 3.5 µm and less than or equal to 8 µm (*i.e.*, 3.5 µm ≤ X50 ≤ 8 µm).

In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 50% of the cabotegravir particles (X50) have a particle diameter smaller than or equal to 3.0 µm, 3.1 µm, 3.2 µm, 3.3 µm, 3.4 µm, 3.5 µm, 3.6 µm, 3.7 µm,

3.8 µm, 3.9 µm, 4.0 µm, 4.1 µm, 4.2 µm, 4.3 µm, 4.4 µm, 4.5 µm, 4.6 µm, 4.7 µm, 4.8 µm, 4.9 µm, 5.0 µm, 5.1 µm, 5.2 µm, 5.3 µm, 5.4 µm, 5.5 µm, 5.6 µm, 5.7 µm, 5.8 µm, 5.9 µm, 6.0 µm, 6.1 µm, 6.2 µm, 6.3 µm, 6.4 µm, 6.5 µm, 6.6 µm, 6.7 µm, 6.8 µm, 6.9 µm, 7.0 µm, 7.1 µm, 7.2 µm, 7.3 µm, 7.4 µm, 7.5 µm, 7.6 µm, 7.7 µm, 7.8 µm, 7.9 µm, or 8.0 µm. In another embodiment, the pharmaceutical composition has a particle size distribution by volume such that 50% of the cabotegravir particles (X50) have a particle diameter smaller than or equal to 4 µm (*i.e.*, X50 is 4 µm). In another embodiment, the pharmaceutical composition has a particle size distribution by volume such that 50% of the cabotegravir particles (X50) have a particle diameter smaller than or equal to 6 µm (*i.e.*, X50 is 6 µm).

In an aspect, the pharmaceutical composition has a particle size distribution by volume such that 10% of the cabotegravir particles have a particle diameter smaller than or equal to 4 µm (*i.e.*, X10 is 4 µm). In an embodiment, cabotegravir particles of the pharmaceutical composition have an X10 value greater than or equal to 0.5 µm and less than or equal to 4 µm (*i.e.*, 0.5 µm ≤ X10 ≤ 4 µm). In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 10% of the cabotegravir particles have a particle diameter less than or equal to 3.5 µm. In an embodiment, cabotegravir particles of the pharmaceutical composition have an X10 value greater than or equal to 1 µm and less than or equal to 3.5 µm (*i.e.*, 1 µm ≤ X10 ≤ 3.5 µm). In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 10% of the cabotegravir particles have a particle diameter less than or equal to 3 µm. In an embodiment, cabotegravir particles of the pharmaceutical composition have an X10 value greater than or equal to 1.5 µm and less than or equal to 3 µm (*i.e.*, 1.5 µm ≤ X10 ≤ 3 µm).

In an embodiment, the pharmaceutical composition has a particle size distribution by volume such that 10% of the cabotegravir particles (X10) have a particle diameter smaller than or equal to 1.0 µm, 1.1 µm, 1.2 µm, 1.3 µm, 1.4 µm, 1.5 µm, 1.6 µm, 1.7 µm, 1.8 µm, 1.9 µm, 2.0 µm, 2.1 µm, 2.2 µm, 2.3 µm, 2.4 µm, 2.5 µm, 2.6 µm, 2.7 µm, 2.8 µm, 2.9 µm, 3.0 µm, 3.1 µm, 3.2 µm, 3.3 µm, 3.4 µm, 3.5 µm, 3.6 µm, 3.7 µm, 3.8 µm, 3.9 µm, or 4.0 µm. In another embodiment, the pharmaceutical composition has a particle size distribution by volume such that 10% of the cabotegravir particles (X10) have a particle diameter smaller than or equal to 1.7 µm (*i.e.*, X10 is 1.7 µm). In another embodiment, the pharmaceutical composition has a particle size distribution by volume such that 10% of the cabotegravir particles (X10) have a particle diameter smaller than or equal to 2.2 µm (*i.e.*, X10 is 2.2 µm). In another embodiment, the pharmaceutical composition has a particle size distribution by volume such that 10% of the cabotegravir particles (X10) have a particle diameter smaller than or equal to 2.6 µm (*i.e.*, X10 is 2.6 µm).

The value X90 refers to the 90% value of the volume distribution measured using a laser diffractometer. For purposes of the present disclosure, the X90 value denotes the particle size below which 90% of the quantity of particles is found based on the volume distribution. Analogously, the value X50 refers to the 50% value (median) of the volume distribution measured using a laser diffractometer. For purposes of the present disclosure, the X50 value denotes the particle size below which 50% of the quantity of particles is found based on the volume distribution. Analogously, the value X10 refers to the 10% value of the volume distribution measured using a laser diffractometer. For purposes of the present disclosure, the X10 value denotes the particle size below which 10% of the quantity of particles is found based on the volume distribution.

In an embodiment, all X90, X50, and X10 values described herein are by volume and determined by laser diffraction method. The laser diffraction method is sensitive to the volume of a particle and provides a volume-average particle size, which is equivalent to the weight-average particle size if the density is constant. It will be apparent to those skilled in the art that the results of the particle size distribution determination by one technique can be correlated with that from another technique, for example on an empirical basis by routine experimentation. Alternatively, particle size distribution can be determined by microscopy, in particular electron microscopy or scanning electron microscopy.

Lyophilized form

For aqueous pharmaceutical suspensions, one pathway of long-term failure is irreversible product settling that creates an inability for these systems to be easily resuspended over the expected product shelf-life. In these cases of physical instability, drug content may not be uniform in the vial at time of administration, which may lead to inconsistent product dosing into patients. The physical stability of suspensions can be greatly influenced by the size of the particle being suspended. Particles size-reduced to under a few hundred nanometers may be stabilized by a variety of factors such as Brownian motion, steric stabilization by excipients, electric stabilization, flocculation, etc., which can all minimize effects of Van der Waals forces between particles that may result in irreversible product settling. However, particles in the range of a few microns may experience greater sedimentation rate and force due to their relatively larger size, which can overpower stabilizing forces separating particles. If these hydrophobic particles directly interact with each other in an aqueous environment, particle agglomeration is likely to occur—leading to irreversible settling. Thus, the inventors' discovery of a lyophilized formulation of micro-particles (as opposed to nano-particles) of cabotegravir is

both surprising and unexpected, as irreversible settling was observed to occur for micro-particles. Indeed, settling of micro-particle suspension of cabotegravir previously believed to be irreversible was surprisingly shown to be reversible following lyophilization. Due to this reversibility, lyophilized micro-particle suspensions of cabotegravir have unexpectedly extended shelf-life (*e.g.*, at least two years when stored at up to 30°C).

Lyophilization comprises at least a freezing step and a sublimation step. Lyophilization may be used in the manufacturing of pharmaceutical products and intermediates thereof. During freezing, the material is cooled to a temperature wherein the solid, liquid, and gas phases of the material may exist. Active pharmaceutical product ingredients (APIs) may be lyophilized to achieve chemical and physical stability allowing room temperature storage. This is different from a conventional method that evaporates water using heat. Advantages of lyophilization may include, but are not limited to, enhanced stability of a dry powder, the removal of water without excessive heating of the product, and enhanced product stability in a dry state.

In an exemplary method of preparing a lyophilized formulation of the invention, micronized cabotegravir free acid is packaged in antistatic linear low-density polyethylene bags. The packaged cabotegravir is enclosed in a corrugated plastic box and gamma irradiated as a bioburden reduction step and referred to as gamma irradiated cabotegravir. Gamma irradiated cabotegravir is dispersed in a filtered aqueous vehicle comprising a stabilizer (e.g., sodium CMC), a tonicity agent (e.g., mannitol), and a wetting agent (e.g., PS80). The resulting suspension is filled into washed, sterilized/depyrogenated 10 mL Type I clear glass vials. Container materials are then processed: vials are depyrogenated by dry heat, and stoppers and overseals are sterilized by steam. Product vials are lyophilized, backflushed with nitrogen, sealed with halobutyl rubber stoppers and secured by an aluminum overseal. The sealed vials are terminally sterilized by gamma irradiation. See FIGs. 1 & 2.

As evidenced in the examples, which illustrate certain representative embodiments of the invention, the inventors have developed lyophilized pharmaceutical compositions and methods to obtain said compositions that allow for larger-size particles of cabotegravir. Data provided herein indicate that such lyophilized pharmaceutical compositions reduce injection site reactions and contribute to improved pharmacokinetic properties, thus addressing one or more above-mentioned problems in the art.

In an embodiment, the lyophilized pharmaceutical composition is a suspension. The lyophilized pharmaceutical composition advantageously suspends when reconstituted in an aqueous or non-aqueous solution, that is, all or substantially all, such as at least 90 percent, at least 95 percent, at least 96 percent, at least 97 percent, at least 98 percent, at

least 99 percent, at least 99.5 percent or 100 percent of the lyophilized pharmaceutical composition is suspended when reconstituted.

Reconstitution can be assessed visually with the naked eye. The lyophilized matter is deemed reconstituted when a homogeneous suspension is observed. In particular, a solution with a cloudy appearance is considered suitably reconstituted.

It will be apparent to those skilled in the art that pharmaceutical compositions of the invention may be reconstituted in an aqueous or non-aqueous solution to a desired concentration. For example, the pharmaceutical composition described below in Examples 1-3 may be reconstituted in 1.7 mL water to achieve a cabotegravir concentration of 400 mg/mL. Similarly, the same pharmaceutical composition described below in Examples 1-3 may be reconstituted in 1.1 mL water to achieve a cabotegravir concentration of 533 mg/mL.

In an embodiment, the present disclosure provides a lyophilized pharmaceutical composition comprising cabotegravir, wherein cabotegravir is present in the form of particles having a mass median diameter (X50) of between (and including) 2.5 µm and 10 µm; a wetting agent; a stabilizer; and a tonicity adjuster; wherein the formulation, when reconstituted in an aqueous solution, has a reconstitution time of 15 minutes or less, 10 minutes or less, or 5 minutes or less. In another embodiment, the present disclosure provides a lyophilized pharmaceutical composition comprising cabotegravir, wherein cabotegravir is present in the form of particles having a mass median diameter (X50) of between (and including) 2.5 µm and 10 µm; PS80; sodium CMC; and mannitol; wherein the formulation, when reconstituted in an aqueous or non-aqueous solution, has a reconstitution time of 15 minutes or less, 10 minutes or less, or 5 minutes or less.

Exemplary embodiments

In an embodiment, the pharmaceutical composition comprises cabotegravir, mannitol, PS80, and sodium CMC; wherein cabotegravir is present in the form of particles having a mass median diameter (X5) of between (and including) 2.5 µm and 10 µm.

In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X50 = 6 µm); 51.8 mg mannitol; 5.9 mg PS80; and 7.4 mg sodium CMC. In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X10 = 2.2 µm); 51.8 mg mannitol; 5.9 mg PS80; and 7.4 mg sodium CMC. In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X90 = 17 µm); 51.8 mg mannitol; 5.9 mg PS80; and 7.4 mg sodium CMC. In an embodiment, the pharmaceutical

composition comprises 800 mg cabotegravir (X10 = 2.2 µm; X50 = 6 µm; X90 = 17 µm); 51.8 mg mannitol; 5.9 mg PS80; and 7.4 mg sodium CMC.

In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X50 = 6 µm); 70.0 mg mannitol; 8.0 mg PS80; and 10.0 mg sodium CMC. In an embodiment, the pharmaceutical composition comprises 800 mg (X10 = 2.6 µm); 70.0 mg mannitol; 8.0 mg PS80; and 10.0 mg sodium CMC. In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X90 = 14 µm); 70.0 mg mannitol; 8.0 mg PS80; and 10.0 mg sodium CMC. In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X10 = 2.6 µm; X50 = 6 µm; X90 = 14 µm); 70.0 mg mannitol; 8.0 mg PS80; and 10.0 mg sodium CMC.

In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X50 = 4 µm); 70.0 mg mannitol; 8.0 mg PS80; and 10.0 mg sodium CMC. In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X10 = 1.7 µm); 70.0 mg mannitol; 8.0 mg PS80; and 10.0 mg sodium CMC. In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X90 = 9 µm); 70.0 mg mannitol; 8.0 mg PS80; and 10.0 mg sodium CMC. In an embodiment, the pharmaceutical composition comprises 800 mg cabotegravir (X10 = 1.7 µm; X50 = 4 µm; X90 = 9 µm); 70.0 mg mannitol; 8.0 mg PS80; and 10.0 mg sodium CMC.

In another embodiment, the pharmaceutical composition comprises cabotegravir, wherein cabotegravir is present in the form of particles having an X50 value greater than or equal to 3.5 µm and less than or equal to 8 µm; PS80; sodium CMC; and mannitol; wherein a weight ratio of cabotegravir:PS80:sodium CMC:mannitol is about 100:1:1.25:8.75.

In another embodiment, the pharmaceutical composition comprises cabotegravir, wherein cabotegravir is present in the form of particles having an X50 value greater than or equal 3.5 µm and less than or equal to 8 µm; PS80; sodium CMC; and mannitol; wherein a weight ratio of cabotegravir:PS80:sodium CMC:mannitol is about 400:3:3.7:25.9.

In another embodiment, the pharmaceutical composition, after lyophilization and reconstitution, is as described in Table 2a:

Table 2a

Ingredient	Concentration (mg/mL)
Cabotegravir	340-500 (X10 = 1.4-3.3 µm; X50 = 3.4-7.5 µm; X90 = 7.6-21.3 µm)
Polysorbate 80	2.5-5.0
Sodium CMC	3.1-6.3
Mannitol	22-44

In another embodiment, the pharmaceutical composition, after lyophilization and reconstitution, is as described in Table 2b:

Table 2b

Ingredient	Concentration (mg/mL)
Cabotegravir	450-667 (X10 = 1.4-3.3 µm; X50 = 3.4-7.5 µm; X90 = 7.6-21.3 µm)
Polysorbate 80	2.5-5.0
Sodium CMC	3.1-6.3
Mannitol	22-44

In another embodiment, the pharmaceutical composition, after lyophilization and reconstitution, is as described in Table 2c:

Table 2c

Ingredient	Concentration (mg/mL)
Cabotegravir	400 (X10 = 2.2 µm; X50 = 6 µm; X90 = 17 µm)
Polysorbate 80	3.0
Sodium CMC	3.7
Mannitol	25.9

In another embodiment, the pharmaceutical composition, after lyophilization and reconstitution, is as described in Table 2d:

Table 2d

Ingredient	Concentration (mg/mL)
Cabotegravir	400 (X10 = 2.6 µm; X50 = 6 µm; X90 = 14 µm)
Polysorbate 80	4.0
Sodium CMC	5.0
Mannitol	35.0

In another embodiment, the pharmaceutical composition, after lyophilization and reconstitution, is as described in Table 2e:

Table 2e

Ingredient	Concentration (mg/mL)
Cabotegravir	400 (X10 = 1.7 µm; X50 = 4 µm; X90 = 9 µm)
Polysorbate 80	4.0
Sodium CMC	5.0
Mannitol	35.0

pH

In an embodiment the pharmaceutical composition of the invention has a pH of about 4 or greater. A pH of about 4 or more reduces pain to the patient if the composition is administered via injection. In an embodiment, the pharmaceutical composition of the invention has a pH of about 6.5.

Optional co-administrations

In an embodiment a pharmaceutical composition described herein is administered in combination with a broadly neutralising antibody. In some embodiments, the broadly neutralizing antibody is selected from the group consisting of VRC01, VRC01-LS, N6, N6LS, VRC07 and VRC07-523. An example of a disclosure of VRC01 is set forth in U.S Patent No. 8,637,036. An example of a disclosure of VRC01-LS is set forth in WO 2012/106578. Examples of disclosures of N6 and N6LS are set forth in WO 2016/196975. Examples of disclosures of VRC07 and VRC07-523 are set forth in U.S. Patent No. 8,637,036, US Patent Publication No. 2014/0322163 A1, WO 2016/196975 and WO 2017/79479.

In an embodiment, the broadly neutralising antibody is an isolated N6 monoclonal antibody or an antigen binding fragment thereof, comprising a heavy chain complementarity determining region (CDRH) having a CDRH1 amino acid sequence of SEQ ID NO: 1, a CDRH2 amino acid sequence of SEQ ID NO: 2, and a CDRH3 amino acid sequence of SEQ ID NO: 3; and a light chain complementarity determining region (CDRL) having a CDRL1 amino acid of SEQ ID NO: 4, a CDRL2 amino acid sequence of SEQ ID NO: 5, and a CDRH3 amino acid sequence of SEQ ID NO: 6.

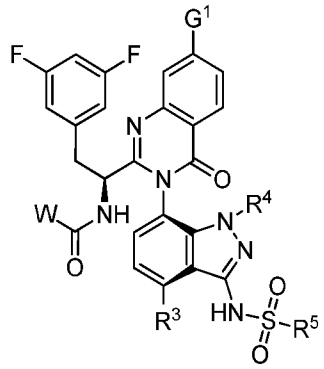
In an embodiment, the broadly neutralising antibody is an isolated N6LS monoclonal antibody or an antigen binding fragment, comprising a heavy chain complementarity determining region (CDRH) having a CDRH1 amino acid sequence of SEQ ID NO: 1, a CDRH2 amino acid sequence of SEQ ID NO: 2, and a CDRH3 amino acid sequence of SEQ ID NO: 3; a light chain complementarity determining region (CDRL) having a CDRL1 amino acid of SEQ ID NO: 4, a CDRL2 amino acid sequence of SEQ ID NO: 5, and a CDRH3 amino acid sequence of SEQ ID NO: 6; and a recombinant constant domain comprising M428L and N434S mutations. In some embodiments, the antigen binding fragment is a Fv, Fab, $F(ab')_2$, scFv or a $scFV_2$ fragment.

In some embodiments, the broadly neutralising antibody includes an amino acid substitution that increases binding to the FcRn. Several such substitutions are known to the person of ordinary skill in the art, such as substitutions at IgG constant regions T250Q and M428L (see, e.g., Hinton *et al.*, J Immunol, 176:346-356, 2006); M428L and N434S (the "LS" mutation, see, e.g., Zalevsky, *et al.*, Nature Biotechnology, 28:157-159, 2010); N434A (see, e.g., Petkova *et al.*, Int. Immunol, 18:1759-1769, 2006); T307A, E380A, and N434A (see, e.g., Petkova *et al.*, Int. Immunol, 18:1759-1769, 2006); and M252Y, S254T, and T256E (see, e.g., Dall'Acqua *et al.*, J. Biol. Chem., 281:23514-23524, 2006). The disclosed antibodies and antigen binding fragments can be linked to a Fc polypeptide including any of the substitutions listed above, for example, the Fc polypeptide can include the M428L and N434S substitutions. In some embodiments, the antibody comprises a recombinant constant domain comprising a modification that increases binding to a neonatal Fc receptor relative to an unmodified constant domain, wherein the recombinant domain is an IgG1 constant domain comprising M428L and N434S mutations.

In an embodiment the neutralising antibody is N6-LS. N6-LS is a broadly neutralising antibody, which comprises (a) a heavy chain variable region (VH) comprising a heavy chain complementarity determining region (HCDR)1, a HCDR2, and a HCDR3 of the VH set forth as SEQ ID NO: 1; (b) a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1, a LCDR2, and a LCDR3 of the VL set forth as SEQ ID NO: 2 or a VL comprising an amino acid sequence at least 90 percent identical to one of SEQ ID NO: 2; or (c) a combination of (a) and (b); further comprising an IgGl constant domain comprising M428L and N434S mutations; and wherein the antibody or antigen binding fragment specifically binds to HIV-1 gpl20 and neutralizes HIV-1 infection.

In an embodiment, a pharmaceutical composition described herein is administered in combination with a capsid inhibitor, a maturation inhibitor, a nucleoside reverse transcriptase translocation inhibitor (NRTTI), or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (optionally, rilpivirine).

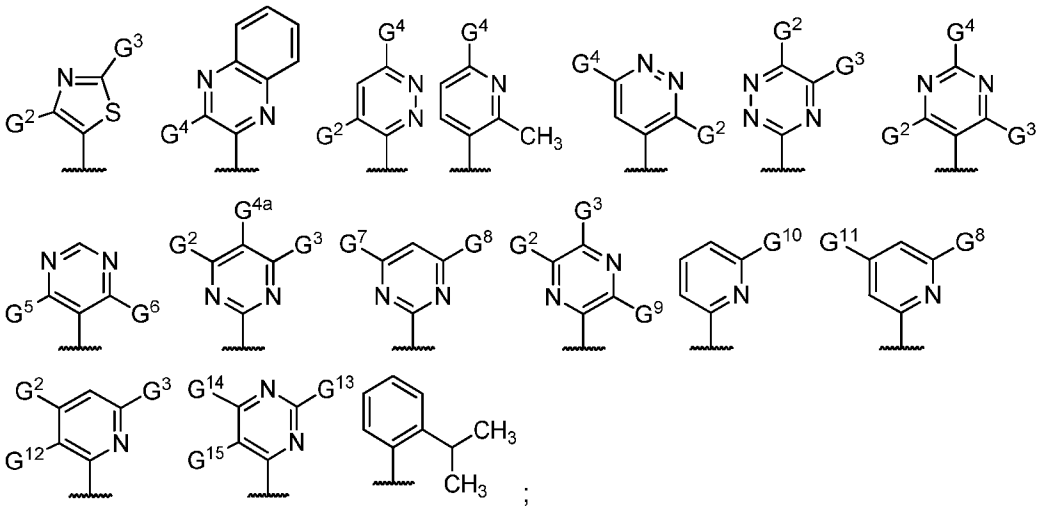
The pharmaceutical composition may be administered in combination with a capsid inhibitor. In an embodiment the capsid inhibitor is a compound of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein:

G^1 is phenyl substituted once with $-N(CH_3)S(O_2)CH_3$, $-S(O_2)C(CH_3)_3$, $-CHF_2$, $-CF_3$, $-OCHF_2$, $-OCF_3$, or $-C(CH_3)_2OH$, with the proviso that when G^1 is $-CHF_2$ or $-CF_3$, G^1 is not in the para position or G^1 is one of the following:



;

G^2 and G^3 are independently selected from is H or $-CH_3$;

G^4 is H, $-CH_3$, or $-OCH_3$;

G^{4a} is $-CH_3$, or $-OCH_3$;

G^5 is $-CH_3$, or CH_2CH_3;

G^6 is H, $-CH_3$, or CH_2CH_3;

G^7 is ethyl, isopropyl, *tert*-butyl, $-CHF_2$, or $-CF_3$;

G^8 is H, methyl, ethyl, $-CHF_2$, $-CF_3$, $-OCH_3$, or $-OCH_2CH_3$;

G^9 is ethyl, isopropyl, cyclopropyl, $-CH_2OH$, $-OCH_3$;

G^{10} is ethyl, isopropyl, cyclopropyl, *tert*-butyl, $-CHF_2$, or $-CF_3$;

G^{11} is methyl, $-OCH_3$, $-CHF_2$, $-CF_3$, $-S(O_2)CH_3$;

G^{12} is F, $-CH_3$, $-CHF_2$, $-CF_3$, $-OCH_3$, $-S(O_2)CH_3$;

G^{13} is C_1-C_4alkyl, C_1-C_6cycloalkyl, $-CH_2O(C_1$-C_3alkyl);

G^{14} is H, C_1-C_4alkyl, -CHF_2, -CF_3, -O(C_1-C_3alkyl);

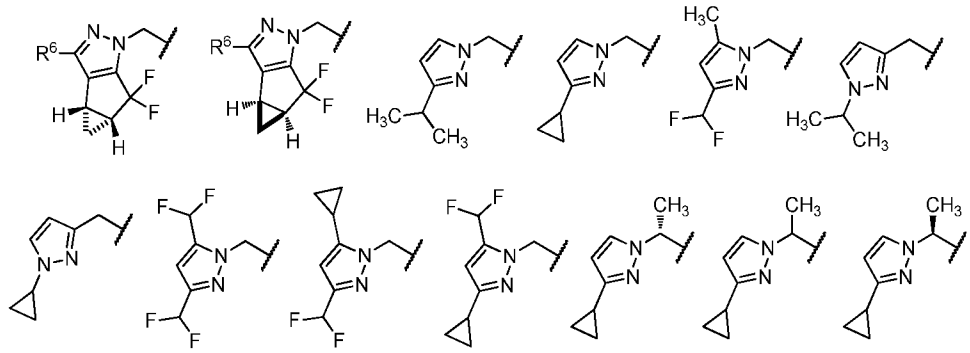
G^{15} is H, F, -CH_3, or OCH_3;

R^3 is H, F, Cl, -CH_3, or -OCH_3;

R^4 is H or C_1-C_3alkyl wherein C_1-C_3alkyl is optionally substituted with 1-3 fluorines;

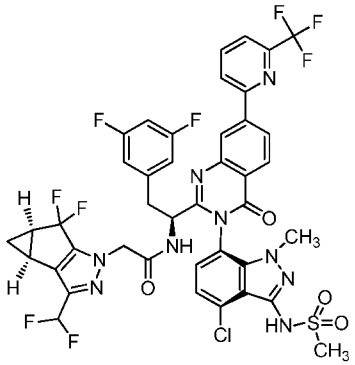
R^5 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

W is selected from:



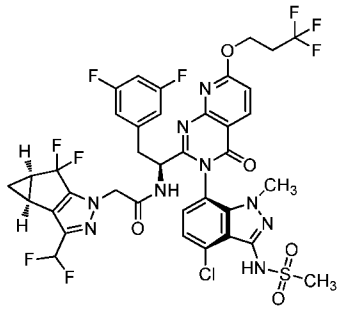
where R^6 is methyl optionally substituted with 1 to 3 fluorines.

Compounds of Formula (III) are described in WO2020/084492 which is incorporated by reference. In an embodiment the capsid inhibitor is Compound 1 or a pharmaceutically acceptable salt thereof. Compound 1 is described in WO 2020/084492 as Example 59 which example is incorporated herein by reference.



Compound 1.

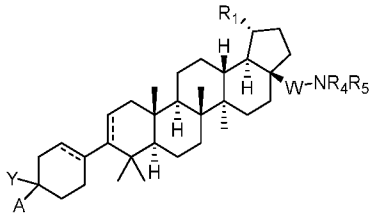
In an embodiment the capsid inhibitor is Compound 2 pharmaceutically acceptable salt thereof. Compound 2 is described in patent application number PCT/IB2020/055653 as Example 1, which example is incorporated herein by reference.



Compound 2.

In an alternative embodiment, the capsid inhibitor is lenacapavir.

The pharmaceutical composition may be administered in combination with a maturation inhibitor. In an embodiment the maturation inhibitor is a compound of Formula (IV) or a pharmaceutically acceptable salt thereof:



Formula (IV)

wherein R_1 is isopropenyl or isopropyl;

A is -C_{1-6} alkyl-OR_0;

wherein R_0 is heteroaryl-Q_0;

Q_0 is selected from the group of -H, -CN, -C_{1-6} alkyl, -COOH, -Ph, -OC_{1-6} alkyl, -halo, -CF_3,

Y is selected from the group of -$COOR_2$, -$C(O)NR_2SO_2R_3$, -$C(O)NHSO_2NR_2R_2$, -$SO_2NR_2C(O)R_2$, -tetrazole, and -CONHOH,

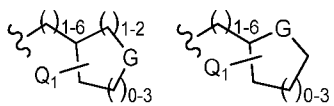
wherein n = 1-6;

R_2 is -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or-arylsubstituted C_{1-6} alkyl;

W is absent, or is -CH_2- or -CO-;

R_3 is –H, -C_{1-6} alkyl or -alkylsubstituted C_{1-6} alkyl;

R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} substituted -C_{1-6} alkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl, -COR_6, -SO_2R_7, -$SO_2NR_2R_2$, and



wherein G is selected from the group of –O-, -SO_2- and -NR_{12}-;

wherein Q_1 is selected from the group of -C_{1-6} alkyl, - C_{1-6} fluoroalkyl, heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_8R_9$ and -SO_2R_7;

R_5 is selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkylsubstituted alkyl, -C_{1-6} alkyl-NR_8R_9, -COR_3, -SO_2R_7 and -$SO_2NR_2R_2$;

with the proviso that R_4 or R_5 is not -COR_6 when W is -CO-;

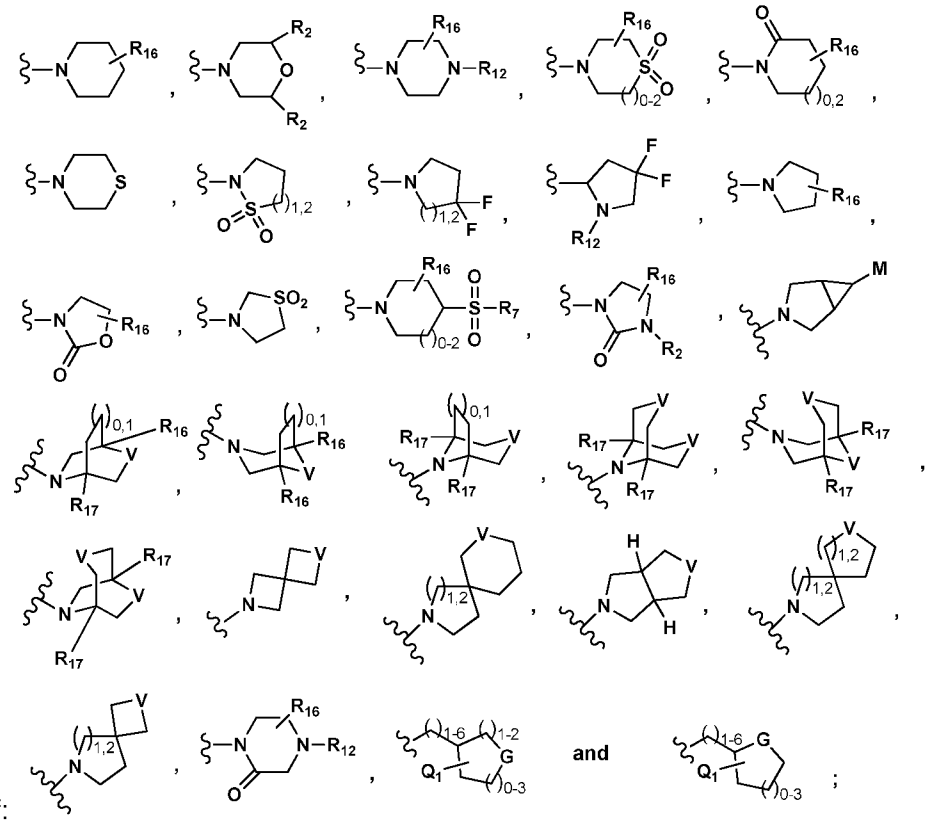
with the further proviso that only one of R_4 or R_5 is selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$;

R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2,-C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -$NR_{13}R_{14}$, and -OR_{15};

wherein Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_2$, -NR_8R_9, SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

R_7 is selected from the group of –H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{3-6} cycloalkyl, -CF_3, aryl, and heteroaryl;

R_8 and R_9 are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C_{1-6} alkyl-Q_2, and -$COOR_3$, or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



M is selected from the group of –R_{15}, -SO_2R_2, -$SO_2NR_2R_2$, -OH and –NR_2R_{12};

V is selected from the group of –$CR_{10}R_{11}$-, -SO_2-, -O- and –NR_{12}-;

with the proviso that only one of R_8 or R_9 can be -$COOR_3$;

R_{10} and R_{11} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl and -C_{3-6} cycloalkyl;

R_{12} is selected from the group of -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl, -$CONR_2R_2$, -SO_2R_3, and -$SO_2NR_2R_2$;

R_{13} and R_{14} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3, and C_{1-6} substituted alkyl-Q_3;

Q_3 is selected from the group of heteroaryl, substituted heteroaryl, -NR_2R_{12}, -$CONR_2R_2$, -$COOR_2$, -OR_2, and -SO_2R_3;

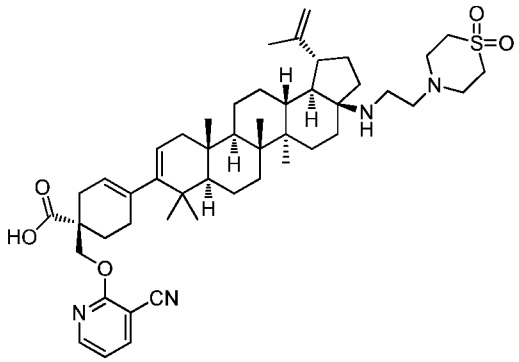
R_{15} is selected from the group of -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3 and -C_{1-6} substituted alkyl-Q_3;

R_{16} is selected from the group of -H, -C_{1-6} alkyl, -NR_2R_2, and –$COOR_2$;

with the proviso that when V is –NR_{12}-; R_{16} is not –NR_2R_2; and

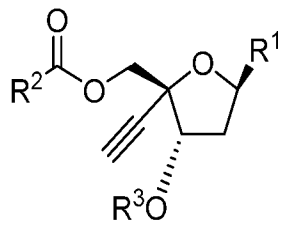
R_{17} is selected from the group of -H, -C_{1-6} alkyl, -$COOR_3$, and aryl.

Compounds of Formula (IV) are described in WO 2017/134596 which is incorporated herein by reference. In an embodiment the maturation inhibitor is Compound 3. Compound 3 is described in WO 2017/134596 as Example 25 which example is incorporated herein by reference.



Compound 3.

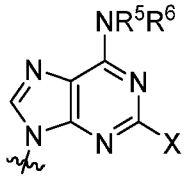
The pharmaceutical composition may be administered in combination with an NRTTI. In an embodiment the NRTTI is a compound of the formula (V):



Formula (V)

wherein:

R^1 is:



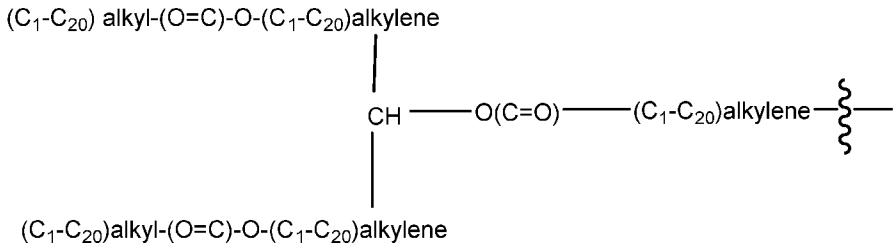
wherein:

X is selected from the group consisting of NH_2, F and Cl;

R^5 is selected from the group consisting of H and (C_1-C_{14}) alkyl;

R^6 is selected from the group consisting of H and -(C=O)-(C_1-C_{14}) alkyl;

R^2 is selected from the group consisting of (C_1-C_{24}) alkyl; $(CH_2)_{n1}$-O-$(CH_2CH_2O)_{n2}$-(C_1-C_{14} alkyl) where n1 and n2 are integers independently selected from 1-4; -R^7-NH-(C=O)-R^8 wherein R^7 may be (C_1-C_{14}) alkyl and R^8 may be independently selected from H and (C_1-C_{14}) alkyl; -R^9-(C_6-C_{14}) aryl, wherein R^9 is a bond or (C_1-C_6) alkyl; -R^{10}-(C_3-C_{14}) cycloalkyl, wherein R^{10} is a bond or (C_1-C_6) alkyl; -(C_1-C_{20}) alkylene-(C=O)-O-R^{11} wherein R^{11} may be selected from H and (C_1-C_{20})alkyl;



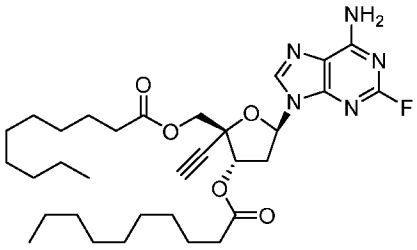
and;

R^3 is selected from the group consisting of H, -(C=O)-(C_1-C_{24}) alkyl; -(C=O)-O-(C_1-C_{24}) alkyl; and C_3-C_{14} cycloalkyl; or

R^2 and R^3 join together to form a C_3 to C_{28} cyclic structure; and

with the proviso that when R^2 is (C_1-C_{14} alkyl) at least one of R^3, R^5 and R^6 is not H.

Compounds of Formula 3 are disclosed in WO 2020/178767 which is incorporated by reference herein. In an embodiment a pharmaceutical composition of the invention is combined with Compound 4. Compound 4 is described in WO 2020/178767 as Example 18, which example is incorporated by reference herein.



Compound 4

In an alternative embodiment the NRTTI is Islatravir.

Methods for treatment and prevention of HIV

In a second aspect, the present invention provides methods for (a) treatment of HIV in a human in need thereof comprising administering to said human a therapeutically effective amount of a pharmaceutical composition as defined herein; and (b) prevention of HIV in a human comprising administering to said human an effective amount of a pharmaceutical composition as defined herein.

In one embodiment, the method comprises administering the pharmaceutical composition parenterally. In an embodiment, the pharmaceutical composition is administered intramuscularly. In an embodiment, the pharmaceutical composition is administered subcutaneously.

In an embodiment the method comprises administering around 1mL to around 8 mL of the pharmaceutical composition to a patient. In an embodiment the method comprises administering around 1mL of the pharmaceutical composition to a patient. In another embodiment the method comprises administering around 2 mL of the pharmaceutical composition to a patient. In an embodiment the method comprises administering around 3 mL of the pharmaceutical composition to a patient. In an embodiment the method comprises administering around 4 mL of the pharmaceutical composition to a patient. In an embodiment the method comprises administering around 5 mL of the pharmaceutical composition to a patient. In an embodiment the method comprises administering around 6 mL of the pharmaceutical composition to a patient. In an embodiment the method comprises administering around 7 mL of the pharmaceutical composition to a patient. In an embodiment the method comprises administering around 8 mL of the pharmaceutical composition to a patient.

In an embodiment, the pharmaceutical composition is administered in more than one injection. In an embodiment, the pharmaceutical composition is administered in two or more injections, which may be simultaneously or consecutively administered. For example, two separate injections of 3 mL (for a total of 6 mL) of the pharmaceutical composition may be consecutively administered to the patient. In an embodiment, the pharmaceutical composition is administered in two injections.

In an embodiment, about 300 mg to about 3200 mg of cabotegravir is administered to the patient in the pharmaceutical composition.

In an embodiment, the pharmaceutical composition has a cabotegravir concentration of about 400 mg/mL and about 800 mg to about 1600 mg of cabotegravir is administered to the patient. In an embodiment, the pharmaceutical composition has a

cabotegravir concentration of about 400 mg/mL and 800 mg of cabotegravir is administered to the patient. In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 400 mg/mL and 1200 mg of cabotegravir is administered to the patient.

In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 533 mg/mL and about 1200 to about 3200 mg of cabotegravir is administered to the patient. In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 533 mg/mL and about 1600 mg of cabotegravir is administered to the patient. In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 533 mg/mL and about 2400 mg of cabotegravir is administered to the patient. In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 533 mg/mL and about 3200 mg of cabotegravir is administered to the patient.

In an embodiment the pharmaceutical composition is administered to a patient once every 1, 2, 3, 4, 5, or 6 months. In an embodiment, the pharmaceutical composition is administered to the human once every month. In an alternative embodiment, the pharmaceutical composition is administered once every two months. In an alternative embodiment, the pharmaceutical composition is administered once every three months. In an alternative embodiment, the pharmaceutical composition is administered once every four months. In an alternative embodiment, the pharmaceutical composition is administered once every five months. In an alternative embodiment, the pharmaceutical composition is administered once every six months.

In an embodiment, the pharmaceutical composition may be administered by any suitable means.

In one embodiment, pharmaceutical composition may be administered subcutaneously. In this embodiment, the pharmaceutical composition may be administered subcutaneously by another (e.g., by a healthcare professional) or may be self-administered by a patient. In this embodiment the pharmaceutical composition may be administered subcutaneously via injection. In an embodiment the pharmaceutical composition is administered subcutaneously via injection. In an embodiment of the invention the pharmaceutical composition is administered or self-administered once monthly by subcutaneous injection. In another embodiment, the pharmaceutical composition is administered or self-administered once every two months by subcutaneous injection. In another embodiment, the pharmaceutical composition is administered or self-administered once every three months by subcutaneous injection. In another embodiment, the pharmaceutical composition is administered or self-administered once every four months by subcutaneous injection. In another embodiment, the pharmaceutical

composition is administered or self-administered once every five months by subcutaneous injection. In another embodiment, the pharmaceutical composition is administered or self-administered once every six months by subcutaneous injection. In an embodiment, the pharmaceutical composition is administered or self-administered in one injection. In another embodiment, the pharmaceutical composition is administered or self-administered in two or more injections, which may be simultaneously or consecutively administered. In an embodiment, the pharmaceutical composition is administered or self-administered in two injections.

In another embodiment the pharmaceutical composition is administered intramuscularly via injection. In this embodiment, the pharmaceutical composition may be administered intramuscularly by another (e.g., by a healthcare professional) or may be self-administered by a patient. In an embodiment of the invention, the pharmaceutical composition is administered or self-administered intramuscularly via injection once every month. In another embodiment, the pharmaceutical composition is administered or self-administered intramuscularly via injection once every two months. In another embodiment, the pharmaceutical composition is administered or self-administered intramuscularly via injection once every three months. In another embodiment, the pharmaceutical composition is administered or self-administered intramuscularly via injection once every four months. In another embodiment, the pharmaceutical composition is administered or self-administered intramuscularly via injection once every five months. In another embodiment, the pharmaceutical composition is administered or self-administered intramuscularly via injection once every six months. In an embodiment the intramuscular injection is administered by a healthcare professional. In an embodiment, the pharmaceutical composition is intramuscularly administered in one injection during a visit with a healthcare professional. In another embodiment, the pharmaceutical composition is intramuscularly administered in two or more injections, which may be simultaneously or consecutively administered, during one visit with a healthcare professional. In an embodiment, the pharmaceutical composition is intramuscularly administered in two injections, which may be simultaneously or consecutively administered, during one visit with a healthcare professional. In another embodiment, the pharmaceutical composition is intramuscularly self-administered in one injection. In another embodiment, the pharmaceutical composition is intramuscularly self-administered in two or more injections, which may be simultaneously or consecutively self-administered. In an embodiment, the pharmaceutical composition is intramuscularly self-administered in two injections, which may be simultaneously or consecutively self-administered.

In an embodiment the pharmaceutical compositions of the present invention are administered in combination with other pharmaceutical compositions as a component of a multi drug treatment regimen. In an embodiment, the other pharmaceutical compositions are drugs which treat or prevent HIV. Marketed medicines are currently available to treat HIV.

In an embodiment the pharmaceutical compositions of the present invention are administered in combination with N6-LS. N6-LS is described above.

In an embodiment the pharmaceutical compositions of the present invention are administered in combination with a capsid inhibitor, a maturation inhibitor or a nucleoside reverse transcriptase translocation inhibitor (NRTTI), or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (optionally, rilpivirine).

Use in treatment or prevention of HIV

In a third aspect, the present invention provides a pharmaceutical composition defined herein for use in the treatment or prevention of HIV.

In one embodiment the use comprises administering the pharmaceutical composition parenterally. In one embodiment, the pharmaceutical composition is suitable for use as an injectable composition. In an embodiment the use comprises administering the pharmaceutical composition intramuscularly. In another embodiment the use comprises administering the pharmaceutical composition subcutaneously.

In an embodiment the use comprises administering around 1mL to around 8 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 1mL of the pharmaceutical composition to a patient. In another embodiment the use comprises administering around 2 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 3 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 4 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 5 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 6 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 7 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 8 mL of the pharmaceutical composition to a patient.

In an embodiment, the use comprises administering the pharmaceutical composition in more than one injection. In an embodiment, the use comprises administering the pharmaceutical composition in two or more injections, which may be simultaneously or consecutively administered. For example, two separate injections of 3

mL (for a total of 6 mL) of the pharmaceutical composition may be consecutively administered to the patient. In an embodiment, the use comprises administering the pharmaceutical composition in two injections.

In an embodiment, about 300 mg to about 3200 mg of cabotegravir is administered to the patient in the pharmaceutical composition.

In an embodiment, the pharmaceutical composition has a cabotegravir concentration of about 400 mg/mL and about 800 mg to about 1600 mg of cabotegravir is administered to the patient. In an embodiment, the pharmaceutical composition has a cabotegravir concentration of about 400 mg/mL and 800 mg of cabotegravir is administered to the patient. In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 400 mg/mL and 1200 mg of cabotegravir is administered to the patient.

In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 533 mg/mL and about 1200 to about 3200 mg of cabotegravir is administered to the patient. In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 533 mg/mL and about 1600 mg of cabotegravir is administered to the patient. In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 533 mg/mL and about 2400 mg of cabotegravir is administered to the patient. In an embodiment the pharmaceutical composition has a cabotegravir concentration of about 533 mg/mL and about 3200 mg of cabotegravir is administered to the patient.

In an embodiment the use comprises administering the pharmaceutical to a patient once every 1, 2, 3, 4, 5, or 6 months. In an embodiment the use comprises administering the pharmaceutical composition to a patient once every month. In an alternative embodiment, the use comprises administering the pharmaceutical composition once every two months. In an alternative embodiment the use comprises administering the pharmaceutical composition once every three months. In an alternative embodiment the use comprises administering the pharmaceutical composition once every four months. In an alternative embodiment the use comprises administering the pharmaceutical composition once every five months. In an alternative embodiment the use comprises administering the pharmaceutical composition once every six months.

In an embodiment, use comprises administering the pharmaceutical composition by any suitable means.

In one embodiment, the use comprises the patient self-administering the pharmaceutical composition. In this embodiment the use may comprise administering the pharmaceutical composition subcutaneously via injection. In one embodiment of the invention the use comprises self-administering the pharmaceutical composition once

monthly by subcutaneous injection. In another embodiment, the use comprises self-administering the pharmaceutical composition once every two months by subcutaneous injection. In another embodiment, the use comprises self-administering the pharmaceutical composition once every three months by subcutaneous injection. In another embodiment, the use comprises self-administering the pharmaceutical composition once every four months by subcutaneous injection. In another embodiment, the use comprises self-administering the pharmaceutical composition once every five months by subcutaneous injection. In another embodiment, the use comprises self-administering the pharmaceutical composition once every six months by subcutaneous injection. In an embodiment, the use comprises self-administering the pharmaceutical composition in one injection. In another embodiment, the use comprises self-administering the pharmaceutical composition in two or more injections, which may be simultaneously or consecutively administered. In an embodiment, the use comprises self-administering the pharmaceutical composition in two injections.

In another embodiment the use comprises administering the pharmaceutical composition intramuscularly via injection. In an embodiment of the invention, the use comprises administering the pharmaceutical composition intramuscularly via injection once every month. In another embodiment, the use comprises administering the pharmaceutical composition intramuscularly via injection once every two months. In another embodiment, the use comprises administering the pharmaceutical composition intramuscularly via injection once every three months. In another embodiment, the use comprises administering the pharmaceutical composition intramuscularly via injection once every four months. In another embodiment, the use comprises administering the pharmaceutical composition intramuscularly via injection once every five months. In another embodiment, the use comprises administering the pharmaceutical composition intramuscularly via injection once every six months. In an embodiment the intramuscular injection is administered by a healthcare professional. In an embodiment, the use comprises intramuscularly administering the pharmaceutical composition in one injection during a visit with a healthcare professional. In another embodiment, the use comprises intramuscularly administering the pharmaceutical composition in two or more injections, which may be simultaneously or consecutively administered, during one visit with a healthcare professional. In an embodiment, the use comprises intramuscularly administering the pharmaceutical composition in two injections during one visit with a healthcare professional.

In an embodiment of the invention use comprises administering the pharmaceutical compositions of the present invention in combination with other pharmaceutical compositions as a component of a multi drug treatment regimen. In an

embodiment, the other pharmaceutical compositions are drugs which treat or prevent HIV. Marketed medicines are currently available to treat HIV.

In an embodiment the use comprises administering the pharmaceutical compositions of the present invention in combination with N6-LS. N6-LS is described above.

In an embodiment the use comprises administering the pharmaceutical compositions of the present invention in combination with a capsid inhibitor, a maturation inhibitor or a nucleoside reverse transcriptase translocation inhibitor (NRTTI), or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (optionally, rilpivirine).

Kit

In a fourth aspect the present invention provides a kit comprising cabotegravir, wherein cabotegravir is present in the form of particles having an X50 value greater than or equal to 2.5 μm and less than or equal to 10 μm; a wetting agent; a stabilizer; and a tonicity adjuster. In an embodiment the kit comprises a syringe or vial comprising a composition of the invention as well as a leaflet comprising use instructions.

In an embodiment the present invention provides a method of preparing a reconstituted solution, the method comprising providing the kit as described here and contacting the lyophilized composition with a suitable liquid to produce a reconstituted solution. In an embodiment the suitable liquid is an aqueous solvent. In an embodiment the suitable liquid is water. In another embodiment the suitable liquid is a non-aqueous solvent.

EXAMPLES

In the following description of the Examples, specific embodiments are described. These embodiments are described in sufficient detail to enable those skilled in the art to practice certain embodiments of the present disclosure. Other embodiments may be utilized and logical and other changes may be made without departing from the scope of the disclosure. The following description is, therefore, not intended to limit the scope of the present disclosure.

Cabotegravir particle sizes in microsuspensions in the following examples were measured according to the below protocol description.

Protocol Description

- Carried out the method for Laser Diffraction Measurement of Particle Size (USP <429>).

- Reconstituted the lyophilized product with water for injection (WFI) (volume of WFI determined by desired concentration of reconstituted suspension)
- Cleaned and filled Malvern Mastersizer 3000 laser diffraction with MV instrument with deionized water.
- Dispersion stirring speed was 2000 rpm, particle refractive index was 1.67, particle absorption Index (imaginary part of refractive index) was 0.01, General Purpose analysis mode with normal sensitivity, dispersant (DI water) refractive index was 1.33, measurement time and background time were both 10 seconds, and 2 measurements were acquired by the instrument per aliquot.
- Performed an alignment and measured the background.
- Agitated suspension (created in below examples) to ensure that all particles are suspended in the drug product vial.
- Withdrew ~0.2mL of content with a 1 mL syringe fitted with a needle (18 G).
- Added two drops of the suspension into a microcentrifuge tube containing 0.5mL of 6.6% w/v P338 in water solution.
- Vortexed gently to create a homogenous dispersion of drug product in P338 dispersant.
- Added appropriate amount of this dispersion to the instrument until obscuration of 5% - 7% is achieved.
- Allowed test suspension to circulate in the instrument for approximately 30 seconds prior to initiating the measurement.
- Performed the measurement, and after each measurement flushed the instrument with deionized water.
- Repeated this three times using a new aliquot of the sample each time and calculated the average values obtained from the volume distribution.

Example 1

Table 3

Ingredient	**Concentration (mg/mL)**
Cabotegravir, micronized	400.0
Sodium Carboxymethylcellulose	3.7
Polysorbate 80	3.0
Mannitol	25.9

Table 3 shows an exemplary pharmaceutical composition of the invention (pharmaceutical compositions are also described in these examples as “suspensions”), which was made using the following method.

A formulation vehicle was prepared by dissolving/diluting 24.0g polysorbate 80 ("PS80") (Croda) in about 300g water. Separately, 30.0g sodium carboxymethylcellulose ("NaCMC") (Ashland, 7L2P) and 210.0g mannitol (Roquette Freres) were dissolved in 4.8kg water for injection (WFI). Once the NaCMC and mannitol were dissolved, the PS80 solution was added to the NaCMC-mannitol solution with stirring. The weighing and dilution vessels were rinsed into the compounding vessel with additional water and the compounded vehicle solution was brought to a final weight of 6.06kg and filtered through a 0.2µm filter. 1.6kg Cabotegravir Micronized Free Acid (target X50 = 5-6µm particle size) was added to 3.0kg filtered vehicle and was mixed to form a homogeneous suspension. The compounded suspension was deaerated while stirring until it reached its target batch volume, and the suspension was then filled into vials. The product was lyophilized by freezing at -45°C for at least 2 hours, annealing at -18°C for at least 2 hours, refreezing at -45°C for at least 2 hours (each transition at a ramp rate of +/- 1°C/min), primary drying at -10°C (ramp rate: 0.15°C/min) for at least 20 hours at approximately 150 mTorr, and secondary drying at 25°C (ramp rate: 0.5°C/min) for at least 6 hours at approximately 150 mTorr. The lyophilized vials were backflushed with nitrogen to about 600 Torr, sealed, and sterilized by gamma irradiation at a minimum dose of 25kGy. The formulation is reconstituted with WFI and briefly shaken to resuspend prior to administration.

Example 2

Table 4

Ingredient	Concentration (mg/mL)
Cabotegravir, micronized	400.0
Sodium Carboxymethylcellulose	5.0
Polysorbate 80	4.0
Mannitol	35.0

Table 4 shows an exemplary pharmaceutical composition of the invention (pharmaceutical compositions are also described in these examples as "suspensions"), which was made using the following method.

A formulation vehicle was prepared by dissolving/diluting 24.0g polysorbate 80 ("PS80") (Croda) in about 300g water. Separately, 30.0g sodium carboxymethylcellulose ("NaCMC") (Ashland, 7L2P) and 210.0g mannitol (Roquette Freres) were dissolved in 3.4kg water for injection (WFI). Once the NaCMC and mannitol were dissolved, the PS80 solution was added to the NaCMC-mannitol solution with stirring. The weighing and dilution vessels were rinsed into the compounding vessel with additional water and the compounded vehicle solution was brought to a final weight of 4.50kg and filtered through a 0.2µm filter. 1.6kg Cabotegravir Micronized Free Acid (target X50 = 5-6µm particle size)

was added to 3.0kg filtered vehicle and was mixed to form a homogeneous suspension. The compounded suspension was deaerated while stirring until it reached its target batch volume, and the suspension was then filled into vials. The product was lyophilized by freezing at -45°C for at least 2 hours, annealing at -18°C for at least 2 hours, refreezing at -45°C for at least 2 hours (each transition at a ramp rate of +/- 1°C/min), primary drying at -10°C (ramp rate: 0.15°C/min) for at least 20 hours at approximately 150 mTorr, and secondary drying at 25°C (ramp rate: 0.5°C/min) for at least 6 hours at approximately 150 mTorr. The lyophilized vials were backflushed with nitrogen to about 600 Torr, sealed, and sterilized by gamma irradiation at a minimum dose of 25kGy. The formulation is reconstituted with WFI and briefly shaken to resuspend prior to administration.

Example 3

Table 5

Ingredient	Concentration (mg/mL)
Cabotegravir, micronized	400.0
Sodium Carboxymethylcellulose	5.0
Polysorbate 80	4.0
Mannitol	35.0

Table 5 shows an exemplary pharmaceutical composition of the invention (pharmaceutical compositions are also described in these examples as “suspensions”), which was made using the following method.

A formulation vehicle was prepared by dissolving/diluting 24.0g polysorbate 80 (“PS80”) (Croda) in about 300g water. Separately, 30.0g sodium carboxymethylcellulose (“NaCMC”) (Ashland, 7L2P) and 210.0g mannitol (Roquette Freres) were dissolved in 3.4kg water for injection (WFI). Once the NaCMC and mannitol were dissolved, the PS80 solution was added to the NaCMC-mannitol solution with stirring. The weighing and dilution vessels were rinsed into the compounding vessel with additional water and the compounded vehicle solution was brought to a final weight of 4.50kg and filtered through a 0.2µm filter. 1.6kg Cabotegravir Micronized Free Acid (target X50 = 3-4µm particle size) was added to 3.0kg filtered vehicle and was mixed to form a homogeneous suspension. The compounded suspension was deaerated while stirring until it reached its target batch volume, and the suspension was then filled into vials. The product was lyophilized by freezing at -45°C for at least 2 hours, annealing at -18°C for at least 2 hours, refreezing at -45°C for at least 2 hours (each transition at a ramp rate of +/- 1°C/min), primary drying at -10°C (ramp rate: 0.15°C/min) for at least 20 hours at approximately 150 mTorr, and secondary drying at 25°C (ramp rate: 0.5°C/min) for at least 6 hours at approximately 150 mTorr. The lyophilized vials were backflushed with nitrogen to about 600 Torr, sealed,

and sterilized by gamma irradiation at a minimum dose of 25kGy. The formulation is reconstituted with WFI and briefly shaken to resuspend prior to administration.

Table 6, below, applies to Examples 4-6.

Table 6

Batch #	Formulation
1	Cabotegravir 400 mg/mL; 0.4 w/v% PS80; 0.5 w/v% NaCMC; 3.5 w/v% Mannitol
2	Cabotegravir 400 mg/mL; 0.4 w/v% PS20; 0.5 w/v% NaCMC; 3.5 w/v% Mannitol
3	Cabotegravir 400 mg/mL; 0.4 w/v% P338; 0.5 w/v% NaCMC; 3.5 w/v% Mannitol

Example 4: Stability of a composition comprising cabotegravir, sodium carboxymethylcellulose, polysorbate 80 and mannitol

A formulation vehicle was prepared by dissolving 2.10g PS80 (Croda), 2.63g NaCMC (Ashland), and 18.38g mannitol (Roquette Freres) in 369.6g WFI and filtering the solution through a 0.2µm filter. The formulation vehicle was added to 210g Cabotegravir (free acid) to prepare a 400 mg/mL coarse suspension. The suspension was covered and stirred for 2 hrs. The suspension was filled into Type I glass vials and lyophilized as described in Examples 1-3. The lyophilized suspension was reconstituted to a cabotegravir concentration of 400 mg/mL.

Table 7: Batch #1 (400 mg/mL cabotegravir; 0.4 w/v% PS80; 0.5 w/v% NaCMC; 3.5 w/v% mannitol)

Storage Condition	Time (Months)	Particle Size by Laser Diffraction (microns)		
		X10	X50	X90
Initial	0	3.1	7.6	15.6
30°C/75% RH Upright	1	3.2	7.7	15.4
	3	3.2	7.5	14.3
	6	3.2	7.6	15.3
	9	3.2	7.5	14.8
	12	3.3	7.5	14.3
40°C/75% RH Upright	1	3.2	7.6	15.0
	3	3.2	7.7	14.9
	6	3.1	7.3	13.9
50°C/AmbH Upright	DY14	3.2	7.7	15.7
	1	3.2	7.6	15.3
	3	3.3	7.7	14.7

Notes:
AmbH Ambient Humidity
RH Relative Humidity
- Denotes testing not scheduled at these timepoints
NGT = Not greater than
NLT = Not less than

Example 5: Stability of a composition comprising cabotegravir, sodium carboxymethylcellulose, polysorbate 20 and mannitol

A formulation vehicle was prepared by dissolving 2.10g polysorbate 20 (Croda), 2.63g sodium CMC (Ashland), and 18.38g mannitol (Roquette Freres) in 550.9g WFI and filtering the solution through a 0.2µm filter. The formulation vehicle was added to 210g cabotegravir (free acid) to prepare a 300 mg/mL coarse suspension. The suspension was covered and stirred for 2 hrs. The suspension was filled into Type I glass vials and lyophilized as described in Examples 1-3. The lyophilized suspension was reconstituted to a cabotegravir concentration of 400 mg/mL.

Table 8: Batch #2 (400 mg/mL cabotegravir; 0.4 w/v% PS20; 0.5 w/v% NaCMC; 3.5 w/v% mannitol)

Storage Condition	Time (Months)	Particle Size by Laser Diffraction (microns)		
		X10	X50	X90
Initial	0	3.0	7.4	14.9
30°C/75% RH Upright	1	3.0	7.4	14.8
	3	3.0	7.4	15.0
	6	2.9	7.0	13.8
	9	3.0	7.3	14.0
	12	3.2	7.4	14.0
40°C/75% RH Upright	1	2.8	7.1	14.2
	3	2.9	7.3	14.6
	6	2.9	7.1	14.4
50°C/AmbH Upright	DY14	2.8	7.2	14.7
	1	2.9	7.3	14.3
	3	3.0	7.4	14.4

Notes:
AmbH Ambient Humidity
RH Relative Humidity
- Denotes testing not scheduled at these timepoints
NGT = Not greater than
NLT = Not less than

Example 6: Stability of a composition comprising cabotegravir, sodium carboxymethylcellulose, poloxamer 338 and mannitol

A formulation vehicle was prepared by dissolving 2.10g poloxamer 338 (BASF), 2.63g sodium CMC (Ashland), and 18.38g mannitol (Roquette Freres) in 369.6g WFI and filtering the solution through a 0.2µm filter. The formulation vehicle was added to 210g Cabotegravir (free acid) to prepare a 400 mg/mL coarse suspension. The suspension was covered and stirred for 2 hrs. The suspension was filled into Type I glass vials and lyophilized as described in Examples 1-3. The lyophilized suspension was reconstituted to a cabotegravir concentration of 400 mg/mL.

Table 9: Batch #3 (400 mg/mL cabotegravir; 0.4 w/v% P338; 0.5 w/v% NaCMC; 3.5 w/v% mannitol)

Storage Condition	Time (Months)	Particle Size by Laser Diffraction (microns)		
		X10	X50	X90
Initial	0	3.4	7.8	15.2
30°C/75% RH Upright	1	3.3	7.6	14.6
	3	3.3	7.7	15.3
	6	3.2	7.3	13.4
	9	3.3	7.8	15.3
	12	3.3	7.5	13.9
40°C/75% RH Upright	1	3.5	7.8	14.8
	3	3.2	7.7	15.4
	6	3.2	7.6	15.6
50°C/AmbH Upright	DY14	3.3	7.7	14.8
	1	3.3	7.6	14.3
	3	3.3	7.5	14.5

Notes:
AmbH Ambient Humidity
RH Relative Humidity
- Denotes testing not scheduled at these timepoints
NGT = Not greater than
NLT = Not less than

Example 7: In vivo rat pharmacokinetic study for compositions comprising cabotegravir, sodium carboxymethylcellulose, mannitol and either polysorbate 80 or poloxamer 338:

Composition preparation was described in Examples 4 and 6. Formulations were dosed in 9 Sprague Dawley male rats at 30mg/kg in the subcutaneous space of the intrascapular region. Briefly, two nanosuspension formulations of Cabotegravir at 200 (group 1) and 400 mg/mL (group 2), also differing in excipient composition, were administered subcutaneously through a single injection at target dose of 30mg/kg in each rat. Similarly, two lyophilized powder formulations of Cabotegravir at micron-size, differing in excipient composition, were reconstituted with WFI to 400mg/mL concentration and

administered subcutaneously through a single injection at target dose of 30mg/kg in each rat. Details of the formulations are described in Table 10.

Table 10: Suspension formulations details for test articles dosed in animal PK study

Group		Cabotegravir Concentration (mg/mL)	Particle size distribution (µm)			Formulation composition
			x10	x50	x90	
1		200.6	0.10	0.23	0.60	2 w/v% Polysorbate 20, 2 w/v% Polyethylene Glycol 3350, 3.5 w/v% Mannitol
2		399.6	0.06	0.15	0.56	3.8 w/v% Poloxamer 338, 3.5 w/v% Polyethylene Glycol 3350 and 2 w/v% Mannitol
3		400	3.1	7.6	15.6	0.4 w/v% Polysorbate 80, 0.5 w/v% Sodium Carboxymethylcellulose and 3.5 w/v% Mannitol
4		400	3.0	7.4	14.9	0.4 w/v% Poloxamer 338, 0.5 w/v% Sodium Carboxymethylcellulose and 3.5 w/v% Mannitol

Table 11 shows Cabotegravir plasma pharmacokinetics for a preclinical study and statistical analysis through t-test for several pharmacokinetic parameters. The lyophilized formulation from Group 3 highlights a significantly reduced C_{max} (1.8 folds) and extended $t_{1/2}$ (1.5 folds) compared to the nanosuspension formulation from Group 1. In addition, the lyophilized formulation from Group 3 demonstrates improved $t_{1/2}$ compared to formulation from Group 4.

Table 11: Cabotegravir pharmacokinetic parameters for PK study in example 7 and statistical analysis through t-test

		C_{max}	T_{max}	$t_{1/2}$	MRT_{inf}	AUC_{last}	AUC_{inf}	Lambda_z
		(ng/mL)	*(h)*	*(h)*	*(h)*	*(h*µg/mL)*	*(h*µg/mL)*	*(1/min)*
Group 1	***Mean***	55250	360	463	859	48559	52816	2.74E-05
	SD	12418	57	151	233	12414	14441	9.21E-06
Group 2	***Mean***	43000	280	280	550	30193	31289	4.90E-05
	SD	29000	120	140	200	20721	22053	1.80E-05
Group 3	***Mean***	31000	470	700	1300	37411	45784	1.90E-05
	SD	11000	110	270	270	12207	14775	9.10E-06
Group 4	***Mean***	40000	450	420	820	37126	39373	3.20E-05
	SD	16000	120	160	170	16465	17500	1.40E-05
p value	G3 vs G4	0.069	0.371	**	***	0.484	0.207	*
	G3 vs G1	***	*	*	**	*	0.169	*

	G3 vs G2	0.127	**	***	****	0.191	0.0604	***

[#] Data from 8 animals (1 animal excluded as outlier)
p value calculated from one-tailed unpaired t-test for significance: * = 0.01<p<0.05; ** = 0.001<p<0.01; *** = 0.0001<p<0.001; **** = p<0.0001

Tolerability, with particular focus on injection site reaction, was assessed as part of the study and results are summarized in table 12. Occurrence of edema and scab formation were minimal and observed in few animals for a short timeframe. Nonetheless, minor differences were recorded among the 4 groups, with Groups 3 and 4 producing a lower frequency of edema, particularly Group 3.

Table 12: Injection site reaction observations

	Edema	**Scab formation**
Group 1	Very slight in **6/9** rats – days 4-22	Slight in 2/9 rats – days 11-43
Group 2	Very slight in **6/9** rats – days 3-57	Slight in 2/9 rats – days 11-15
Group 3	Very slight in **2/9** rats – days 6-8	Slight in 2/9 rats – days 11-57
Group 4	Very slight in **4/9** rats – days 4-15	Slight in 3/9 rats – days 29-43

Example 8

Example 8 evaluated the safety, tolerability and pharmacokinetics of single-dose administration of a pharmaceutical composition of the invention in 16 healthy adult participants. The formulation of Example 8 is provided in Table 13 below:

Table 13

Component	Quantity (mg/vial)
Cabotegravir	800
Mannitol	51.8
Polysorbate 80	5.9
Sodium Carboxymethylcellulose	7.4
Water for injection*	q.s.
Nitrogen**	q.s.

*Water is removed during manufacturing process.

** Nitrogen is utilized as a processing aid during vial stoppering.

Cabotegravir particle size by diffraction (micron) is described in Table 14 below:

Table 14

Quantile	Micron (µm)
X10	2
X50	6
X90	17

The formulation of Table 13 was administered in two cohorts: 800 mg (2 ml of 400 mg/mL suspension) via the subcutaneous (SC) abdominal route (Cohort C1; 8 participants) and via the intramuscular (IM) (*gluteus medius*) route (Cohort C2; 8 participants).

Safety and Tolerability

The safety and tolerability profile of the pharmaceutical composition of Table 13 dosed in Example 8 was acceptable. Adverse events (AEs) occurred in all participants receiving the pharmaceutical composition of Table 13 via the SC route in Cohort C1 and in 50% of participants who received the pharmaceutical composition of Table 13 via an IM injection in Cohort C2 (Table 15). Injection site reactions (ISRs) were the most common AEs and were mostly Grade 1 (Table 16). In Cohort C2, ISRs were reported in 3 of 8 participants and limited to Grade 1 (4 events) or 2 (1 event) (Table 16). SC administration of the same 800 mg dose (Cohort C1) was associated with more ISR events than by the IM route; however, ISRs were predominantly Grade 1 (18 of 20 total events) (Table 16).

Table 15: Summary of most frequent (≥2 participants in either cohort) AEs (ISR and non-ISR) by cohort

Most Frequent Adverse Events	**Cohort C1 800 mg SC (N = 8)**	**Cohort C2 800 mg IM (N = 8)**
Any event, n(%)	8 (100)	4 (50)
Any ISR, n(%)	8 (100)	3 (38)
ISRs		
Injection site erythema	8 (100)	0
Injection site pain	3 (38)	2 (25)
Injection site swelling	8 (100)	2 (25)
Injection site warmth	1 (13)	0
Injection site pruritus	0	0
Injection site discoloration	0	0
Non-ISRs		
Headache	0	1 (13)
Upper-airway cough syndrome	0	0
Blood creatine phosphokinase increased	0	0
Neutrophil count increased	0	0
White blood cell count increased	0	0

Table 16: Summary of ISRs

PARAMETER, N (% OF PARTICIPANTS)	COHORT C1 SC **800 mg [2 mL] (n = 8)**	COHORT C2 IM **800 mg [2 mL] (n = 8)**
Any ISR	8 (100)	3 (38)
Drug-related	8 (100)	3 (38)
Serious	0	0
Grade 3	0	0
Grade 4	0	0
Pain	3 (38)	2 (25)
Grade 1	3 (38)	1 (13)
Grade 2	0	1 (13)
Grade 3	0	0
Erythema	8 (100)	0
Grade 1	6 (75)	0
Grade 2	2 (25)	0
Grade 3	0	0
Grade 4	0	0
Swelling/induration	8 (100)	2 (25)
Grade 1	8 (100)	2 (25)
Grade 2	0	0
Grade 3	0	0
Total ISRs (% of total ISRs)	20	5
Grade 1	18 (90)	4 (80)
Grade 2	2 (10)	1 (20)
Grade 3	0	0
Grade 4	0	0
Median ISR duration (IQR), days [n = events with non-missing end date/total number of events] [a]		
Pain	n = 3/3 7 (6-12)	n = 2/2 6.5 (5-8)
Erythema	n = 8/8 18 (10-41)	N/A
Swelling/induration	n = 4/8 52 (41.5 - 65)	n = 3/3 5 (4-43)

a. ISR duration is not calculated if end date is missing.

PK of a single SC injection of pharmaceutical composition of Table 13

Cabotegravir plasma Cmax following a single SC injection of the pharmaceutical composition of Table 13 was lower than that following a single IM injection of the

pharmaceutical composition of Table 13 (Table 17). Table 17 exhibited half-life values ($t_{1/2}$) demonstrating that the pharmaceutical composition of Table 13 exhibited favorable safety and PK commensurate with dose intervals of ≥4 months.

Table 17. Plasma Pharmacokinetic and Safety Results in Healthy Adult Participants (Cohorts C1-C2)

Parameter	Cohort C1 (2 mL) SC (N=8)	Cohort C2 (2 mL) IM (N=8)
$AUC_{0-\infty}$, µg·h/mL[a]	14,895.5 (762.1)	5345.4 (27.4)
Cmax, µg/mL[a]	0.7 (35.5)	1.8 (53.5)
$t_{1/2}$, d[a]	135.3 (2.5)[b]	59.3 (106.1)[c]
Grade 1 ISRs, n (%)	6 (75)	2 (25)
Grade 2 ISRs, n (%)	2 (25)	1 (13)
Grade ≥3 ISRs, n (%)	0	0

[a]Value reported as geometric mean (%CVb). [b]Calculated for 2 participants; insufficient follow-up time for remaining participants. [c]6/8 participants had valid values for calculation.

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications, and non-patent publications referred to in this specification are incorporated herein by reference, in their entirety to the extent not inconsistent with the present description.

From the foregoing it will be appreciated that, although specific embodiments have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the disclosure. Accordingly, the disclosure is not limited except as by the appended claims.

SEQUENCE LISTINGS

SEQ ID NO:	DESCRIPTION	SEQUENCE
1	N6 HCDR1	AHILF
2	N6 HCDR2	WIKPQYGAVNFGGGFRD
3	N6 HCDR3	DRSYGDSSWALDA
4	N6 LCDR1	QTSQGVGSDLH
5	N6 LCDR2	HTSSVED
6	N6 LCDR3	QVLQF
7	N6 VH	RAHLVQSGTAMKKPGASVRVSCQTSGYTFTAHIL FWFRQAPGRGLEWVGWIKPQYGAVNFGGGFRD RVTLTRDVYREIAYMDIRGLKPDDTAVYYCARDRS YGDSSWALDAWGQGTTVVVSA
8	N6 VL	YIHVTQSPSSLSVSIGDRVTINCQTSQGVGSDLHW YQHKPGRAPKLLIHHTSSVEDGVPSRFSGSGFHT SFNLTISDLQADDIATYYCQVLQFFGRGSRLHIK

CLAIMS

1. A pharmaceutical composition comprising:
   cabotegravir;
   a wetting agent;
   a stabilizer; and
   a tonicity adjuster;
   wherein cabotegravir is present in the form of particles having a mass median diameter (X50) of between (and including) 2.5 μm and 10 μm.

2. The pharmaceutical composition according to claim 1, wherein the wetting agent is selected from the group consisting of polysorbate 20, polysorbate 80, sorbitan monolaurate, sorbitan monooleate, poloxamer 188, poloxamer 338, and poloxamer 407.

3. The pharmaceutical composition according to claim 1 or claim 2, wherein the wetting agent is polysorbate 80.

4. The pharmaceutical composition according to any one of claims 1-3, wherein the stabilizer is selected from the group consisting of sodium carboxymethylcellulose, polyethylene glycol 3350, polyethylene glycol 4000, povidone K12, and povidone K17.

5. The pharmaceutical composition according to any one of claims 1-4, wherein the stabilizer is sodium carboxymethylcellulose.

6. The pharmaceutical composition according to any one of claims 1-5, wherein the tonicity adjuster is selected from the group consisting of mannitol, sorbitol, lactose, trehalose, raffinose, dextrose, maltose, galactose, sucrose, and polysucrose.

7. The pharmaceutical composition according to any one of claims 1-6, wherein the tonicity adjuster is mannitol.

8. The pharmaceutical composition according to any one of claims 1-7, wherein the cabotegravir particles have an X90 value greater than or equal to 5 μm and less than or equal to 25 μm.

9. The pharmaceutical composition according to any one of claims 1-8, wherein the cabotegravir particles have an X50 value greater than or equal to 3 µm and less than or equal to 8.5 µm.

10. The pharmaceutical composition according to claim 9, wherein the cabotegravir particles have an X50 value greater than or equal to 3 µm and less than or equal to 8.5 µm, and wherein the cabotegravir particles have an X90 value greater than or equal to 6 µm and less than or equal to 20 µm.

11. The pharmaceutical composition according to any one of claims 1-10, wherein the cabotegravir particles have an X50 value greater than or equal to 3.5 µm and less than or equal to 8.0 µm.

12. The pharmaceutical composition according to any one of claims 1-11, wherein the cabotegravir particles have an X50 value greater than or equal to 3.5 µm and less than or equal to 8.0 µm, and wherein the cabotegravir particles have an X90 value greater than or equal to 7.0 µm and less than or equal to 18.0 µm.

13. The pharmaceutical composition according to any one of claims 1-12, wherein cabotegravir is present in an amount of from about 300 mg to about 1800 mg.

14. The pharmaceutical composition according to any one of claims 1-12, wherein cabotegravir is present in an amount of from about 350 mg to about 1650 mg.

15. The pharmaceutical composition according to any one of claims 1-12, wherein cabotegravir is present in an amount of about 800 mg.

16. The pharmaceutical composition according to any one of claims 13-15, wherein a weight ratio of the wetting agent to cabotegravir is in a range of from about 1:10 to about 1:400.

17. The pharmaceutical composition according to any one of claims 13-16, wherein a weight ratio of the wetting agent to cabotegravir is in a range of from about 1:50 to about 1:200.

18. The pharmaceutical composition according to any one of claims 13-17, wherein a weight ratio of the wetting agent to cabotegravir is in a range of from about 1:100 to about 1:150.

19. The pharmaceutical composition according to any one of claims 13-18, wherein a weight ratio of the stabilizer to cabotegravir is in a range of from about 1:10 to about 1:400.

20. The pharmaceutical composition according to any one of claims 13-19, wherein a weight ratio of the stabilizer to cabotegravir is in a range of from about 1:40 to about 1:200.

21. The pharmaceutical composition according to any one of claims 13-20, wherein a weight ratio of the stabilizer to cabotegravir is in a range of from about 1:70 to about 1:120.

22. The pharmaceutical composition according to any one of claims 13-21, wherein a weight ratio of the tonicity adjuster to cabotegravir is in a range of from about 1:1 to about 1:100.

23. The pharmaceutical composition according to any one of claims 13-22, wherein a weight ratio of the tonicity adjuster to cabotegravir is in a range of from about 1:5 to about 1:50.

24. The pharmaceutical composition according to any one of claims 13-23, wherein a weight ratio of the tonicity adjuster to cabotegravir is in a range of from about 1:8 to about 1:25.

25. The pharmaceutical composition according to any one of claims 1-24, wherein the wetting agent is polysorbate 80, wherein the wherein the stabilizer is sodium carboxymethylcellulose, wherein the tonicity adjuster is mannitol, and wherein a weight ratio of cabotegravir:PS80:sodium CMC:mannitol is about 100:1:1.25:8.75.

26. The pharmaceutical composition according to any one of claims 1-24, wherein the wetting agent is polysorbate 80, wherein the wherein the stabilizer is sodium carboxymethylcellulose, wherein the tonicity adjuster is mannitol, and wherein a weight ratio of cabotegravir:PS80:sodium CMC:mannitol is about 400:3:3.7:25.9.

27. The pharmaceutical composition according to any one of claims 1-26, wherein the pharmaceutical composition is provided as a lyophilized powder.

28. The pharmaceutical composition according to any one of claims 1-27, wherein a concentration of cabotegravir is in a range of from about 100 mg/mL to about 800 mg/mL.

29. The pharmaceutical composition according to claim 28, wherein the concentration of cabotegravir is in a range of from about 200 mg/mL to about 700 mg/mL.

30. The pharmaceutical composition according to claim 28, wherein the concentration of cabotegravir is in a range of from about 300 mg/mL to about 650 mg/mL.

31. The pharmaceutical composition according to claim 28, wherein the concentration of cabotegravir is about 400 mg/mL.

32. The pharmaceutical composition according to claim 28, wherein the concentration of cabotegravir is about 533 mg/mL.

33. The pharmaceutical composition according to any one of claims 1-32, wherein the pharmaceutical composition is
(a) reconstituted from a lyophilized powder with a suitable liquid, or
(b) provided as a liquid composition.

34. The pharmaceutical composition according to claim 33, wherein the suitable liquid is an aqueous solvent.

35. The pharmaceutical composition according to claim 33 or claim 34, wherein the suitable liquid is water.

36. The pharmaceutical composition according to claim 33, wherein the suitable liquid is a non-aqueous solvent.

37. The pharmaceutical composition according to any one of claims 1-36, wherein the pharmaceutical composition is formulated as a parenteral pharmaceutical composition.

38. The pharmaceutical composition according to any one of claims 1-37, wherein the pharmaceutical composition is suitable for injection.

39. The pharmaceutical composition according to claim 38, wherein the pharmaceutical composition is suitable for subcutaneous, subdermal, or intramuscular injection.

40. A pharmaceutical composition according to any one of claims 1-39 for use in treatment or prevention of HIV.

41. The pharmaceutical composition for use according to claim 40, wherein the use comprises a step of administering the pharmaceutical composition subcutaneously or intramuscularly to a human.

42. The pharmaceutical composition for use according to claim 41, wherein about 300 mg to about 3200 mg of cabotegravir is administered to the human.

43. The pharmaceutical composition for use according to any one of claims 41 to 42, wherein the use comprises administering the pharmaceutical composition to the human once every month, once every 2 months, once every 3 months, once every 4 months, once every 5 months, or once every 6 months.

44. The pharmaceutical composition for use in treatment of HIV according to claim 37, wherein the pharmaceutical composition is administered in combination with one or more nucleoside reverse transcriptase inhibitors (NRTTIs), one or more non-nucleoside reverse transcriptase inhibitors (NNRTIs), one or more capsid inhibitors, and/or one or more broadly neutralizing antibodies (bnAbs).

45. A method for treating HIV in a human in need thereof comprising administering to said human a therapeutically effective amount of the pharmaceutical composition according to any one of claims 1-40.

46. A method for preventing HIV in a human comprising administering to said human an effective amount of the pharmaceutical composition according to any one of claims 1-40.

47. The method according to claim 45 or claim 46, wherein the method comprises a step of administering the pharmaceutical composition subcutaneously or intramuscularly.

48. The method according to any one of claims 45-47, wherein about 300 mg to about 3200 mg of cabotegravir is administered to the human.

49. The method according to any one of claims 45-47, wherein the method comprises administering the pharmaceutical composition to the human once every month, once every 2 months, once every 3 months, once every 4 months, once every 5 months, or once every 6 months.

50. The method according to any one of claims 45-49, wherein the method comprises administering the pharmaceutical composition intramuscularly to a human once every 4 months.

51. The method according to any one of claims 45-50, wherein the method comprises administering the pharmaceutical composition in combination with with one or more nucleoside reverse transcriptase inhibitors (NRTTIs), one or more non-nucleoside reverse transcriptase inhibitors (NNRTI), one or more capsid inhibitors, and/or one or more broadly neutralizing antibodies (bnAbs).

52. A kit comprising a container that contains the pharmaceutical composition according to any one of claims 1-41 as a lyophilized powder.

53. A method of preparing a reconstituted solution, the method comprising providing the kit of claim 52 and contacting the lyophilized composition with a suitable liquid to produce a reconstituted solution.

54. The method according to claim 53, wherein the suitable liquid is an aqueous solvent.

55. The method according to claim 53 or claim 54, wherein the suitable liquid is water.

56. The method according to claim 53, wherein the suitable liquid is a non-aqueous solvent.

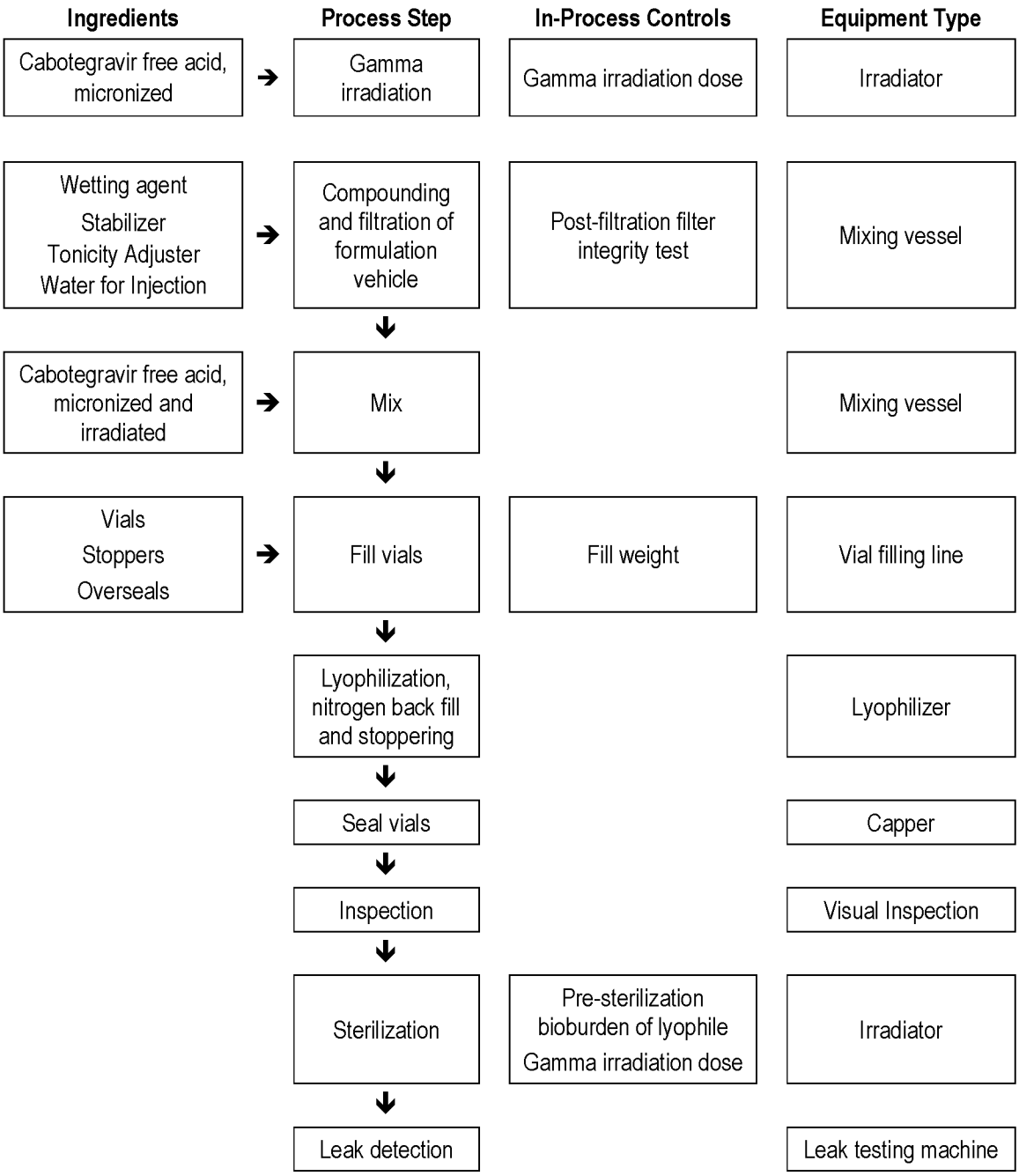

Ingredients
Process Step
In-Process Controls
Equipment Type
Cabotegravir free acid, micronized
Gamma irradiation
Gamma irradiation dose
Irradiator
Wetting agent
Stabilizer
Tonicity Adjuster
Water for Injection
Compounding and filtration of formulation vehicle
Post-filtration filter integrity test
Mixing vessel
Cabotegravir free acid, micronized and irradiated
Mix
Mixing vessel
Vials
Stoppers
Overseals
Fill vials
Fill weight
Vial filling line
Lyophilization, nitrogen back fill and stoppering
Lyophilizer
Seal vials
Capper
Inspection
Visual Inspection
Sterilization
Pre-sterilization bioburden of lyophile
Gamma irradiation dose
Irradiator
Leak detection
Leak testing machine

FIG. 1

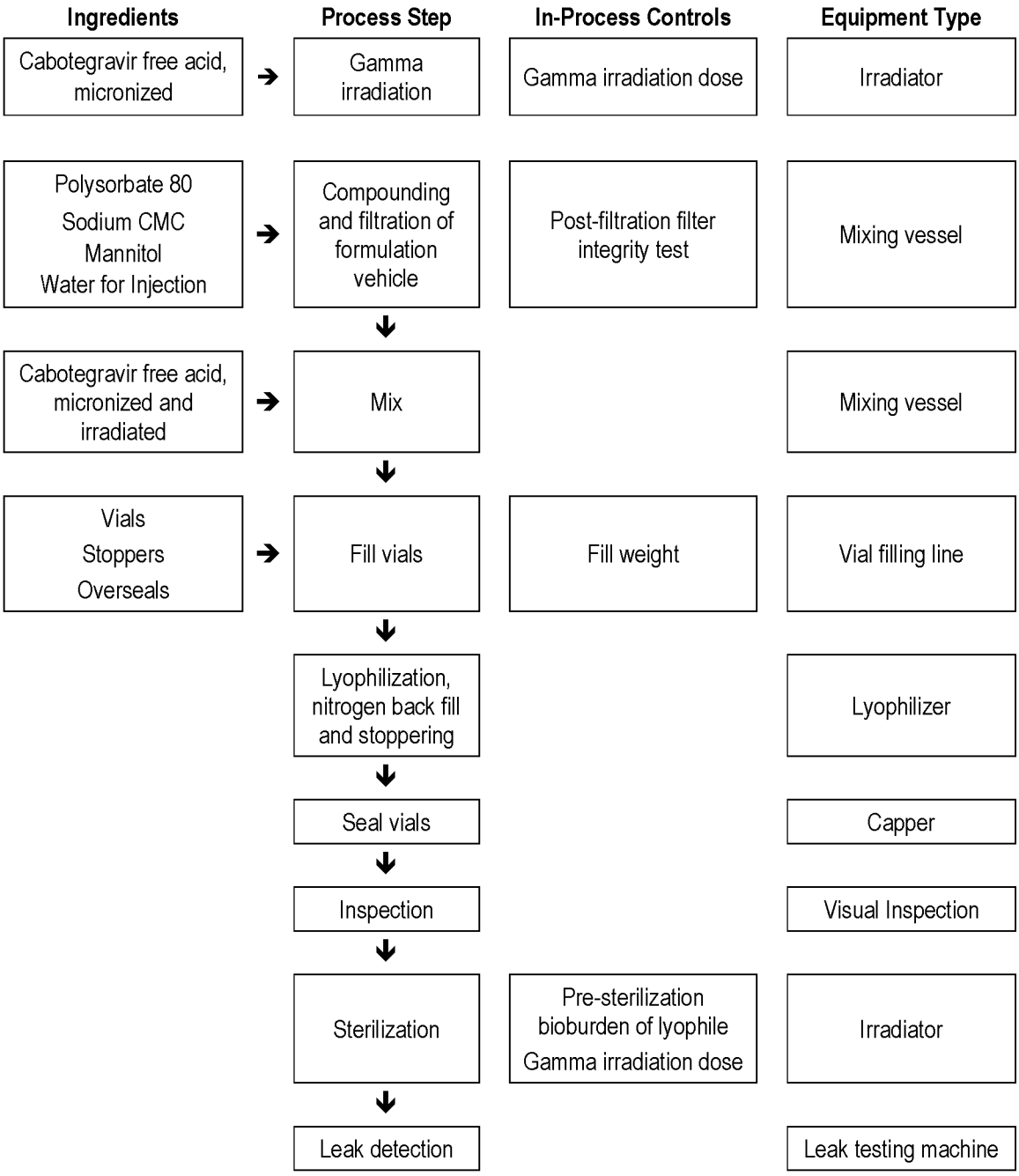

Ingredients
Process Step
In-Process Controls
Equipment Type
Cabotegravir free acid, micronized
Gamma irradiation
Gamma irradiation dose
Irradiator
Polysorbate 80
Sodium CMC
Mannitol
Water for Injection
Compounding and filtration of formulation vehicle
Post-filtration filter integrity test
Mixing vessel
Cabotegravir free acid, micronized and irradiated
Mix
Mixing vessel
Vials
Stoppers
Overseals
Fill vials
Fill weight
Vial filling line
Lyophilization, nitrogen back fill and stoppering
Lyophilizer
Seal vials
Capper
Inspection
Visual Inspection
Sterilization
Pre-sterilization bioburden of lyophile
Gamma irradiation dose
Irradiator
Leak detection
Leak testing machine

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2023/059640

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/10 A61K9/14 A61K47/26
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/116872 A1 (VIIV HEALTHCARE CO [US]) 17 June 2021 (2021-06-17)	1,2,4, 6-15,35, 37-40, 43,49,51
Y	claims 1-9	1-56

X	WO 2022/125378 A2 (VIIV HEALTHCARE CO [US]) 16 June 2022 (2022-06-16)	1,2,4,6, 7,16, 33-35, 37-40, 42,43, 49,52,53
Y	pages 2, 24-25; example 1; table 3	1-56

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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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 May 2024	31/05/2024

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	Erdmann, Mona

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2023/059640

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/051198 A1 (VIIV HEALTHCARE CO [US]) 10 March 2022 (2022-03-10)	1,2,4, 6-12,34, 35,37, 39-43,49
Y	example 1	1-56

A	BOWEN P: "Particle Size Distribution Measurement from Millimeters to Nanometers and from Rods to Platelets", JOURNAL OF DISPERSION SCIENCE AND TECHNOLOGY, TAYLOR AND FRANCIS GROUP, NEW YORK, NY, US, vol. 23, no. 5, 1 January 2002 (2002-01-01), pages 631-662, XP009102859, ISSN: 0193-2691, DOI: 10.1081/DIS-120015368 the whole document	1,8-12

3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2023/059640

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. [X] 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

Information on patent family members

International application No
PCT/IB2023/059640

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2021116872 A1	17-06-2021	AU 2020402659 A1	02-06-2022
		BR 112022010574 A2	23-08-2022
		CA 3164528 A1	17-06-2021
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		IL 293566 A	01-08-2022
		JP 2023505543 A	09-02-2023
		KR 20220112771 A	11-08-2022
		TW 202135815 A	01-10-2021
		US 2023045509 A1	09-02-2023
		UY 38982 A	30-06-2021
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		JP 2024500322 A	09-01-2024
		WO 2022125378 A2	16-06-2022
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		JP 2023539344 A	13-09-2023
		US 2023321089 A1	12-10-2023
		WO 2022051198 A1	10-03-2022