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(54) Title: INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION

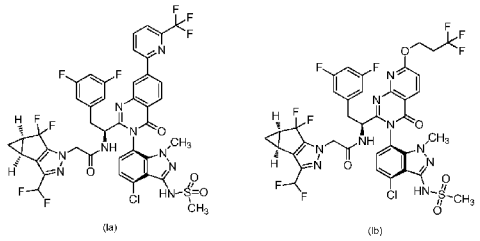
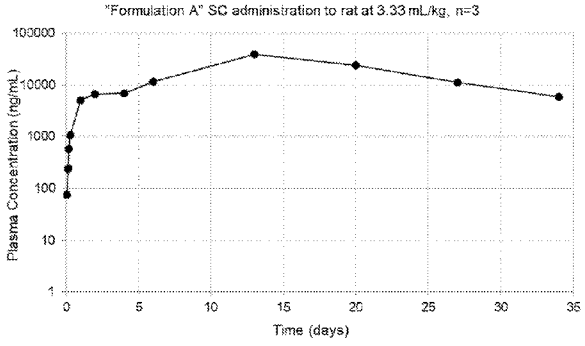


Figure 2



(57) Abstract: A pharmaceutical composition comprising the compound of Formula (Ia), or Formula (Ib), or a pharmaceutically acceptable salt thereof, is set forth.

[Continued on next page]

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INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION

FIELD OF THE INVENTION

The invention relates to compounds, pharmaceutical compositions, and methods for the treatment of human immunodeficiency virus (HIV) infection. More particularly, the invention provides pharmaceutical compositions containing inhibitors of HIV, and methods for using these compositions in the treatment of HIV infection.

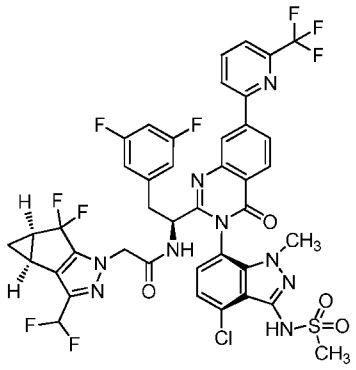
BACKGROUND OF THE INVENTION

Acquired immunodeficiency syndrome (AIDS) is the result of infection by HIV. HIV continues to be a major global public health issue. In 2015, an estimated 36.7 million people were living with HIV (including 1.8 million children) – a global HIV prevalence of 0.8%. The vast majority of this number live in low- and middle- income countries. In the same year, 1.1 million people died of AIDS-related illnesses.

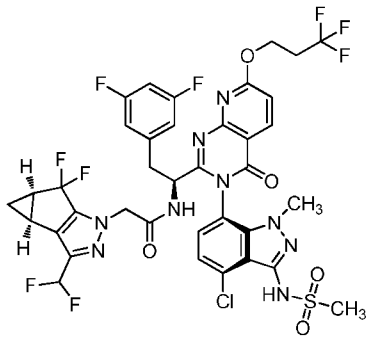
Current therapy for HIV-infected individuals consists of a combination of approved anti-retroviral agents. Close to four dozen drugs are currently approved for HIV infection, either as single agents, fixed dose combinations or single tablet regimens; the latter two containing 2-4 approved agents. These agents belong to a number of different classes, targeting either a viral enzyme or the function of a viral protein during the virus replication cycle. Thus, agents are classified as either nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), or entry inhibitors (one, maraviroc, targets the host CCR5 protein, while the other, enfuvirtide, is a peptide that targets the gp41 region of the viral gp160 protein). In addition, a pharmacokinetic enhancer (cobicistat or ritonavir) can be used in combinations with antiretroviral agents (ARVs) that require boosting.

Certain potentially therapeutic compounds which appear to act by disrupting the normal functions of the HIV virus capsid have been described in the art. No currently approved drugs act by this mechanism and thus a compound acting through this mechanism would be a useful addition to the options available for the treatment of HIV infection.

WO 2020/084492 and WO 2020/254985 disclose certain Capsid Inhibitor compounds including the two compounds shown below which will be referred to in this application as the compounds of Formula Ia and Formula Ib.



Formula Ia

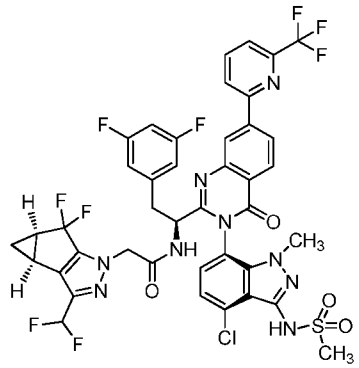


Formula Ib

These compound provide advantages for pharmaceutical uses, for example, with regard to one or more of their mechanisms of action, binding, inhibition efficacy, target selectivity, solubility, safety profiles, bioavailability and/or reduced frequency of dosing. This disclosure teaches pharmaceutical compositions, methods of administration and methods of treatment utilizing these compounds.

SUMMARY OF THE INVENTION

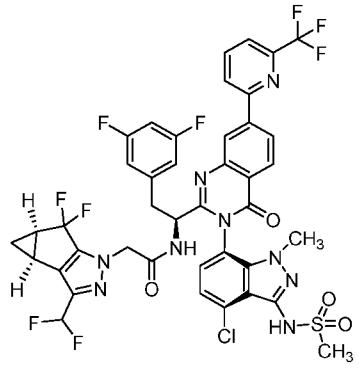
In one aspect, the present invention provides a pharmaceutical composition comprising a compound of Formula Ia or a pharmaceutically acceptable salt thereof,



Formula Ia

wherein the composition comprising polyethylene glycol (PEG) and ethanol.

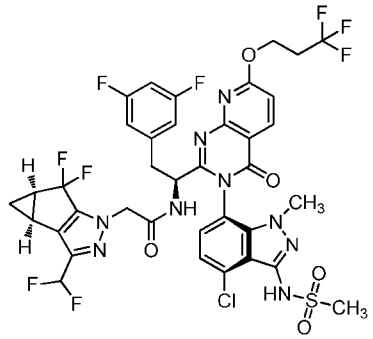
In another aspect, the present invention provides a pharmaceutical composition comprising a compound of Formula Ia or a pharmaceutically acceptable salt thereof,



Formula Ia

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

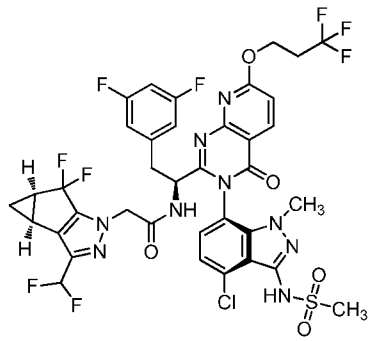
In still another aspect, the present invention provides a pharmaceutical composition comprising the compound of Formula Ib or a pharmaceutically acceptable salt thereof,



Formula Ib

wherein the composition comprises polyethylene glycol (PEG) and ethanol.

In a further aspect, the invention provides a pharmaceutical composition comprising a compound of Formula Ia or a pharmaceutically acceptable salt thereof,



Formula Ib

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

In another aspect, the present invention provides a method of treating HIV infection in a patient comprising administering a therapeutically effective amount of a pharmaceutical composition of the invention, as described below, to said patient.

In another aspect, the present invention provides a pharmaceutical composition of the invention, as described below, for use in therapy.

In another aspect, the present invention provides a pharmaceutical composition of the invention, as described below, for use in treating HIV infection in a patient.

In another aspect, the present invention provides the use of a pharmaceutical composition of the invention, as described below, in the manufacture of a medicament for the treatment of HIV infection in a patient.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1-3 summarize the results of PK experiments described below and summarized in Tables 1-3.

Figures 4-6 summarize the results of PK experiments described below and summarized in Tables 4-6.

Figures 7-9 summarize the results of PK experiments described below and summarized in Tables 7-9.

Figures 10-12 summarize the results of PK experiments described below and summarized in Tables 10-12.

Figures 13-14 summarize the results of PK experiments described below and summarized in Tables 13-14.

Figures 15-16 summarize the results of PK experiments described below and summarized in Tables 15-16.

Figures 17-18 summarize the results of PK experiments described below and summarized in Tables 17-18.

Figures 19-20 summarize the results of PK experiments described below and summarized in Tables 19-20.

Figures 21-22 summarize the results of PK experiments described below and summarized in Tables 21-22.

DETAILED DESCRIPTION OF THE INVENTION

A compound of Formula Ia is known by the chemical name N-((S)-1-((3P)-3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-4-oxo-7-(6-(trifluoromethyl)pyridin-2-yl)-3,4-dihydroquinazolin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide. A

method for making the compound of Formula Ia is found in published patent application WO 2020/084492.

A compound of Formula Ib is known by the chemical name N-((S)-1-(3-(4-chloro-1-methyl-3-(methylsulfonamido)-1H-indazol-7-yl)-4-oxo-7-(3,3,3-trifluoropropoxy)-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-((3bS,4aR)-3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide. A method for making the compound of Formula Ib is found in published patent application WO 2020/254985.

Suitably, the compositions of the invention comprise a therapeutically effective amount of a compound of Formula Ia or a pharmaceutically acceptable salt thereof. In one embodiment, the compositions of the invention comprise a therapeutically effective amount of a compound of Formula Ia as a free base.

In one embodiment, the compositions of the invention comprise a therapeutically effective amount of a compound of Formula Ia which is amorphous.

Suitably, the compositions of the invention comprise a therapeutically effective amount of a compound of Formula Ib or a pharmaceutically acceptable salt thereof. In one embodiment, the compositions of the invention comprise a therapeutically effective amount of a compound of Formula Ib as a free base.

In one embodiment, the compositions of the invention comprise a therapeutically effective amount of a compound of Formula Ib which is amorphous.

As used herein, "therapeutically effective amount" in reference to a compound, its salt, or a pharmaceutical composition of the invention comprising said compound or its salt, or other pharmaceutically-active agent or composition, means an amount of the compound, its salt or a pharmaceutical composition of the invention comprising said compound or its salt, sufficient to treat the patient's condition but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. Thus, e.g., a therapeutically effective amount of a compound of Formula Ia or Formula Ib, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound of Formula Ia or the compound of Formula Ib, or its salt, in a quantity that, when administered to a patient in need thereof, is sufficient to modulate the activity of HIV capsid such that the disease condition which is mediated by that activity is treated, including reduced, alleviated, or prevented. A therapeutically effective amount of a compound, its salt or a pharmaceutical composition comprising the compound or its salt, will vary with the particular compound chosen (e.g., consider the potency, efficacy, and half-life of the compound); the route of administration chosen; the condition being treated; the severity of the condition being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient to be treated; the duration of the treatment; the

nature of concurrent therapy; the desired therapeutic effect; and like factors, but can nevertheless be routinely determined by the skilled artisan.

In one aspect, a composition of this invention comprises polyethylene glycol and ethanol. It will be understood by the skilled artisan that he chemical formula for polyethylene glycol (PEG) can be generally written as $H-(O-CH_2-CH_2)_n-OH$. In one embodiment, the composition of the invention is a homogeneous solution.

In one embodiment, the invention provides a composition further comprising water. In another embodiment, the invention provides a composition further comprising lecithin. In yet another embodiment, the invention provides a composition further comprising propylene glycol. In still another embodiment, the invention provides a composition further comprising benzyl alcohol. In still yet another embodiment, the invention provides a composition further comprising benzyl benzoate. In another embodiment, the invention provides a composition further comprising sucrose acetate isobutyrate (SAIB). In yet another embodiment, the invention provides a composition further comprising sesame oil.

In still yet another embodiment, the invention provides a composition further comprising one or more components which are water, lecithin, propylene glycol, benzyl alcohol, benzyl benzoate, SAIB, or sesame oil. In one embodiment, the invention provides a composition further comprising one or more components which are water, lecithin, propylene glycol, benzyl alcohol, benzyl benzoate, or sesame oil. In one embodiment, the invention provides a composition further comprising one or more components which are water, lecithin, propylene glycol, benzyl alcohol, or sesame oil. In one embodiment, the invention provides a composition further comprising one or more components which are propylene glycol, benzyl alcohol, or sesame oil.

In one embodiment, the lecithin is egg-based. In another embodiment, the lecithin is soy-based and is about 80 weight% phosphatidylcholine or is about 100 weight% phosphatidylcholine.

In one aspect of the invention, the average molecular weight of polyethylene glycol is about 200 (PEG 200).

In another aspect of the invention, the average molecular weight of polyethylene glycol is about 300 (PEG 300).

In another aspect of the invention, the average molecular weight of polyethylene glycol is about 400 (PEG 400).

Suitably, the amount of a component present in the composition is expressed as a weight% relative to total mass of the formulation.

In one aspect of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition expressed as weight%, is between about 5-50%. In one embodiment of the invention, the amount of a compound of

Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is between about 5-30%. In one embodiment of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is between about 5-35%. In one embodiment of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is about 10-25%. In one embodiment of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is about 10-30%. In one embodiment of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is between about 15-30%. In one embodiment of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is between about 20-30%. In one embodiment of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is between about 25-35%. In one embodiment of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is between about 30-40%. In one embodiment of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is between about 35-45%. In one embodiment of the invention, the amount of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, present in the composition is between about 40-50%.

In one aspect of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition, expressed as weight%, is between about 5-50%.

In one embodiment of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition is between about 5-30%. In one embodiment of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition is between about 5-35%. In one embodiment of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition is between about 10-25%. In one embodiment of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition is between about 10-30%. In one embodiment of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition is between about 15-30%. In one embodiment of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition is between about 20-30%. In one embodiment of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition is between about 25-35%. In one embodiment of the invention, the amount of a compound of Formula Ib, or a

pharmaceutically acceptable salt thereof, present in the composition is between about 30-40%. In one embodiment of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition is between about 35-45%. In one embodiment of the invention, the amount of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, present in the composition is between about 40-50%.

Suitably, the compositions of the invention are administered subcutaneously.

In one embodiment, the invention provides a homogeneous solution for subcutaneous administration. In one embodiment, the invention provides a homogeneous solution comprising an amorphous form of a compound of Formula Ia for subcutaneous administration. In one embodiment, the invention provides a homogeneous solution comprising an amorphous form of a compound of Formula Ib for subcutaneous administration.

In one embodiment, the invention provides a heterogeneous suspension for subcutaneous administration. In one embodiment, the invention provides a heterogeneous suspension comprising an amorphous form of a compound of Formula Ia for subcutaneous administration. In one embodiment, the invention provides a heterogeneous suspension comprising an amorphous form of a compound of Formula Ib for subcutaneous administration.

Suitably, the compositions of the invention are administered intramuscularly.

Suitably, the compositions of the invention are administered intravenously.

The compositions of the invention comprise a vehicle or carrier, which is an inert medium used as a solvent or diluent in which the active agent, Formula Ia or Formula Ib, is formulated or administered. Suitable vehicles for the compositions of this invention include, but are not limited to, ethanol (up to about 35 weight%), polyethylene glycol (up to about 85 weight%), modified polyethylene glycol (up to about 85 weight%), propylene glycol (up to about 60 weight%), N-Methyl-2-pyrrolidone (NMP) (up to about weight%), Dimethylacetamide (DMA) (up to about 50%), dimethylsulfoxide (DMSO) (up to about 5 weight %), water, ethyl lactate, dimethyl isosorbide, and the like. It will be understood that one or more solvents may comprise the vehicle for a particular pharmaceutical composition.

The compositions of the invention optionally comprise an oil. Suitable oils for the compositions of this invention include, but are not limited to, sesame oil, soyabean oil, castor oil, medium chain triglyceride, safflower oil, and the like. Suitably, for an emulsion the oil is present in an amount of from about 0 to about 50 weight%. Suitably, for an oily solution, the oil is present in an amount of up to about 100 weight%. In one embodiment, the invention provides a homogeneous solution comprising an oil.

The compositions of the invention optionally comprise a surfactant. Suitable surfactants include, but are not limited to, a phospholipid (up to about 25 weight%), a poloxamer (up to about 7 weight%), a polysorbate (up to about 7 weight%), a sorbitan ester

(aka spans) (up to about 7 weight%), and the like. In one embodiment, the invention provides a composition comprising a phospholipid surfactant. In one embodiment, the invention provides a composition comprising a phospholipid surfactant which is lecithin. In one embodiment, the invention provides a composition comprising Poloxamer 338. In one embodiment, the invention provides a composition comprising Poloxamer 188. In one embodiment, the invention provides a composition comprising Poloxamer 338 or Poloxamer 188.

In one embodiment, the invention provides a heterogeneous suspension comprising a surfactant. In one embodiment, the invention provides a heterogeneous suspension comprising a surfactant. In one embodiment, the invention provides a heterogeneous suspension comprising lecithin. In one embodiment, the invention provides a heterogeneous suspension comprising Poloxamer 338. In one embodiment, the invention provides a heterogeneous suspension comprising Poloxamer 188. In one embodiment, the invention provides a heterogeneous suspension comprising Poloxamer 338 or Poloxamer 188.

If the composition of the invention is a heterogeneous suspension, it optionally comprises an iso-osmolarity/tonicity agent. Suitable iso-osmolarity/tonicity agents include but are not limited to, mannitol (about 1 to about 5 weight%), trehalose (about 7 to about 10 weight%), sucrose (about 7 to about 10 weight%), glucose (about 3 to about 5 weight%), dextrose (about 3 to about 5 weight%), sodium chloride (about 0.45 to about 0.9 weight%), potassium chloride (about 0.45 to about 0.9 weight%), and the like. In one embodiment, the invention provides a heterogeneous suspension comprising mannitol.

The compositions of the invention optionally comprise a buffering agent. Suitable buffering agents for the compositions of the invention include, but are not limited to, acetate, citrate, tartrate, malic acid and its salt, NaOH and HCl, format histidine, phosphate, TRIS, borate, and the like. In one embodiment, the invention provides a composition comprising a buffering agent in the amount of about 1 mM to about 20 mM.

In one aspect, the invention provides a composition which is a micro-suspension. In one embodiment, the invention provides a micro-suspension composition comprising a viscosity modifying agent. Suitable viscosity modifying agents for the compositions of the invention include, but are not limited to, sodium carboxymethyl cellulose, hyaluronic acids, PVP-K-12, K-19, hydroxy ethyl starch, and the like. In one embodiment, the invention provides a composition comprising levels of viscosity modifying agents from 0 to about 1 weight%. In another embodiment, the invention provides a micro-suspension composition comprising a bulking agent. Suitable bulking agents for the compositions of the invention include, but are not limited to, mannitol (about 3 to about 5 weight%), trehalose (about 7 to about 10 weight%), sucrose (about 7 to about 10 weight%), glucose (about 3 to about 5

weight%), dextrose (about 3 to about 5 weight%), and the like. In one embodiment, the invention provides a composition which is a lyophilized micro-suspension.

In another aspect, the invention provides a pharmaceutical composition wherein the amount of polyethylene glycol present in the composition, expressed as weight%, is between about 10-55%. In one embodiment of the invention, the amount of polyethylene glycol present in the composition is between about 15-50%. In a second embodiment of the invention, the amount of polyethylene glycol present in the composition is between about 20-50%. In one embodiment of the invention, the amount of polyethylene glycol present in the composition is between about 20-40%. In one embodiment of the invention, the amount of polyethylene glycol present in the composition is between about 30-50%. In one embodiment of the invention, the amount of polyethylene glycol present in the composition is between about 40-50%.

In another aspect, the invention provides a pharmaceutical composition wherein the amount of ethanol present in the composition, expressed as weight%, is between about 1-35%. In one embodiment of the invention, the amount of ethanol present in the composition is between about 5-30%. In one embodiment of the invention, the amount of ethanol present in the composition is between about 5-25%. In one embodiment of the invention, the amount of ethanol present in the composition is between about 10-30%. In one embodiment of the invention, the amount of ethanol present in the composition is between about 10-25%. In one embodiment of the invention, the amount of ethanol present in the composition is between about 15-30%. In one embodiment of the invention, the amount of ethanol present in the composition is between about 15-20%. In one embodiment of the invention, the amount of ethanol present in the composition is between about 15-25%. In one embodiment of the invention, the amount of ethanol present in the composition is between about 20-25%. In one embodiment of the invention, the amount of ethanol present in the composition is between about 25-35%.

Suitably, the pharmaceutical composition comprises mannitol. In another aspect, the invention provides a pharmaceutical composition wherein the amount of mannitol is present in the composition expressed as weight% is between 1-5%. In one embodiment of the invention, the amount of mannitol present in the composition is between about 2-4%.

Suitably, the pharmaceutical composition comprises lecithin. In another aspect, the invention provides a pharmaceutical composition wherein the amount of lecithin present in the composition expressed as weight% is between about 1-25%. In one embodiment of the invention, the amount of lecithin in the composition is between about 5-25%. In one embodiment of the invention, the amount of lecithin in the composition is between about 10-20%. In one embodiment of the invention, the amount of lecithin in the composition is

between about 1-5%. In another embodiment of the invention, the amount of lecithin present in the composition is about 1%, 2%, 3%, 4%, or 5%.

In one embodiment of the invention, the lecithin is egg-based. In another embodiment of the invention, the lecithin is soy-based. In one embodiment, if soy-based, the lecithin is about 80 weight% phosphatidylcholine. In one embodiment, if soy-based, the lecithin is 100 weight% phosphatidylcholine.

In another aspect, the invention provides a composition which is a homogeneous solution.

In yet another aspect, the invention provides a composition which is a heterogeneous suspension.

In one aspect, the invention provides a pharmaceutical composition wherein the amount of water present in the composition, as measured by Karl Fischer titration, is about 1%, 2%, 3%, 4%, or 5%. In one embodiment of the invention, the amount of water present in the composition is less than about 3%. In one embodiment of the invention, the amount of water present in the composition is less than about 2.5%. In one embodiment of the invention, the amount of water present in the composition is less than about 2%. In one embodiment of the invention, the amount of water present in the composition is less than about 1.5%. In one embodiment of the invention, the amount of water in the composition is less than about 1%.

It will be understood that all the above embodiments apply to compositions of the invention comprising Formula Ia, or a pharmaceutically acceptable salt thereof. It will be understood that all the above embodiments apply to compositions of the invention comprising Formula Ib, or a pharmaceutically acceptable salt thereof. It will be understood that the above embodiments apply to compositions of the invention comprising a compound of Formula Ia as a free base. It will be understood that the above embodiments apply to compositions of the invention comprising a compound of Formula Ia as a free base. It will be understood that the above embodiments apply to compositions of the invention comprising a compound of Formula Ia as an amorphous compound, either as a pharmaceutically acceptable salt thereof, or as a free base. It will be understood that the above embodiments apply to compositions of the invention comprising a compound of Formula Ib as an amorphous compound, either as a pharmaceutically acceptable salt thereof, or as a free base.

In another aspect, the invention provides a pharmaceutical composition comprising about 20% by weight of a compound of Formula Ia or a compound of Formula Ib, about 45% by weight of PEG200, about 20% by weight of ethanol, and about 15% by weight of lecithin. In another aspect, the invention provides a pharmaceutical composition comprising about 30% by weight of a compound of Formula Ia or a compound of Formula Ib, about 45% by weight of PEG200, and about 25% by weight of ethanol. In another aspect, the invention

provides a composition comprising about 30% by weight of a compound of Formula Ia or a compound of Formula Ib, about 50% by weight of PEG200, and about 20% by weight of ethanol. In another aspect, the invention provides a composition comprising about 20% by weight of a compound of Formula Ia or a compound of Formula Ib, about 55% by weight of PEG200, and about 20% by weight of ethanol. In yet another aspect, the invention provides a composition comprising about 19% by weight of a compound of Formula Ia, about 61% by weight of PEG200 and about 20% by weight of ethanol.

HETEROGENEOUS SUSPENSION

In one aspect, the composition of the invention comprises water and contains less than 1% by weight of polyethylene glycol. In another aspect, the composition of the invention is a heterogeneous suspension.

In one aspect, the invention provides a composition in which the suspended solids comprise a compound of Formula Ia, or a pharmaceutically acceptable salt thereof. In another aspect, the invention provides a composition in which the suspended solids comprise a compound of Formula Ib, or a pharmaceutically acceptable salt thereof. In one aspect, the invention provides a composition in which the suspended solids comprise a compound of Formula Ia, as the free base. In one aspect, the invention provides a composition in which the suspended solids comprise a compound of Formula Ib, as the free base. It will be understood that the above embodiments apply to compositions of the invention in which the suspended solids comprise a compound of Formula Ia as an amorphous compound, either as a pharmaceutically acceptable salt thereof, or as a free base. It will be understood that the above embodiments apply to compositions of the invention in which the suspended solids comprise a compound of Formula Ib as an amorphous compound, either as a pharmaceutically acceptable salt thereof, or as a free base.

In one embodiment of the invention, the composition of the solids which are suspended is about 20% by weight of a compound of Formula Ia. In another embodiment of the invention, the composition of the solids which are suspended is about 25% by weight of a compound of Formula Ia. In another embodiment of the invention, the composition of the solids which are suspended is about 30% by weight of a compound of Formula Ia. In another embodiment of the invention, the composition of the solids which are suspended is about 35% by weight of a compound of Formula Ia. In another embodiment of the invention, the composition of the solids which are suspended is about 40% by weight of a compound of Formula Ia. In another embodiment of the invention, the composition of the solids which are suspended is about 45% by weight of a compound of Formula Ia. In another embodiment of the invention, the composition of the solids which are suspended is about 50% by weight of a compound of Formula Ia. It will be understood that these embodiments apply to compositions

of the invention in which the suspended solids comprise a compound of Formula Ia as a pharmaceutically acceptable salt or as a free base, or as an amorphous compound, either as a pharmaceutically acceptable salt thereof, or as a free base.

In one embodiment of the invention, the composition of the solids which are suspended is about 20% by weight of a compound of Formula Ib. In another embodiment of the invention, the composition of the solids which are suspended is about 25% by weight of a compound of Formula Ib. In another embodiment of the invention, the composition of the solids which are suspended is about 30% by weight of a compound of Formula Ib. In another embodiment of the invention, the composition of the solids which are suspended is about 35% by weight of a compound of Formula Ia. In another embodiment of the invention, the composition of the solids which are suspended is about 40% by weight of a compound of Formula Ib. In another embodiment of the invention, the composition of the solids which are suspended is about 45% by weight of a compound of Formula Ib. In another embodiment of the invention, the composition of the solids which are suspended is about 50% by weight of a compound of Formula Ib. It will be understood that these embodiments apply to compositions of the invention in which the suspended solids comprise a compound of Formula Ib as a pharmaceutically acceptable salt or as a free base, or as an amorphous compound, either as a pharmaceutically acceptable salt thereof, or as a free base.

In one aspect, the invention provides a composition further comprising one or more of the following excipients, sodium acetate, acetic acid, mannitol, sodium chloride, Poloxamer 338, or Poloxamer 188. In one embodiment, the invention provides a pharmaceutical composition comprising Poloxamer 338 or Poloxamer 188. In one embodiment, the invention provides a pharmaceutical composition comprising Poloxamer 338 and Poloxamer 188. In one embodiment, the invention provides a pharmaceutical composition comprising mannitol or sodium chloride. In one embodiment, the invention provides a pharmaceutical composition comprising mannitol and sodium chloride. In one embodiment, the invention provides a pharmaceutical composition comprising sodium acetate or acetic acid. In one embodiment, the invention provides a pharmaceutical composition comprising sodium acetate and acetic acid.

Suitably, the mass of a compound of Formula Ia or a compound of Formula Ib is expressed relative to the total volume of the formulation. In one embodiment, the composition comprises a compound of Formula Ia or a compound of Formula Ib at a concentration between about 50-500 mg/mL. In another embodiment, the composition comprises a compound of Formula Ia or a compound of Formula Ib at a concentration between about 150-300 mg/mL. In yet another embodiment, the composition comprises a compound of Formula Ia or a compound of Formula Ib at a concentration between about 200-300 mg/mL. In still another embodiment, the composition comprises a compound of Formula

Ia or a compound of Formula Ib at a concentration between about 250-350 mg/mL. In still yet another embodiment, the composition comprises a compound of Formula Ia or a compound of Formula Ib at a concentration between about 300-400 mg/mL. In a further embodiment, the composition comprises a compound of Formula Ia or a compound of Formula Ib at a concentration between about 350-450 mg/mL. In another embodiment, the composition comprises a compound of Formula Ia or a compound of Formula Ib at a concentration between about 400-500 mg/mL. In one aspect, the composition comprises a compound of Formula Ia or a compound of Formula Ib at a concentration of about 200 mg/mL, about 225 mg/mL, about 250 mg/mL, about 275 mg/mL, about 300 mg/mL, about 325 mg/mL, about 350 mg/mL, about 375 mg/mL, about 400 mg/mL, about 450 mg/mL or about 500 mg/mL. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia or a compound of Formula Ib at a concentration of about

In one aspect, the invention provides a composition comprising about 300 mg/mL of a compound of Formula Ia or a compound of Formula Ib, about 5.4% by weight of P338, about 3.5% by weight of mannitol, and the remainder of the formulation as water or aqueous acetate buffer.

In one aspect the compositions of this invention further comprise one or more of glycerol, polyvinylpyrrolidone K19, polyvinylpyrrolidone K12, Span, urea, NMP, ethyl lactate, polysorbate 80, or Polysorbate 20.

In one aspect, the pharmaceutical composition of this invention comprises a therapeutically effective amount of the compound of Formula Ia, or a pharmaceutically acceptable salt thereof.

In one aspect, the pharmaceutical composition of this invention comprises a therapeutically effective amount of the compound of Formula Ib, or a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutical composition of this invention comprises about 20%-30% by weight of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition of this invention comprises about 20%-30% by weight of a compound of Formula Ia as the free base. In another embodiment, the pharmaceutical composition of the invention comprises about 20%-30% by weight of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition of this invention comprises about 20%-30% by weight of a compound of Formula Ib as the free base.

In one embodiment, the pharmaceutical composition of this invention comprises about 20% by weight of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition of this invention comprises about 20%

by weight of a compound of Formula Ia as the free base. In another embodiment, the pharmaceutical composition of the invention comprises about 20% by weight of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition of this invention comprises about 20% by weight of a compound of Formula Ib as the free base.

In one embodiment, the pharmaceutical composition of this invention comprises about 30% by weight of a compound of Formula Ia, or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition of this invention comprises about 30% by weight of a compound of Formula Ia as the free base. In another embodiment, the pharmaceutical composition of the invention comprises about 30% by weight of a compound of Formula Ib, or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition of this invention comprises about 30% by weight of a compound of Formula Ib as the free base.

It will be understood that the above embodiments apply to compositions of the invention comprising a compound of Formula Ia as an amorphous compound, either as a pharmaceutically acceptable salt thereof, or as a free base. It will be understood that the above embodiments apply to compositions of the invention comprising a compound of Formula Ib as an amorphous compound, either as a pharmaceutically acceptable salt thereof, or as a free base.

Suitably, in one aspect, the particle diameter of a compound of Formula Ia or a compound of Formula Ib is measured with a laser diffraction technique. This type of analysis is used in general practice for particle size characterization. An example of equipment capable of performing this analysis is a Malvern Mastersizer MS3000 instrument. Particle sizes are reported as percentiles of a distribution. Percentiles (e.g. X50) refer to the percent volume out of the total volume of the material tested which has an equivalent spherical diameter less than the reported value. The term "mean particle diameter" refers to X50 which is interchangeable with D50 or the 50^{th} percentile distribution.

In one embodiment, the mean particle diameter of a compound of Formula Ia or a compound of Formula Ib is ≤ about 0.2 μm. In another embodiment, the mean particle diameter of a compound of Formula Ia or a compound of Formula Ib ranges between about 0.2 μm to about 0.5 μm. In another embodiment, the mean particle diameter of a compound of Formula Ia or a compound of Formula Ib ranges between about 0.5 μm to about 3 μm. In another embodiment, the mean particle diameter of a compound of Formula Ia or a compound of Formula Ib ranges between about 3 μm to about 5 μm. In another embodiment, the mean particle diameter of a compound of Formula Ia or a compound of Formula Ib ranges between about 5 μm to about 10 μm.

In one embodiment of the invention, for a compound of Formula Ia, the D10 is <0.9 μM, the D50 is <2 μM and the D90 is <4 μM. In one embodiment of the invention, for a compound of Formula Ib, the D10 is <0.9 μM, the D50 is <2 μM and the D90 is <4 μM.

In one aspect, instead of the specific stereoisomers depicted above in Formula Ia and Formula Ib, the composition of the invention comprises any of the isomers of a compound of Formula Ia or a compound of Formula Ib and they are included in the scope of this invention.

In one aspect the depicted stereoisomers in Formulas Ia and Ib are ≥95% of all stereoisomers of the same chemical formula.

The salts of the invention are pharmaceutically acceptable. Such salts may be acid addition salts or base addition salts. For a review of suitable pharmaceutically acceptable salts see, for example, Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977.

Representative pharmaceutically acceptable acid addition salts include, but are not limited to, 4-acetamidobenzoate, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate (besylate), benzoate, bisulfate, bitartrate, butyrate, calcium edetate, camphorate, camphorsulfonate (camsylate), caprate (decanoate), caproate (hexanoate), caprylate (octanoate), cinnamate, citrate, cyclamate, digluconate, 2,5-dihydroxybenzoate, disuccinate, dodecylsulfate (estolate), edetate (ethylenediaminetetraacetate), estolate (lauryl sulfate), ethane-1,2-disulfonate (edisylate), ethanesulfonate (esylate), formate, fumarate, galactarate (mucate), gentisate (2,5-dihydroxybenzoate), glucoheptonate (gluceptate), gluconate, glucuronate, glutamate, glutarate, glycerophosphorate, glycolate, hexylresorcinate, hippurate, hydrabamine (*N,N'*-di(dehydroabietyl)-ethylenediamine), hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, isobutyrate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, methanesulfonate (mesylate), methylsulfate, mucate, naphthalene-1,5-disulfonate (napadisylate), naphthalene-2-sulfonate (napsylate), nicotinate, nitrate, oleate, palmitate, *p*-aminobenzenesulfonate, *p*-aminosalicyclate, pamoate (embonate), pantothenate, pectinate, persulfate, phenylacetate, phenylethylbarbiturate, phosphate, polygalacturonate, propionate, *p*-toluenesulfonate (tosylate), pyroglutamate, pyruvate, salicylate, sebacate, stearate, subacetate, succinate, sulfamate, sulfate, tannate, tartrate, teoclate (8-chlorotheophyllinate), thiocyanate, triethiodide, undecanoate, undecylenate, and valerate.

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-pyrrolildine-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.

In one embodiment, the salt of a compound of Formula Ia is a sodium salt. In another embodiment, the salt of a compound of Formula Ib is a sodium salt. In another embodiment, the salt of a compound of Formula Ia is a potassium salt. In another embodiment, the salt of a compound of Formula Ib is a potassium salt.

In another aspect the present invention discloses methods of preventing HIV infection in a patient or reducing the risk of infection, comprising administering a pharmaceutical composition of the invention. Pre-exposure prophylaxis (or PrEP) is when people at risk for HIV infection take HIV antiretroviral medicine to lower their chances of acquiring HIV infection. PrEP has been shown to be effective in reducing the risk of infection. As used herein, "HIV" or "Human Immunodeficiency Virus" refers to HIV-1 and/or HIV-2.

As used herein, "patient" refers to a human.

The compounds, salts and compositions of this invention are believed to have as their biological target the HIV capsid and thus their mechanism of action is to modify in one or more ways the function of the HIV capsid.

The compound of Formula Ia and Formula Ib and salts thereof, may be employed alone or in combination with other therapeutic agents, or a prodrug thereof. Combination therapies according to the present invention thus comprise the administration of at least one compound or a pharmaceutically acceptable salt thereof, of the invention, and the administration of at least one other agent which may be useful in the treatment of HIV infection. A compound or a pharmaceutically acceptable salt thereof, of the present invention, and the other agent may be formulated and administered together in a single pharmaceutical composition or may be formulated and administered separately. When formulated and administered separately, administration may occur simultaneously or sequentially in any order.

Suitable other agents are selected from the group consisting of, abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, GSK3640254, GSK3739937/VH3739937, indinavir, islatravir, lamivudine, lopinavir, maraviroc, N6LS, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, S-648414, saquinavir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, zidovudine, and S-365598. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia, or pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, GSK3640254, GSK3739937/VH3739937, indinavir, islatravir, lamivudine, lopinavir,

maraviroc, N6LS, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, S-648414, saquinavir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, zidovudine, and S-365598. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib, or pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, GSK3640254, GSK3739937/VH3739937, indinavir, islatravir, lamivudine, lopinavir, maraviroc, N6LS, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, S-648414, saquinavir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, zidovudine, and S-365598.

In one embodiment, the invention provides a therapeutically effective pharmaceutical composition comprising a compound of Formula Ia, and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, GSK3640254, GSK3739937/VH3739937, indinavir, islatravir, lamivudine, lopinavir, maraviroc, N6LS, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, S-648414, saquinavir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, zidovudine, and S-365598. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, GSK3640254, GSK3739937/VH3739937, indinavir, islatravir, lamivudine, lopinavir, maraviroc, N6LS, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, S-648414, saquinavir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, zidovudine, and S-365598.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia which is amorphous, and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, GSK3640254, GSK3739937/VH3739937, indinavir, islatravir, lamivudine, lopinavir, maraviroc, N6LS, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, S-648414, saquinavir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, zidovudine, and S-365598. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib which is amorphous, and another therapeutic agent selected from the group consisting of

abacavir, atazanavir, bictegravir, cabotegravir, darunavir, delavirdine, didanosine, dideoxyinosine, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, etavirine, fosamprenavir, fostemsavir, GSK3640254, GSK3739937/VH3739937, indinavir, islatravir, lamivudine, lopinavir, maraviroc, N6LS, nelfinavir, nevirapine, raltegravir, rilpiverine, ritonavir, S-648414, saquinavir, stavudine, tipranavir, tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, zalcitabine, zidovudine, and S-365598.

In one embodiment, the other agent is selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, dolutegravir, fostemsavir, lamivudine, maraviroc, rilpiverine, tenofovir disoproxil, tenofovir, tenofovir afenamide, islatravir, doravirine, preziata, S-648414, GSK3640254, N6LS, GSK3739937/VH3739937, and S-365598.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, dolutegravir, fostemsavir, lamivudine, maraviroc, rilpiverine, tenofovir disoproxil, tenofovir, tenofovir afenamide, islatravir, doravirine, preziata, S-648414, GSK3640254, N6LS, GSK3739937/VH3739937, and S-365598. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, dolutegravir, fostemsavir, lamivudine, maraviroc, rilpiverine, tenofovir disoproxil, tenofovir, tenofovir afenamide, islatravir, doravirine, preziata, S-648414, GSK3640254, N6LS, GSK3739937/VH3739937, and S-365598.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, dolutegravir, fostemsavir, lamivudine, maraviroc, rilpiverine, tenofovir disoproxil, tenofovir, tenofovir afenamide, islatravir, doravirine, preziata, S-648414, GSK3640254, N6LS, GSK3739937/VH3739937, and S-365598. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, dolutegravir, fostemsavir, lamivudine, maraviroc, rilpiverine, tenofovir disoproxil, tenofovir, tenofovir afenamide, islatravir, doravirine, preziata, S-648414, GSK3640254, N6LS, GSK3739937/VH3739937, and S-365598.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia which is amorphous, and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, dolutegravir, fostemsavir, lamivudine, maraviroc, rilpiverine, tenofovir disoproxil, tenofovir, tenofovir afenamide, islatravir, doravirine, preziata, S-648414, GSK3640254, N6LS, GSK3739937/VH3739937, and S-365598. In one embodiment, the invention provides a

pharmaceutical composition comprising a compound of Formula Ib which is amorphous, and another therapeutic agent selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, dolutegravir, fostemsavir, lamivudine, maraviroc, rilpiverine, tenofovir disoproxil, tenofovir, tenofovir afenamide, islatravir, doravirine, preziata, S-648414, GSK3640254, N6LS, GSK3739937/VH3739937, and S-365598.

In one embodiment, the other agent is selected from the group consisting of, dolutegravir, lamivudine, fostemsavir, cabotegravir, N6LS, GSK3739937/VH3739937, GSK4000422/VH4000422, and S-365598.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of dolutegravir, lamivudine, fostemsavir, cabotegravir, N6LS, GSK3739937/VH3739937, GSK4000422/VH4000422, and S-365598. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of dolutegravir, lamivudine, fostemsavir, cabotegravir, N6LS, GSK3739937/VH3739937, GSK4000422/VH4000422, and S-365598.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia and another therapeutic agent selected from the group consisting of dolutegravir, lamivudine, fostemsavir, cabotegravir, N6LS, GSK3739937/VH3739937, GSK4000422/VH4000422, and S-365598. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib and another therapeutic agent selected from the group consisting of dolutegravir, lamivudine, fostemsavir, cabotegravir, N6LS, GSK3739937/VH3739937, GSK4000422/VH4000422, and S-365598.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia which is amorphous, and another therapeutic agent selected from the group consisting of dolutegravir, lamivudine, fostemsavir, cabotegravir, N6LS, GSK3739937/VH3739937, GSK4000422/VH4000422, and S-365598. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib which is amorphous, and another therapeutic agent selected from the group consisting of dolutegravir, lamivudine, fostemsavir, cabotegravir, N6LS, GSK3739937/VH3739937, GSK4000422/VH4000422, and S-365598.

In another embodiment, the other agent is selected from the group consisting of dolutegravir, bictegravir, islatravir, lamivudine, fostemsavir, S-365598, and cabotegravir.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, islatravir, lamivudine, fostemsavir, S-365598, and cabotegravir. In one embodiment, the invention

provides a pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, islatravir, lamivudine, fostemsavir, S-365598, and cabotegravir.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, islatravir, lamivudine, fostemsavir, S-365598, and cabotegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, islatravir, lamivudine, fostemsavir, S-365598, and cabotegravir.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia which is amorphous, and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, islatravir, lamivudine, fostemsavir, S-365598, and cabotegravir. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib which is amorphous, and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, islatravir, lamivudine, fostemsavir, S-365598, and cabotegravir.

In another embodiment, the other agent is selected from the group consisting of dolutegravir, bictegravir, S-365598, and cabotegravir.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, S-365598, and cabotegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, S-365598, and cabotegravir.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, S-365598, and cabotegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, S-365598, and cabotegravir.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia which is amorphous, and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, S-365598, and cabotegravir. In another embodiment, the invention provides a pharmaceutical composition comprising a

compound of Formula Ib which is amorphous, and another therapeutic agent selected from the group consisting of dolutegravir, bictegravir, S-365598, and cabotegravir.

In another embodiment, the other agent is dolutegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, and another therapeutic agent is dolutegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, and another therapeutic agent is dolutegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia and another therapeutic agent is dolutegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib and another therapeutic agent is dolutegravir. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia which is amorphous, and another therapeutic agent is dolutegravir. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib which is amorphous, and another therapeutic agent is dolutegravir.

In another embodiment, the other agent is cabotegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, and another therapeutic agent is cabotegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, and another therapeutic agent is cabotegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia and another therapeutic agent is cabotegravir. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib and another therapeutic agent is cabotegravir. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia which is amorphous, and another therapeutic agent is cabotegravir. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib which is amorphous, and another therapeutic agent is cabotegravir.

In still another embodiment, the other agent is S-365598. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, and another therapeutic agent is S-365598. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof, and another therapeutic agent is S-365598. In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia and another therapeutic agent is S-365598. In one embodiment,

the invention provides a pharmaceutical composition comprising a compound of Formula Ib and another therapeutic agent is S-365598. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ia which is amorphous, and another therapeutic agent is S-365598. In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula Ib which is amorphous, and another therapeutic agent is S-365598.

It will be understood that GSK3640254 is a compound as described in Dicker I, Jeffrey JL, Protack T, et al.; GSK3640254 Is a Novel HIV-1 Maturation Inhibitor with an Optimized Virology Profile' *Antimicrob Agents Chemother*. 2022;66(1):e0187621. doi:10.1128/AAC.01876-21; GSK3739937, also known as VH3739937; is an HIV maturation inhibitor and the compound of clinical trial NCT04493684; N6LS: also known as VRC-HIVMAB091-00-AB, is a human monoclonal antibody and the compound of clinical trial NCT03538626; S-365598: is a third-generation HIV integrase strand-transfer inhibitor (INSTI) discovered by Shionogi; and S-648414 is the compound of clinical trial NCT04147715.

EXAMPLES

Formulation A (heterogeneous suspension) is found in Table A.

TABLE A

Ingredient	Function	Quantity (mg/mL)	Quantity (%w/v)	Quantity
Cmpd of Formula Ia	Active agent	300 mg/mL	30%	600 mg
Poloxamer 388	Surfactant	54 mg/mL	5.4%	108 mg
Mannitol	Tonicity adjuster	35 mg/mL	3.5%	70 mg
Acetic Acid, Glacial	Buffer	0.155 mg/mL	0.016%	0.31 mg
Sodium Acetate	Buffer	0.625 mg/mL	0.063%	1.25 mg
Water	Vehicle	QS ML	N/A	QS ML
Nitrogen	Processing aid	QS ML	N/A	QS ML

Preparation of Formulation A:

Sodium acetate (438.36 mg) and glacial acetic acid (104 uL) were dissolved in water (500 mL) to afford a 10 mM acetate buffer solution. The acetate buffer solution (440.41 g) was combined with Poloxamer 338 (34.88 g) and mannitol (24.43 g) and the resulting solution was filtered through a 0.2 μm filter. The pH of the solution was measured as pH 5.04. The solution (278.25 g) was combined with the compound of Formula Ia (110.25 g). The stirred suspension was maintained between 1-25 °C and was circulated at 45-145 mL/min through a wet bead mill (Netzsch Minicer) set at 5.5 m/s agitator tip speed, containing 0.3 mm YTZ grinding beads (Nikkato Corp) until the desired mean particle diameter of about 0.3 μm was achieved. The concentration of the formulation was about 300 mg/mL of a suspended amorphous form of the compound of Formula Ia, with 5.4 w/vol% P338 and 3.5 w/vol% mannitol and the remainder of the composition comprised of the aqueous acetate buffer described above.

Formulation B (heterogeneous suspension) is found in Table B.

TABLE B

Ingredient	Function	Quantity (mg/mL)	Quantity (%w/v)	Quantity
Cmpd of Formula Ib	Active agent	300 mg/mL	30%	600 mg
Poloxamer 388	Surfactant	54 mg/mL	5.4%	108 mg
Mannitol	Tonicity adjuster	35 mg/mL	3.5%	70 mg
Acetic Acid, Glacial	Buffer	0.41 mg/mL	0.041%	0.31 mg
Sodium Acetate	Buffer	1.43 mg/mL	0.143%	1.25 mg
Water	Vehicle	QS ML	N/A	QS mL
Nitrogen	Processing aid	QS ML	N/A	QS mL

Preparation of Formulation B:

Sodium acetate (435.72 mg) and glacial acetic acid (104 uL) were dissolved in water (500 mL) to afford a 10 mM acetate buffer solution. The acetate buffer solution (440.85 g) was combined with Poloxamer 338 (34.89 g) and mannitol (24.46 g) and the resulting solution was filtered through a 0.2 μm filter. The pH of the vehicle was measured as pH 5.02. The solution (278.25 g) was combined with the compound of Formula Ib (110.25 g). The stirred suspension was maintained between 1-25 °C and was circulated at 45-145 mL/min through a wet bead mill (Netzsch Minicer) set at 5.8 m/s agitator tip speed, containing 0.3 mm YTZ grinding beads (Nikkato Corp) until the desired mean particle diameter of about 0.2 μm was achieved. The concentration of the formulation was about 300 mg/mL of a suspended amorphous form of the compound of Formula Ib, with 5.4% w/vol P338 and 3.5% w/vol mannitol and the remainder of the composition comprised of the aqueous acetate buffer described above.

Preparation of Formulation C:

A glass bottle equipped with a lid was charged with PEG200 (135 g) and the solution was heated to 45 °C with stirring. To the solution was slowly added the compound of Formula Ia (60 g) while stirring and heating were maintained. Following the addition, heating and stirring were maintained until a homogeneous solution was obtained. The solution was cooled to room temperature while stirring. To the bottle was added a solution of Lecithin (45 g, "Lipoid E80", egg-based containing 80 weight% phosphatidylcholine) in ethanol (60 g, anhydrous). The mixture was stirred for 15 to 30 min. to afford a clear, homogeneous solution. The composition of the solution is 20 w/w% the compound of Formula Ia, 45 w/w% PEG200, 20 w/w% ethanol, and 15 w/w% lecithin.

Preparation of Formulation D:

A glass bottle equipped with a lid was charged with PEG200 (67.5 g) and the solution was heated to 45 °C with stirring. To the solution was slowly added the compound of Formula Ib (45 g) while heating and stirring were maintained. Following the addition, heating and stirring were maintained until a homogeneous solution was obtained. The solution was cooled to room temperature while stirring. To the solution was added ethanol (37.5 g, anhydrous), and the mixture was stirred for 15 to 30 min. to afford a clear, homogeneous solution. The composition of the solution is 30 w/w% the compound of Formula Ib, 45 w/w% PEG200, and 25 w/w% ethanol.

Preparation of Formulation E:

A glass bottle equipped with a lid was charged with PEG200 (150 g) and the solution was heated to 45 °C with stirring. To the solution was slowly added the compound of Formula Ia (90 g) while heating and stirring were maintained. Following the addition, heating and stirring were maintained until a homogeneous solution was obtained. The solution was cooled to room temperature while stirring. To the solution was added ethanol (60 g, anhydrous), and the mixture was stirred for 15 to 30 min. to afford a clear, homogeneous solution. The composition of the solution is 30 w/w% the compound of Formula Ia, 50 w/w% PEG200, and 20 w/w% ethanol; density = 1.11 g/mL; viscosity = 49.9 mPa-s.

Preparation of Formulation F:

A glass bottle equipped with a lid was charged with PEG200 (3.99 mL), ethanol (0.52 mL) and water (0.67 mL), and the mixture was then vortexed. To the solution was slowly added the compound of Formula Ib (931 mg) and the mixture was then vortexed. The mixture was sonicated to afford a clear, homogeneous solution. The composition of the solution is PEG200 (69%), ethanol (6.3%), water (10.3%), compound of Formula Ib (14.3%).

Preparation of Formulation G:

A glass bottle equipped with a lid was charged with PEG200 (2.54 mL), ethanol (0.52 mL), propylene glycol (0.73 mL), and water (0.52 mL), and the mixture was then vortexed. To the solution was slowly added the compound of Formula Ib (772 mg), and the mixture was then vortexed. The mixture was sonicated to afford a clear, homogeneous solution. The composition of the solution is PEG200 (53.7%), ethanol (7.7%), propylene glycol (14.2%), water (9.8%), compound of Formula Ib (14.5%).

Preparation of Formulation H:

A glass bottle equipped with a lid was charged with PEG200 (1.75 mL), ethanol (0.35 mL), and sesame oil (1.40 mL), and the mixture was then vortexed. To the solution was slowly added the compound of Formula Ib (628 mg), and the mixture was then vortexed. The solution was sonicated to afford a clear, homogeneous solution. The composition of the solution is PEG200 (47.3%), ethanol (6.6%), sesame oil (31%), compound of Formula Ib (15.1%).

Preparation of Formulation I:

Water (455.94 g) was combined with poloxamer 338 (31.26 g) and mannitol (25.07 g) and the resulting solution was filtered through a 0.2 µm filter to afford the "vehicle". To the vehicle (247.63 g) was added the compound of Formula Ib (64.09 g). The stirred suspension maintained between 1-25 °C was circulated after the vehicle (50.40g) at 50-145 mL/min through a wet bead mill (Netzsch Minicer) set at 5.8 m/s agitator tip speed containing 0.3 mm YTZ grinding beads (Nikkato Corp) until the desired mean particle diameter of about 0.78 µm was achieved. The concentration of the formulation was about 168.95 mg/mL of the compound of Formula Ib, with about 6.49% wt/vol P338 and about 5.2% wt/vol mannitol, with the remainder of the composition comprised of water.

Preparation of Formulation J:

Water (455.13 g) was combined with poloxamer 338 (31.29 g) and mannitol (25.01 g) and the resulting solution was filtered through a 0.2 µm filter to afford the "vehicle". To the vehicle (238.34 g) was added the compound of Formula Ia (64.51 g). The stirred suspension maintained between 1-25 °C was circulated after the vehicle (50.40g) at 73-145 mL/min through a wet bead mill (Netzsch Minicer) set at 5.8 m/s agitator tip speed containing 0.3 mm YTZ grinding beads (Nikkato Corp) until the desired mean particle diameter of about 0.40 µm was achieved. The concentration of the formulation was about 177 mg/mL of the compound of Formula Ia, with about 6.3% wt/vol P338 and about 5.03% wt/vol mannitol, with the remainder of the composition comprised of water.

Preparation of Formulation K:

To a mixing vessel, 1299.8 grams of PEG200 and 427.2 grams of ethanol were charged to a mixing vessel. The solution was stirred at ambient temperature for 15 minutes while gradually adding 40.85 grams of a compound of Formula Ia. The solution was stirred for approximately 2 hours until the compound was completely dissolved to yield a clear uniform solution. The resulting solution had a viscosity of 25 cP and a density of 1.089 g/mL.

General procedures for analysis of blood samples:

General Procedure A:

Blood samples were collected into K_2EDTA tubes, placed on water ice immediately after collection, and centrifuged as soon as possible to obtain plasma. Plasma samples were stored at -70°C or colder until analysis by LC-MS/MS. All *in vitro* samples were injected on an MDS Sciex 5000 triple-quadrupole LC-MS/MS system. The analytical column used was a Waters Acquity 1.7 µm CSH Fluror Phenyl (2.1mm x 50 mm) maintained at 50°C. Mobile Phase A consisted of 0.1% (v/v) formic acid in MilliQ-purified water. Mobile Phase B consisted of 0.1% (v/v) formic acid in acetonitrile. The flow rate was 0.80 mL/min. The gradient was as follows: Mobile B was held for 0.2 minutes at 20% and then linearly increased from 20% to 75% over 0.4 min, followed by another linear increase from 75-95% over 0.55 min. It was then maintained at 95% for 0.35 min, and maintained at 20% for 0.49 min.

General Procedure B:

Blood samples were collected into K_2EDTA tubes, placed on water ice immediately after collection, and centrifuged as soon as possible to obtain plasma. Plasma samples were stored at -70°C or colder until analysis by LC-MS/MS. All *in vitro* samples were injected on a MDS Sciex 6500+ triple-quadrupole LC-MS/MS system. The analytical column used was a Waters Acquity 1.7 µm BEH (C18, 2.1mm x 50 mm, 1.7 µm) maintained at 35 °C. Mobile Phase A consisted of 0.1% (v/v) formic acid in MilliQ-purified water. Mobile Phase B consisted of 0.1% (v/v) formic acid in acetonitrile. The flow rate was 0.80 mL/min. The gradient was as follows: Mobile B was held for 0.2 minutes at 2% and then linearly increased from 2% to 75% over 0.4 min, followed by another linear increase from 75-95% over 0.55 min. It was then maintained at 95% for 0.35 min, and maintained at 2% for 0.49 min.

Procedure for measuring pharmacokinetic parameters for Formulation A in an *in vivo* experiment

"Formulation A" was administered to Wistar Han Rats as either a subcutaneous injection at a dose of 1 mL/kg; a subcutaneous injection at a dose of 3.33 mL/kg; or as an intramuscular injection at a dose of 0.5 mL/kg. Blood samples were collected at the times indicated in Tables 1-3 and were analyzed according to General Procedure A. Results of the PK experiments are described in Tables 1-3 and Figures 1-3.

Table 1. Plasma concentration vs. time data for a study evaluating Formulation A administered to rats subcutaneously at 1 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	52.7	83.6	48.5	62	19.2
0.13	3	166	172	152	163	10.3
0.21	5	309	439	356	368	65.8
0.29	7	576	577	620	591	25.1
1	24	1100	1350	1570	1340	235.2
2	48	1010	1810	2350	1723	674.2
4	96	671	1780	2110	1520	753.8
6	144	858	2490	6490	3279	2897.8
13	312	3050	5280	9130	4165	1576.8
20	480	2410	2580	2940	2495	120.2
27	648	1710	1480	1520	1595	162.6
34	816	1090	999	863	1045	64.3

LOD = Limit of detection

Table 2. Plasma concentration vs. time data for a study evaluating Formulation A administered to rats subcutaneously at 3.33 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	107	67.5	52.7	76	28.1
0.13	3	284	275	173	244	61.7
0.21	5	627	730	396	584	171.0
0.29	7	983	1340	854	1059	251.8
1	24	5290	5940	3890	5040	1047.6
2	48	7900	7940	4460	6767	1997.7
4	96	6200	10800	3520	6840	3682.0
6	144	8300	19900	5950	11383	7468.7
13	312	31000	47400	37600	38667	8251.9
20	480	23300	27300	20600	23733	3371.0
27	648	11900	13200	8580	11227	2382.5
34	816	7120	6240	4350	5903	1415.4

LOD = Limit of detection

Table 3. Plasma concentration vs. time data for a study evaluating Formulation A administered to rats intramuscularly at 0.5 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	247	356	640	414	202.9
0.13	3	598	1060	1160	939	299.8
0.21	5	1080	1920	1890	1630	476.6
0.29	7	1710	2880	2850	2480	667.0
1	24	5410	6840	5870	6040	730.0
2	48	6870	8480	6400	7250	1090.8
4	96	4910	6300	4520	5243	935.6
6	144	6260	5230	4590	5360	842.6
13	312	1650	1990	3390	2343	922.2
20	480	287	556	615	486	174.8
27	648	77.4	208	198	161	72.7

LOD = Limit of detection

Procedure for measuring pharmacokinetic parameters for Formulation B in an *in vivo* experiment

"Formulation B" was administered to Wistar Han Rats as a either a subcutaneous injection at a dose of 1.04 mL/kg; a subcutaneous injection at a dose of 3.46 mL/kg; or as an intramuscular injection at a dose of 0.52 mL/kg. Blood samples were collected at the times indicated in Tables 4-6 and were analyzed according to General Procedure B. Results of the PK experiments are described in Tables 4-6 and Figures 4-6.

Table 4. Plasma concentration vs. time data for a study evaluating Formulation B administered to rats subcutaneously at 1.04 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	113.0	82.7	75.2	90.3	20.0
0.13	3	326.0	214.0	208.0	249.3	66.5
0.21	5	600.0	558.0	461.0	539.7	71.3
0.29	7	894.0	733.0	754.0	793.7	87.5
1	24	2200.0	2500.0	2640.0	2446.7	224.8
2	48	3120.0	2790.0	2310.0	2740.0	407.3
4	96	3780.0	3020.0	1900.0	2900.0	945.7
6	144	5190.0	3400.0	2970.0	3853.3	1177.4
13	312	2120.0	2150.0	3340.0	2536.7	695.9
20	480	808.0	1110.0	1590.0	1169.3	394.4
27	648	685.0	985.0	1500.0	1056.7	412.2
34	816	175.0	369.0	462.0	335.3	146.4
41	984	92.2	125.0	242.0	153.1	78.7
48	1152	47.5	55.0	133.0	78.5	47.3

LOD = Limit of detection

Table 5. Plasma concentration vs. time data for a study evaluating Formulation B administered to rats subcutaneously at 3.46 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	220.0	260.0	168.0	216.0	46.1
0.13	3	580.0	587.0	454.0	540.3	74.8
0.21	5	1120.0	1420.0	1120.0	1220.0	173.2
0.29	7	1360.0	1750.0	1440.0	1516.7	206.0
1	24	6480.0	7390.0	4200.0	6023.3	1643.3
2	48	10300.0	5720.0	3610.0	6543.3	3420.2
4	96	10800.0	4280.0	2680.0	5920.0	4301.3
6	144	9620.0	6520.0	4710.0	6950.0	2483.1
13	312	16100.0	13700.0	11200.0	13666.7	2450.2
20	480	4990.0	8720.0	7310.0	7006.7	1883.4
27	648	3090.0	4580.0	5530.0	4400.0	1229.9
34	816	1200.0	1720.0	2860.0	1926.7	849.1
41	984	442.0	877.0	1820.0	1046.3	704.4
48	1152	141.0	317.0	1080.0	512.7	499.1

LOD = Limit of detection

Table 6. Plasma concentration vs. time data for a study evaluating Formulation B administered to rats intramuscularly at 0.52 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	386.0	942.0	680.0	669.3	278.2
0.13	3	1020.0	1790.0	1690.0	1500.0	418.7
0.21	5	1200.0	3370.0	2490.0	2353.3	1091.4
0.29	7	1630.0	4990.0	2580.0	3066.7	1732.1
1	24	4050.0	7750.0	4950.0	5583.3	1929.6
2	48	2380.0	5720.0	3560.0	3886.7	1693.8
4	96	2690.0	2340.0	2320.0	2450.0	208.1
6	144	3000.0	2090.0	3300.0	2796.7	630.1
13	312	1150.0	761.0	448.0	786.3	351.7
20	480	219.0	189.0	119.0	175.7	51.3
27	648	94.3	64.8	69.8	76.3	15.8
34	816	24.2	16.2	8.9	16.4	7.7
41	984	4.7	4.6	<LOD	4.6	N/A
48	1152	<LOD	<LOD	<LOD	<LOD	N/A

LOD = Limit of detection

Procedure for measuring pharmacokinetic parameters for Formulation C in an *in vivo* experiment

"Formulation C" was administered to Wistar Han Rats as either a subcutaneous injection at a dose of 1.5 mL/kg; a subcutaneous injection at a dose of 5 mL/kg; or as an intramuscular injection at a dose of 0.5 mL/kg. Blood samples were collected at the times indicated in Tables 7-9 and were analyzed according to General Procedure A. Results of the PK experiments are described in Tables 7-9 and Figures 7-9.

Table 7. Plasma concentration vs. time data for a study evaluating Formulation C administered to rats subcutaneously at 1.5 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1					
0.13	3	15.5	10.8		13.15	3.3
0.21	5	18.7	25.2	26	23.3	4.0
0.29	7	25.9	48.4	42.4	38.9	11.7
1	24	145	148	187	160	23.4
2	48	209	209	241	220	18.5
4	96	294	298	198	263	56.6
6	144	400	536	245	394	145.6
13	312	746	748	859	784	64.7
20	480	749	460	460	556	166.9
27	648	656	473	460	530	109.6
34	816	603	440	484	509	84.3
41	984	617	510	459	529	80.6
48	1152	545	472	477	498	40.8
55	1320	569	362	420	450	106.8
62	1488	423	369	421	404	30.6
69	1656	477	384	407	423	48.4
76	1824	392	321	385	366	39.1
83	1992	375	327	344	349	24.3

LOD = Limit of detection

Table 8. Plasma concentration vs. time data for a study evaluating Formulation C administered to rats subcutaneously at 5 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1		37.3	17.5	27	14.0
0.13	3	15.6	135	59.3	70	60.4
0.21	5	36.6	202	142	127	83.7
0.29	7	75.8	328	245	216	128.5
1	24	314	1020	765	700	357.5
2	48	446	1040	1240	909	413.0
4	96	404	681	1120	735	361.0
6	144	932	1060	1800	1264	468.6
13	312	3910	3220	3490	3540	347.7
20	480	3720	3790	3040	3517	414.3
27	648	2750	2000	1250	2000	750.0
34	816	2530	2140	1160	1943	705.9
41	984	2980	2260	974	2071	1016.2
48	1152	2710	2010	841	1854	944.3
55	1320	2320	1840	769	1643	794.0
62	1488	1810	1710	671	1397	630.7
69	1656	1780	1490	695	1322	561.7
76	1824	1410	1390	555	1118	488.0
83	1992	1350	1360	517	1076	483.8

LOD = Limit of detection

Table 9. Plasma concentration vs. time data for a study evaluating Formulation C administered to rats intramuscularly at 0.5 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	21.6	11		16	7.5
0.13	3	73.8	30.8	13.2	39	31.2
0.21	5	125	71.9	27.6	75	48.8
0.29	7	128	95.7	46.6	90	41.0
1	24	362	201	150	238	110.7
2	48	334	317	153	268	100.0
4	96	400	276	145	274	127.5
6	144	556	442	236	411	162.2
13	312	495	376	196	356	150.5
20	480	531	411	205	382	164.9
27	648	376	438	140	318	157.2
34	816	407	384	155	315	139.3
41	984	325	405	133	288	139.8
48	1152	226	279	100	202	91.9
55	1320	186	249	91.3	175	79.4
62	1488	128	204	62.6	132	70.8
69	1656	119	182	62.2	121	59.9
76	1824	85.2	115	45	82	35.1
83	1992	66.1	102	31	66	35.5

LOD = Limit of detection

Procedure for measuring pharmacokinetic parameters for Formulation D in an *in vivo* experiment

"Formulation D" was administered to Wistar Han Rats as either a subcutaneous injection at a dose of 0.91 mL/kg; a subcutaneous injection at a dose of 3.03 mL/kg; or as an intramuscular injection at a dose of 0.45 mL/kg. Blood samples were collected at the times indicated in Tables 10-12 and were analyzed according to General Procedure B. Results of the PK experiments are described in Tables 10-12 and Figures 10-12.

Table 10. Plasma concentration vs. time data for a study evaluating Formulation D administered to rats subcutaneously at 0.91 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	46.9	4.8	7.2	19.6	23.6
0.13	3	118.0	22.7	24.4	55.0	54.5
0.21	5	171.0	46.4	41.4	86.3	73.4
0.29	7	212.0	62.9	62.2	112.4	86.3
1	24	330.0	146.0	147.0	207.7	105.9
2	48	113.0	153.0	354.0	206.7	129.2
4	96	253.0	92.0	114.0	153.0	87.3
6	144	268.0	53.9	90.3	137.4	114.6
13	312	200.0	180.0	406.0	262.0	125.1
20	480	282.0	185.0	195.0	220.7	53.4
27	648	507.0	344.0	288.0	379.7	113.8
34	816	289.0	248.0	211.0	249.3	39.0
41	984	302.0	223.0	254.0	259.7	39.8

LOD = Limit of detection

Table 11. Plasma concentration vs. time data for a study evaluating Formulation D administered to rats subcutaneously at 3.03 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	10.3	32.4	15.7	19.5	11.5
0.13	3	70.5	169.0	79.7	106.4	54.4
0.21	5	176.0	296.0	167.0	213.0	72.0
0.29	7	222.0	369.0	263.0	284.7	75.9
1	24	470.0	816.0	514.0	600.0	188.4
2	48	535.0	785.0	511.0	610.3	151.7
4	96	506.0	1140.0	557.0	734.3	352.2
6	144	301.0	837.0	462.0	533.3	275.0
13	312	701.0	1000.0	664.0	788.3	184.2
20	480	637.0	1200.0	663.0	833.3	317.8
27	648	1210.0	1930.0	822.0	1320.7	562.2
34	816	776.0	1280.0	717.0	924.3	309.4
41	984	1210.0	1540.0	828.0	1192.7	356.3

LOD = Limit of detection

Table 12. Plasma concentration vs. time data for a study evaluating Formulation D administered to rats intramuscularly at 0.45 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	55.8	38.9	28.5	41.1	13.8
0.13	3	167.0	79.0	53.9	100.0	59.4
0.21	5	261.0	127.0	72.0	153.3	97.2
0.29	7	248.0	136.0	92.8	158.9	80.1
1	24	516.0	287.0	156.0	319.7	182.2
2	48	331.0	247.0	118.0	232.0	107.3
4	96	233.0	182.0	81.8	165.6	76.9
6	144	358.0	288.0	146.0	264.0	108.0
13	312	495.0	785.0	228.0	502.7	278.6
20	480	381.0	594.0	194.0	389.7	200.1
27	648	513.0	685.0	273.0	490.3	206.9
34	816	321.0	426.0	179.0	308.7	124.0
41	984	293.0	426.0	173.0	297.3	126.6

LOD = Limit of detection

Procedure for measuring pharmacokinetic parameters for Formulation F in an in vivo experiment

"Formulation F" was administered to Wistar Han Rats as either a subcutaneous injection at a dose of 0.33 mL/kg or as an intramuscular injection at a dose of 0.33 mL/kg. Blood samples were collected at the times indicated in Tables 13-14 and were analyzed according to General Procedure B. Results of the PK experiments are described in Tables 13-14 and Figures 13-14.

Table 13. Plasma concentration vs. time data for a study evaluating Formulation F administered to rats subcutaneously at 0.33 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.0	1.0	16.1	12.3	8.2	12.2	4.0
0.2	4.0	39.7	46.2	22.8	36.2	12.1
0.3	7.0	53.2	68.2	25.3	48.9	21.8
1	24	75.4	81.0	49.1	68.5	17.0
2	48	59.1	83.2	45.0	62.4	19.3
4	96	59.2	64.8	52.6	58.9	6.1
6	144	77.5	166.0	51.7	98.4	59.9
13	312	88.4	159.0	105.0	117.5	36.9
20	480	93.5	186.0	108.0	129.2	49.8
27	648	173.0	241.0	157.0	190.3	44.6
34	816	210.0	245.0	180.0	211.7	32.5
41	984	179.0	266.0	270.0	238.3	51.4
48	1152	172.0	195.0	245.0	204.0	37.3
55	1320	107.0	122.0	165.0	131.3	30.1
62	1488	87.0	106.0	151.0	114.7	32.9
69	1656	78.6	78.2	123.0	93.3	25.8
76	1824	62.6	66.9	117.0	82.2	30.2
83	1992	90.4	80.4	125.0	98.6	23.4
90	2160	64.4	57.1	84.7	68.7	14.3
97	2328	45.0	49.3	75.1	56.5	16.3
104	2496	35.7	37.5	54.7	42.6	10.5

LOD = Limit of detection

Table 14. Plasma concentration vs. time data for a study evaluating Formulation F administered to rats intramuscularly at 0.33 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.0	1.0	30.5	25.5	45.5	33.8	10.4
0.2	4.0	69.7	63.4	110.0	81.0	25.3
0.3	7.0	91.3	99.2	148.0	112.8	30.7
1	24	175.0	153.0	280.0	202.7	67.9
2	48	119.0	120.0	168.0	135.7	28.0
4	96	96.0	71.7	122.0	96.6	25.2
6	144	297.0	99.2	228.0	208.1	100.4
13	312	240.0	76.6	189.0	168.5	83.6
20	480	254.0	105.0	211.0	190.0	76.7
27	648	248.0	89.3	170.0	169.1	79.4
34	816	135.0	82.5	209.0	142.2	63.6
41	984	111.0	58.5	256.0	141.8	102.3
48	1152	63.6	34.7	80.4	59.6	23.1
55	1320	28.1	18.1	54.8	33.7	19.0
62	1488	25.4	13.4	62.6	33.8	25.7
69	1656	18.5	9.3	31.5	19.8	11.2
76	1824	14.9	6.7	25.0	15.5	9.2
83	1992	12.4	4.5	21.0	12.6	8.2

LOD = Limit of detection

Procedure for measuring pharmacokinetic parameters for Formulation G in an *in vivo* experiment

"Formulation G" was administered to Wistar Han Rats as either a subcutaneous injection at a dose of 0.33 mL/kg or as an intramuscular injection at a dose of 0.33 mL/kg. Blood samples were collected at the times indicated in Tables 15-16 and were analyzed according to General Procedure B. Results of the PK experiments are described in Tables 15-16 and Figures 15-16.

Table 15. Plasma concentration vs. time data for a study evaluating Formulation G administered to rats subcutaneously at 0.33 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.0	1.0	5.1	8.3	6.0	6.5	1.7
0.2	4.0	19.1	29.1	21.9	23.4	5.2
0.3	7.0	39.0	56.6	43.0	46.2	9.2
1	24	57.0	103.0	63.2	74.4	25.0
2	48	48.1	78.9	62.2	63.1	15.4
4	96	25.1	40.1	39.3	34.8	8.4
6	144	21.1	29.6	49.1	33.3	14.4
13	312	102.0	72.7	116.0	96.9	22.1
20	480	136.0	52.9	125.0	104.6	45.1
27	648	87.6	72.7	146.0	102.1	38.7
34	816	108.0	65.6	183.0	118.9	59.4
41	984	109.0	54.0	146.0	103.0	46.3
48	1152	98.4	61.2	110.0	89.9	25.5
55	1320	141.0	92.7	140.0	124.6	27.6
62	1488	121.0	86.8	119.0	108.9	19.2
69	1656	107.0	101.0	103.0	103.7	3.1
76	1824	82.4	65.3	50.2	66.0	16.1
83	1992	80.6	57.1	43.5	60.4	18.8
90	2160	71.8	51.2	38.9	54.0	16.6

LOD = Limit of detection

5

Table 16. Plasma concentration vs. time data for a study evaluating Formulation G administered to rats intramuscularly at 0.33 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.0	1.0	24.9	10.5	14.2	16.5	7.5
0.2	4.0	61.2	38.8	71.6	57.2	16.8
0.3	7.0	110.0	56.6	77.8	81.5	26.9
1	24	155.0	119.0	103.0	125.7	26.6
2	48	108.0	74.4	98.2	93.5	17.3
4	96	123.0	75.5	85.8	94.8	25.0
6	144	269.0	161.0	203.0	211.0	54.4
13	312	402.0	292.0	366.0	353.3	56.1
20	480	343.0	338.0	261.0	314.0	46.0
27	648	224.0	276.0	334.0	278.0	55.0
34	816	147.0	215.0	169.0	177.0	34.7
41	984	71.3	99.6	84.9	85.3	14.2
48	1152	30.2	68.3	44.9	47.8	19.2
55	1320	54.9	74.4	37.1	55.5	18.7
62	1488	30.8	50.9	25.8	35.8	13.3
69	1656	22.8	38.1	18.1	26.3	10.5

LOD = Limit of detection

Procedure for measuring pharmacokinetic parameters for Formulation H in an *in vivo* experiment

"Formulation H" was administered to Wistar Han Rats as either a subcutaneous injection at a dose of 0.33 mL/kg or as an intramuscular injection at a dose of 0.33 mL/kg. Blood samples were collected at the times indicated in Tables 17-18 and were analyzed according to General Procedure B. Results of the PK experiments are described in Tables 17-18 and Figures 17-18.

Table 17. Plasma concentration vs. time data for a study evaluating Formulation H administered to rats subcutaneously at 0.33 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.0	1.0	13.5	4.0	4.8	7.4	5.3
0.2	4.0	46.7	17.7	24.0	29.5	15.3
0.3	7.0	70.3	35.9	46.8	51.0	17.6
1	24	113.0	75.2	70.9	86.4	23.2
2	48	113.0	72.6	83.4	89.7	20.9
4	96	70.2	58.5	62.9	63.9	5.9
6	144	69.7	41.5	70.4	60.5	16.5
13	312	81.1	52.8	125.0	86.3	36.4
20	480	89.3	60.9	162.0	104.1	52.1
27	648	90.9	80.8	241.0	137.6	89.7
34	816	115.0	96.2	211.0	140.7	61.6
41	984	171.0	111.0	227.0	169.7	58.0
48	1152	176.0	98.6	201.0	158.5	53.4
55	1320	176.0	130.0	233.0	179.7	51.6
62	1488	145.0	130.0	210.0	161.7	42.5
69	1656	108.0	131.0	159.0	132.7	25.5
76	1824	138.0	102.0	121.0	120.3	18.0
83	1992	141.0	125.0	120.0	128.7	11.0
90	2160	87.9	110.0	104.0	100.6	11.4
97	2328	116.0	147.0	105.0	122.7	21.8
104	2496	79.5	92.6	67.8	80.0	12.4

LOD = Limit of detection

Table 18. Plasma concentration vs. time data for a study evaluating Formulation H administered to rats intramuscularly at 0.33 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.0	1.0	60.0	44.9	36.2	47.0	12.0
0.2	4.0	187.0	185.0	130.0	167.3	32.3
0.3	7.0	340.0	312.0	206.0	286.0	70.7
1	24	456.0	441.0	411.0	436.0	22.9
2	48	305.0	341.0	286.0	310.7	27.9
4	96	295.0	437.0	268.0	333.3	90.8
6	144	482.0	676.0	528.0	562.0	101.4
13	312	344.0	415.0	392.0	383.7	36.2
20	480	315.0	454.0	448.0	405.7	78.6
27	648	185.0	297.0	348.0	276.7	83.4
34	816	119.0	183.0	273.0	191.7	77.4
41	984	102.0	186.0	212.0	166.7	57.5
48	1152	65.1	131.0	156.0	117.4	47.0
55	1320	42.5	113.0	121.0	92.2	43.2
62	1488	27.6	79.7	98.0	68.4	36.5
69	1656	16.5	49.6	59.5	41.9	22.5
76	1824	11.9	53.4	48.9	38.1	22.8
83	1992	8.2	47.4	41.6	32.4	21.2
90	2160	4.6	44.5	33.7	27.6	20.7
97	2328	3.9	33.2	33.3	23.5	16.9

LOD = Limit of detection

Procedure for measuring pharmacokinetic parameters for Formulation I in an *in vivo* experiment

"Formulation I" was administered to Wistar Han Rats as either a subcutaneous injection at a dose of 0.25 mL/kg or as an intramuscular injection at a dose of 0.25 mL/kg. Blood samples were collected at the times indicated in Tables 19-20 and were analyzed according to General Procedure A. Results of the PK experiments are described in Tables 19-20 and Figures 19-20.

Table 19. Plasma concentration vs. time data for a study evaluating Formulation I administered to rats subcutaneously at 0.25 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1.0	79.2	64.9	49.6	64.6	14.8
0.17	4.0	253.0	217.0	159.0	209.7	47.4
0.29	7.0	302.0	426.0	284.0	337.3	77.3
1	24	465.0	580.0	504.0	516.3	58.5
2	48	344.0	427.0	475.0	415.3	66.3
4	96	257.0	340.0	370.0	322.3	58.5
6	144	360.0	437.0	647.0	481.3	148.5
13	312	212.0	352.0	338.0	300.7	77.1
20	480	118.0	109.0	173.0	133.3	34.6
27	648	72.9	49.9	78.1	67.0	15.0
34	816	43.7	24.8	49.4	39.3	12.9
41	984	24.7	14.9	27.9	22.5	6.8
48	1152	22.5	10.2	12.1	14.9	6.6

LOD = Limit of detection

Table 20. Plasma concentration vs. time data for a study evaluating Formulation I administered to rats intramuscularly at 0.25 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.0	1.0	694.0	468.0	462.0	541.3	132.2
0.2	4.0	1480.0	1330.0	1020.0	1276.7	234.6
0.3	7.0	2100.0	1940.0	1580.0	1873.3	266.3
1	24	2490.0	2680.0	1950.0	2373.3	378.7
2	48	1650.0	2040.0	1300.0	1663.3	370.2
4	96	794.0	1120.0	947.0	953.7	163.1
6	144	679.0	768.0	812.0	753.0	67.8
13	312	142.0	212.0	167.0	173.7	35.5
20	480	10.4	41.0	51.2	34.2	21.2
27	648	<LOD	4.7	10.9	7.8	
34	816	<LOD	1.2	4.2	2.7	

LOD = Limit of detection

Procedure for measuring pharmacokinetic parameters for Formulation J in an *in vivo* experiment

"Formulation J" was administered to Wistar Han Rats as either a subcutaneous injection at a dose of 0.28 mL/kg or as an intramuscular injection at a dose of 0.28 mL/kg. Blood samples were collected at the times indicated in Tables 21-22 and were analyzed according to General Procedure A. Results of the PK experiments are described in Tables 21-22 and Figures 21-22.

Table 21. Plasma concentration vs. time data for a study evaluating Formulation J administered to rats subcutaneously at 0.28 mL/kg (n = 3).

Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	17.2	12.8	114	48.0	57.2
0.13	3	57	59.4	232	116.1	100.4
0.21	5	116	134	507	252.3	220.7
0.29	7	182	198	611	330.3	243.2
1	24	850	730	1520	1033.3	425.7
2	48	1400	1270	1340	1336.7	65.1
4	96	1240	1190	1020	1150.0	115.3
6	144	1520	1760	1230	1503.3	265.4
13	312	1230	1560	725	1171.7	420.5
20	480	492	823	261	525.3	282.5
27	648	250	545	134	309.7	211.9
34	816	124	250	50.8	141.6	100.8
41	984	62.5	103	19.6	61.7	41.7

LOD = Limit of detection

Table 22. Plasma concentration vs. time data for a study evaluating Formulation J administered to rats intramuscularly at 0.28 mL/kg (n = 3).

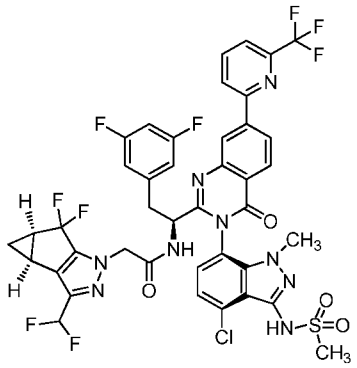
Days	Hours	Rat 1 (ng/mL)	Rat 2 (ng/mL)	Rat 3 (ng/mL)	Avg. Conc. (ng/mL)	Std. Dev. Conc. (ng/mL)
0.04	1	190	237	262	229.7	36.6
0.13	3	405	503	676	528.0	137.2
0.21	5	830	1110	1310	1083.3	241.1
0.29	7	1100	1470	1970	1513.3	436.6
1	24	2670	4650	3650	3656.7	990.0
2	48	2710	3850	3060	3206.7	584.0
4	96	2760	2400	1670	2276.7	555.4
6	144	3300	2090	753	2047.7	1274.0
13	312	1050	803	231	694.7	420.1
20	480	387	274	40.1	233.7	176.9
27	648	135	55.6		95.3	56.1
34	816	63.5	11.5		37.5	36.8
41	984	23.7			23.7	

LOD = Limit of detection

The data generated above and depicted in the Figures shows that the pharmaceutical compositions of the invention extend the release profile of the compounds of Formula Ia and Formula Ib and suggest their use in long-acting administration of the compounds.

What is claimed is:

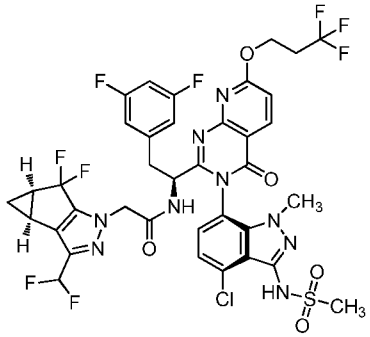
1. A pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof,



Formula Ia

wherein the composition comprises polyethylene glycol and ethanol.

2. A pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof,



Formula Ib

wherein the composition comprises polyethylene glycol and ethanol.

3. The pharmaceutical composition according to Claim 1 or Claim 2 wherein the composition further comprises one or more of water, lecithin, propylene glycol, benzyl alcohol, or sesame oil.

4. The pharmaceutical composition according to Claim 3 wherein the composition comprises lecithin.

5. The pharmaceutical composition according to Claim 4 wherein the lecithin is egg-based or soy-based and is about 80 weight% phosphatidylcholine.

6. The pharmaceutical composition according to Claim 4 wherein the lecithin is egg-based or soy-based and is about 100 weight% phosphatidylcholine.

7. The pharmaceutical composition according to any of Claims 4 to 6 further comprising propylene glycol, benzyl alcohol, or sesame oil.

8. The pharmaceutical composition according to any of Claims 1-7 wherein the average molecular weight of polyethylene glycol is about 200 (PEG 200).

9. The pharmaceutical composition according to any of Claims 1-7 wherein the average molecular weight of polyethylene glycol is about 300 (PEG 300).

10. The pharmaceutical composition according to any of Claims 1-7 wherein the average molecular weight of polyethylene glycol is about 400 (PEG 400).

11. The pharmaceutical composition according to any of Claims 1-10 wherein the amount of ethanol is about 5-25 weight%.

12. The pharmaceutical composition according to any of Claims 1-10 wherein the amount of ethanol is about 20 weight%.

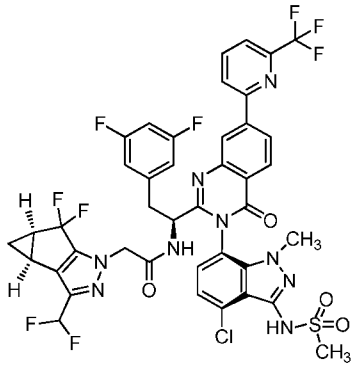
13. The pharmaceutical composition according to any of Claims 1-10 wherein the amount of polyethylene glycol is about 40-50% by weight.

14. The pharmaceutical composition according to any of Claims 1-13 wherein the composition is a homogeneous solution.

15. The pharmaceutical composition according to any of Claims 1 and 3-14 comprising about 20% by weight of the compound of Formula Ia, or a pharmaceutically acceptable salt thereof, about 45% by weight of PEG200, about 20% by weight of ethanol, and about 15% by weight of lecithin.

16. The pharmaceutical composition according to any of Claims 2-14 comprised of about 20% by weight of the compound of Formula Ib, or a pharmaceutically acceptable salt thereof, about 45% by weight of PEG200, about 20% by weight of ethanol, and about 15% by weight of lecithin.

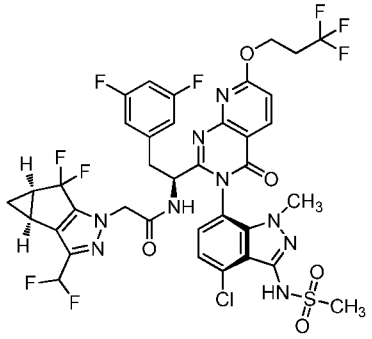
17. A pharmaceutical composition comprising a compound of Formula Ia,



Formula Ia

wherein the composition comprises polyethylene glycol and ethanol.

18. A pharmaceutical composition comprising a compound of Formula Ib,



Formula Ib

wherein the composition comprises polyethylene glycol and ethanol.

19. The pharmaceutical composition according to Claim 17 or Claim 18 wherein the composition further comprises one or more of water, lecithin, propylene glycol, benzyl alcohol, or sesame oil.

20. The pharmaceutical composition according to Claim 19 wherein the composition comprises lecithin.

21. The pharmaceutical composition according to Claim 20 wherein the lecithin is egg-based or soy-based and is about 80 weight% phosphatidylcholine.

22. The pharmaceutical composition according to Claim 20 wherein the lecithin is egg-based or soy-based and is about 100 weight% phosphatidylcholine.

23. The pharmaceutical composition according to any of Claims 20-22 further comprising propylene glycol, benzyl alcohol, or sesame oil.

24. The pharmaceutical composition according to any of Claims 17-23 wherein the average molecular weight of polyethylene glycol is about 200 (PEG 200).

25. The pharmaceutical composition according to any of Claims 17-23 wherein the average molecular weight of polyethylene glycol is about 300 (PEG 300).

26. The pharmaceutical composition according to any of Claims 17-23 wherein the average molecular weight of polyethylene glycol is about 400 (PEG 400).

27. The pharmaceutical composition according to any of Claims 17-26 wherein the amount of ethanol is about 5-25 weight%.

28. The pharmaceutical composition according to any of Claims 17-26 wherein the amount of ethanol is about 20 weight%.

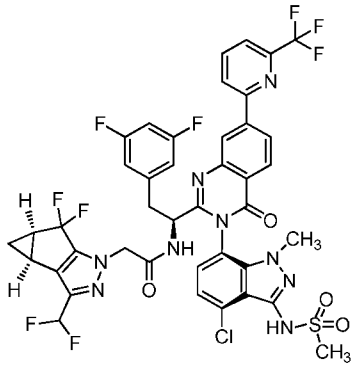
29. The pharmaceutical composition according to any of Claims 17-26 wherein the amount of polyethylene glycol is about 40-50% by weight.

30. The pharmaceutical composition according to any of Claims 17-29 wherein the composition is a homogeneous solution.

31. The pharmaceutical composition according to any of Claims 17 and 19-30 comprised of about 20% by weight of the compound of Formula Ia, about 45% by weight of PEG200, about 20% by weight of ethanol, and about 15% by weight of lecithin.

32. The pharmaceutical composition according to any of Claims 18-30 comprised of about 20% by weight of the compound of Formula Ib, about 45% by weight of PEG200, about 20% by weight of ethanol, and about 15% by weight of lecithin.

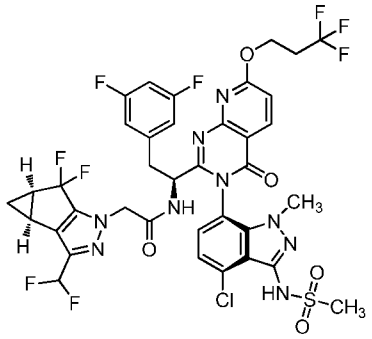
33. A pharmaceutical composition comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof,



Formula Ia

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

34. A pharmaceutical composition comprising a compound of Formula Ib, or a pharmaceutically acceptable salt thereof,



Formula Ib

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

35. The pharmaceutical composition according to Claim 33 or Claim 34 further comprising one or more of sodium acetate, acetic acid, mannitol, sodium chloride, Poloxamer 338, or Poloxamer 188.

36. The pharmaceutical composition according to Claim 35 wherein the composition comprises Poloxamer 338 or Poloxamer 188.

37. The pharmaceutical composition according Claim 36 wherein the composition further comprises sodium acetate and acetic acid.

38. The pharmaceutical composition according to Claim 37 wherein the composition further comprises mannitol or sodium chloride.

39. The pharmaceutical composition according any of Claims 33 and 35-38 wherein the mean particle diameter of the compound of Formula Ia is 0.2 μm to 0.5 μm.

40. The pharmaceutical composition according any of Claims 33 and 35-38 wherein the mean particle diameter of the compound of Formula Ia is ≤ 0.2 μm.

41. The pharmaceutical composition according any of Claims 34-38 wherein the mean particle diameter of the compound of Formula Ib is 0.2 μm to 0.5 μm.

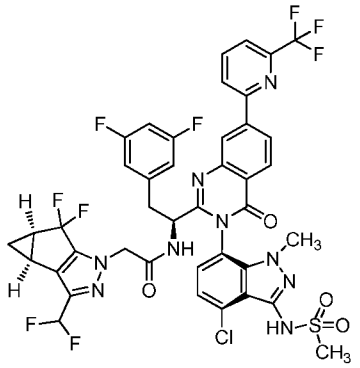
42. The pharmaceutical composition according any of Claims 34-38 wherein the mean particle diameter of the compound of Formula Ib is ≤ 0.2 μm.

43. The pharmaceutical composition according any of Claims 33 or Claims 35-40 comprising about 300 mg/mL of the compound of Formula Ia, or a pharmaceutically acceptable salt thereof, about 5.4% by weight of P338, about 3.5% by weight of mannitol, and the remainder of the composition as water or aqueous acetate buffer.

44. The pharmaceutical composition according any of Claims 34, Claims 35-38 or Claims 41-42 comprising about 300 mg/mL of the compound of Formula Ib, or a pharmaceutically acceptable salt thereof, about 5.4% by weight of P338, about 3.5% by weight of mannitol, and the remainder of the composition as water or aqueous acetate buffer.

45. The pharmaceutical composition according to any of Claims 33-44 which is a heterogeneous suspension.

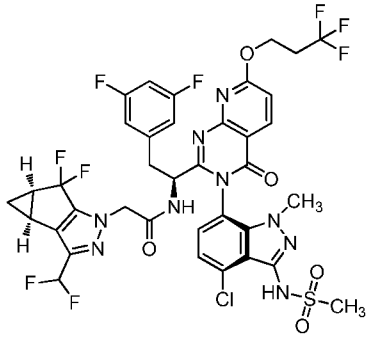
46. A pharmaceutical composition comprising a compound of Formula Ia,



Formula Ia

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

47. A pharmaceutical composition comprising a compound of Formula Ib,



Formula Ib

wherein the composition comprises water and contains less than 1% by weight of polyethylene glycol.

48. The pharmaceutical composition according to Claim 46 or Claim 47 further comprising one or more of sodium acetate, acetic acid, mannitol, sodium chloride, Poloxamer 338, or Poloxamer 188.

49. The pharmaceutical composition according to Claim 48 wherein the composition comprises Poloxamer 338 or Poloxamer 188.

50. The pharmaceutical composition according Claim 49 wherein the composition further comprises sodium acetate and acetic acid.

51. The pharmaceutical composition according to Claim 50 wherein the composition further comprises mannitol or sodium chloride.

52. The pharmaceutical composition according any of Claims 46 and 48-51 wherein the mean particle diameter of the compound of Formula Ia is 0.2 μm to 0.5 μm.

53. The pharmaceutical composition according any of Claims 46 and 48-51 wherein the mean particle diameter of the compound of Formula Ia is ≤ 0.2 μm.

54. The pharmaceutical composition according any of Claims 47-51 wherein the mean particle diameter of the compound of Formula Ib is 0.2 μm to 0.5 μm.

55. The pharmaceutical composition according any of Claims 47-51 wherein the mean particle diameter of the compound of Formula Ib is ≤ 0.2 μm.

56. The pharmaceutical composition according any of Claims 46 or Claims 48-53 comprising about 300 mg/mL of the compound of Formula Ia, about 5.4% by weight of P338, about 3.5% by weight of mannitol, and the remainder of the composition as water or aqueous acetate buffer.

57. The pharmaceutical composition according any of Claims 47, Claims 48-51 or Claims 54-55 comprising about 300 mg/mL of the compound of Formula Ib, about 5.4% by weight of P338, about 3.5% by weight of mannitol, and the remainder of the composition as water or aqueous acetate buffer.

58. The pharmaceutical composition according to any of Claims 46-57 which is a heterogeneous suspension.

59. A method of treating HIV infection in a human comprising administration of a therapeutically effective amount of a pharmaceutical composition according to any of Claims 1-58.

60. The method according to Claim 59 wherein said administration is via intramuscular injection.

61. The method according to Claim 59 wherein said administration is via subcutaneous injection.

62. The method according to Claim 59 wherein said method further comprises administration of at least one other agent used for treating HIV infection in a human.

63. The method according to Claim 62 wherein the at least one other agent is selected from the group consisting of abacavir, atazanavir, bictegravir, cabotegravir, dolutegravir, fostemsavir, lamivudine, maraviroc, rilpiverine, tenofovir disoproxil, tenofovir, tenofovir afenamide, islatravir, doravirine, preziata, S-648414, GSK3640254, N6LS, GSK3739937/VH3739937, GSK4000422/VH4000422, GSK4023991/VH4023991 and S-365598.

64. The method according to Claim 62 wherein the at least one other agent is selected from the group consisting of dolutegravir, lamivudine, fostemsavir, cabotegravir, N6LS, GSK3739937/VH3739937, GSK4000422/VH4000422, GSK4023991/VH4023991 and S-365598.

65. The method according to Claim 62 wherein the at least one other agent is selected from the group consisting of dolutegravir, bictegravir, islatravir, lamivudine, fostemsavir, and cabotegravir.

66. A pharmaceutical composition according to any of Claims 1-58 for use in therapy.

67. A pharmaceutical composition according to any of Claims 1-58 for use in treating HIV infection in a human.

68. A pharmaceutical composition according to any of Claims 1-58 for use in the manufacture of a medicament for the treatment of HIV infection in a human.

Figure 1

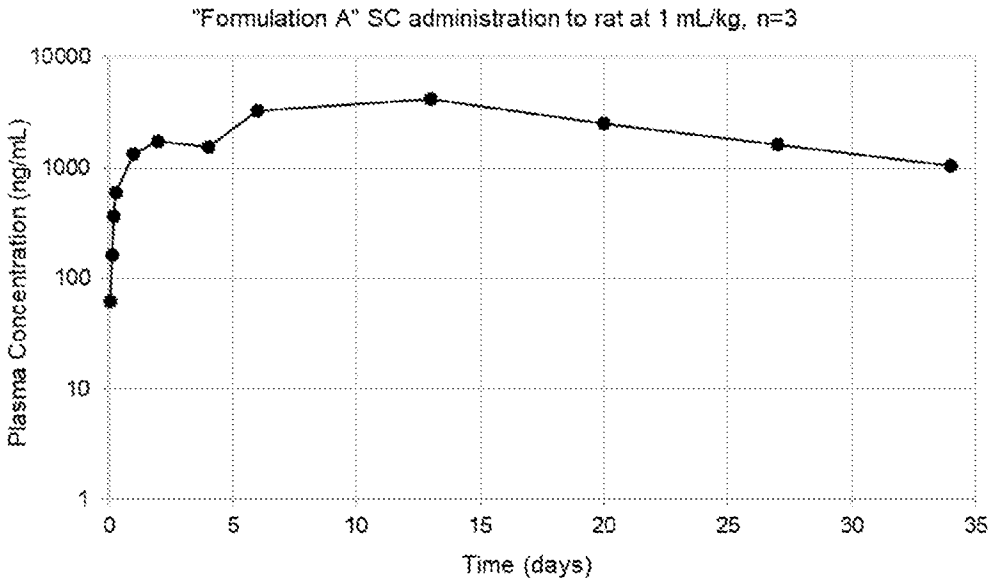

"Formulation A" SC administration to rat at 1 mL/kg, n=3
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
5
10
15
20
25
30
35
Time (days)

Figure 2

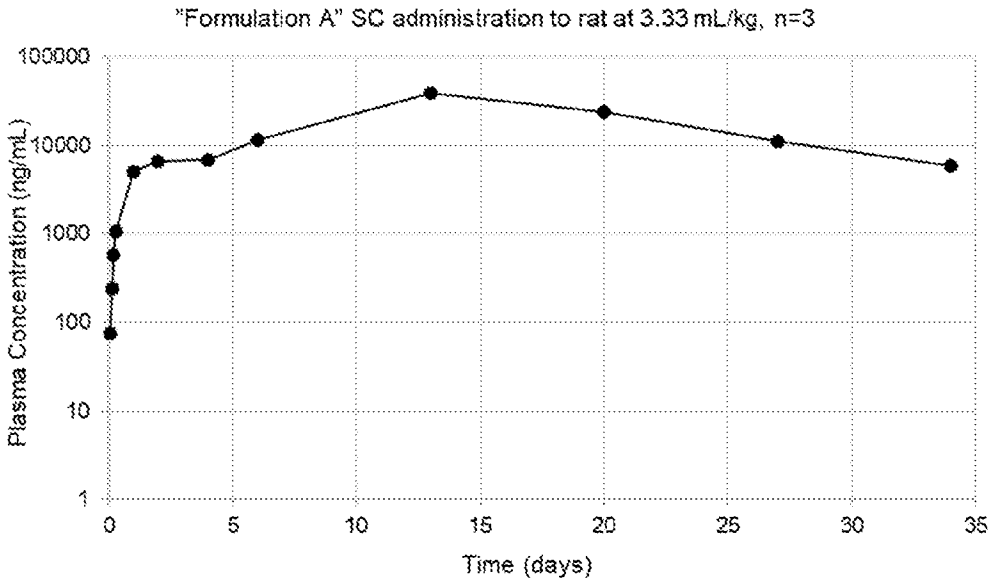

"Formulation A" SC administration to rat at 3.33 mL/kg, n=3
Plasma Concentration (ng/mL)
100000
10000
1000
100
10
1
0
5
10
15
20
25
30
35
Time (days)

Figure 3

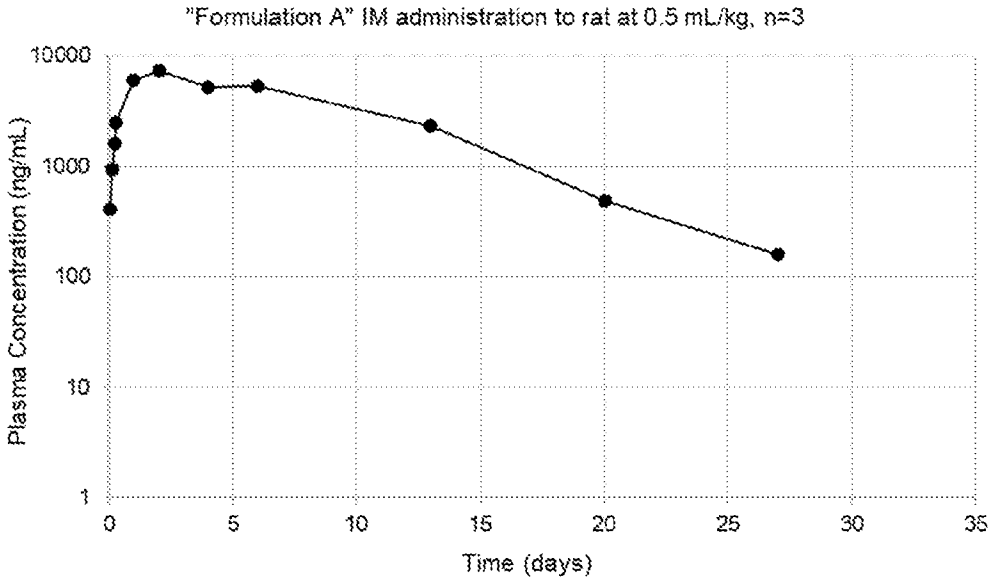

"Formulation A" IM administration to rat at 0.5 mL/kg, n=3
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
5
10
15
20
25
30
35
Time (days)

Figure 4

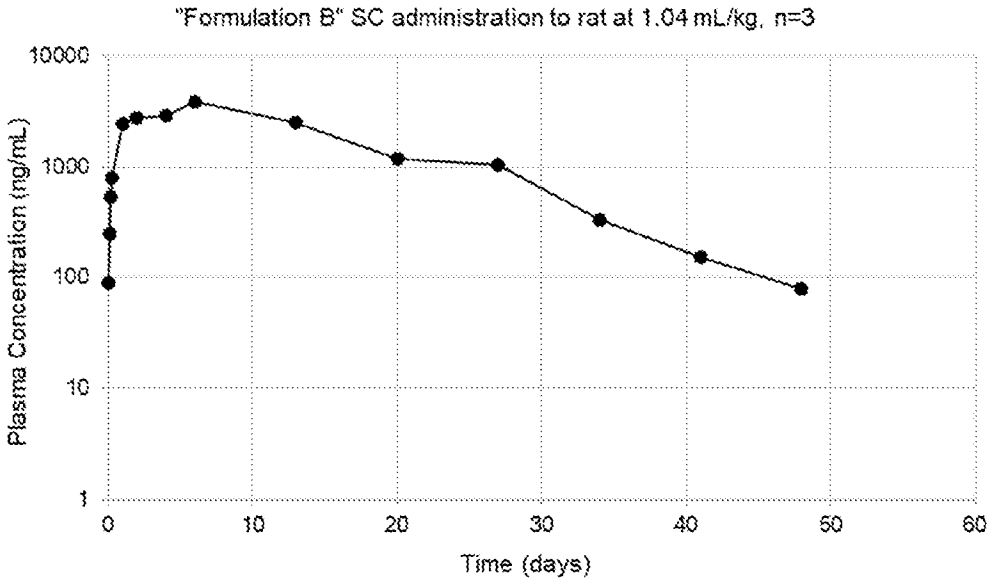

"Formulation B" SC administration to rat at 1.04 mL/kg, n=3
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
10
20
30
40
50
60
Time (days)

Figure 5

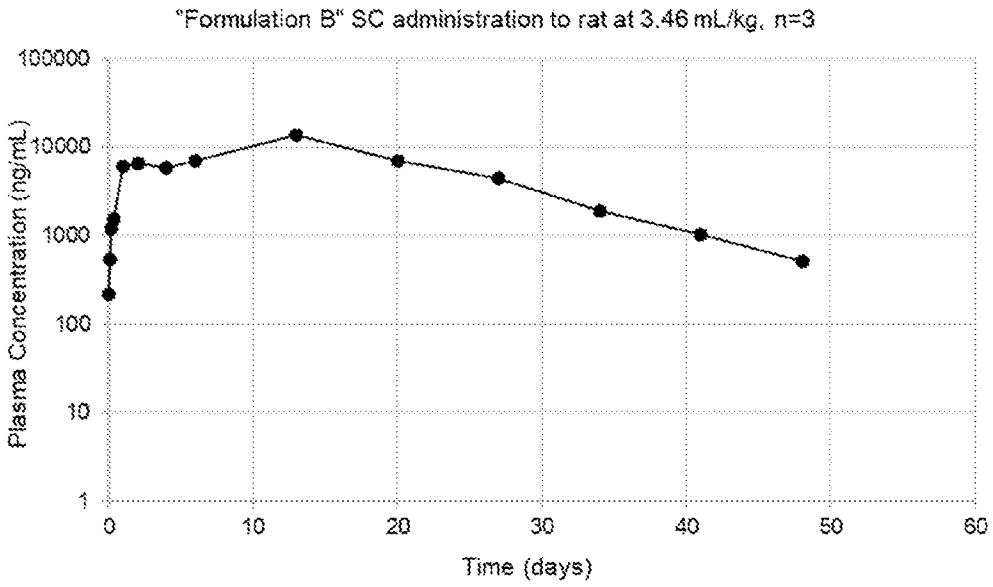

"Formulation B" SC administration to rat at 3.46 mL/kg, n=3
Plasma Concentration (ng/mL)
100000
10000
1000
100
10
1
0
10
20
30
40
50
60
Time (days)

Figure 6

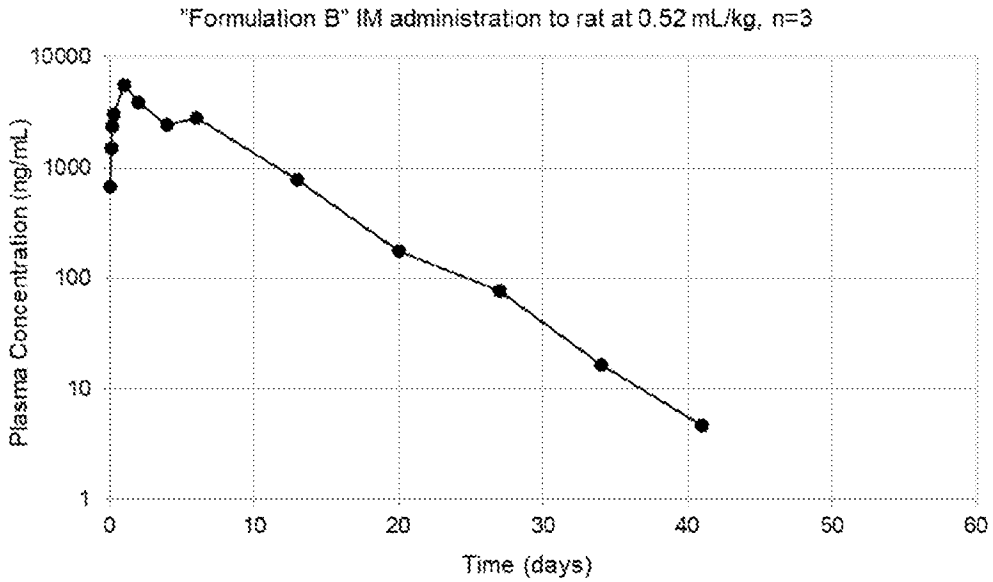

"Formulation B" IM administration to rat at 0.52 mL/kg, n=3
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
10
20
30
40
50
60
Time (days)

Figure 7

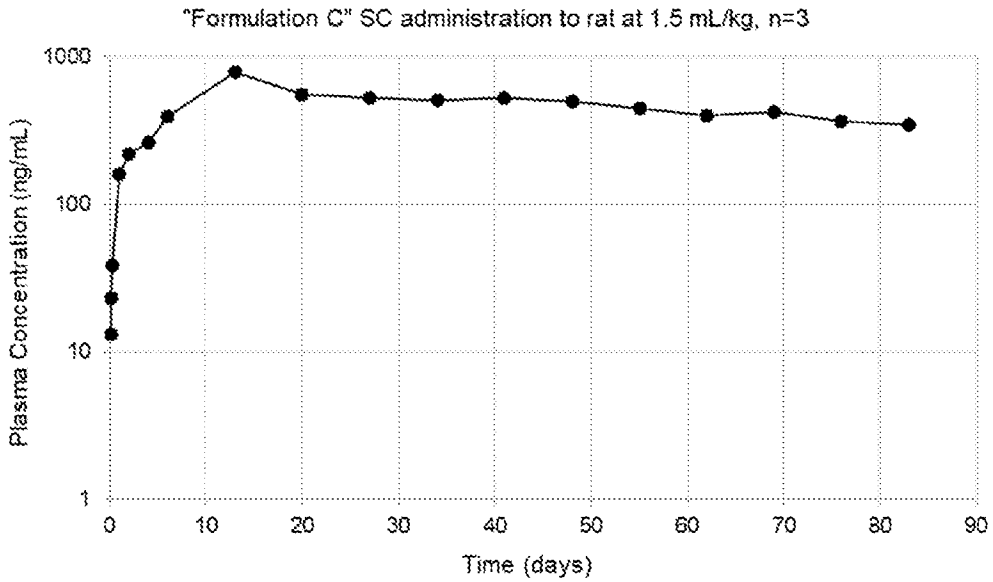

"Formulation C" SC administration to rat at 1.5 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
10
20
30
40
50
60
70
80
90
Time (days)

Figure 8

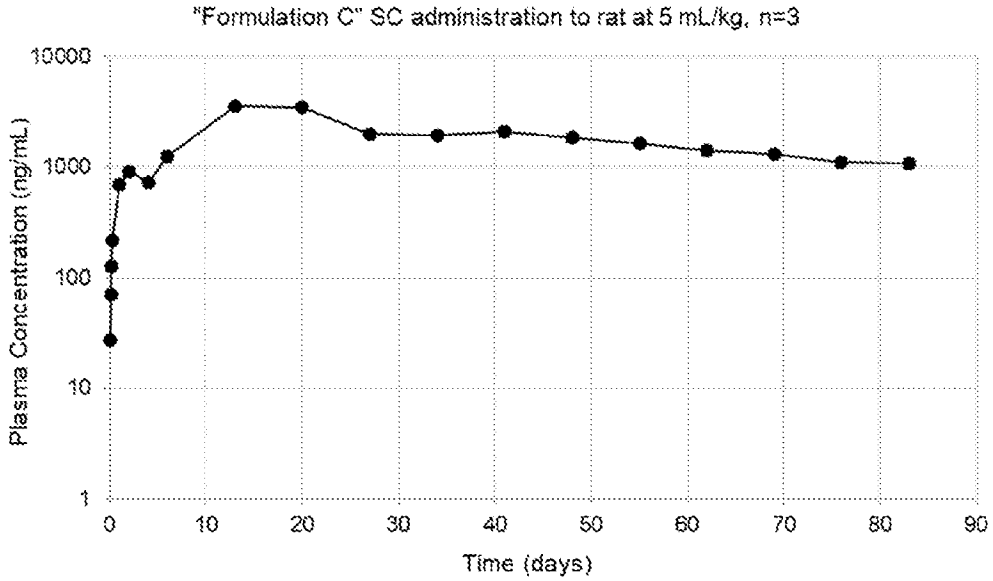

"Formulation C" SC administration to rat at 5 mL/kg, n=3
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
10
20
30
40
50
60
70
80
90
Time (days)

Figure 9

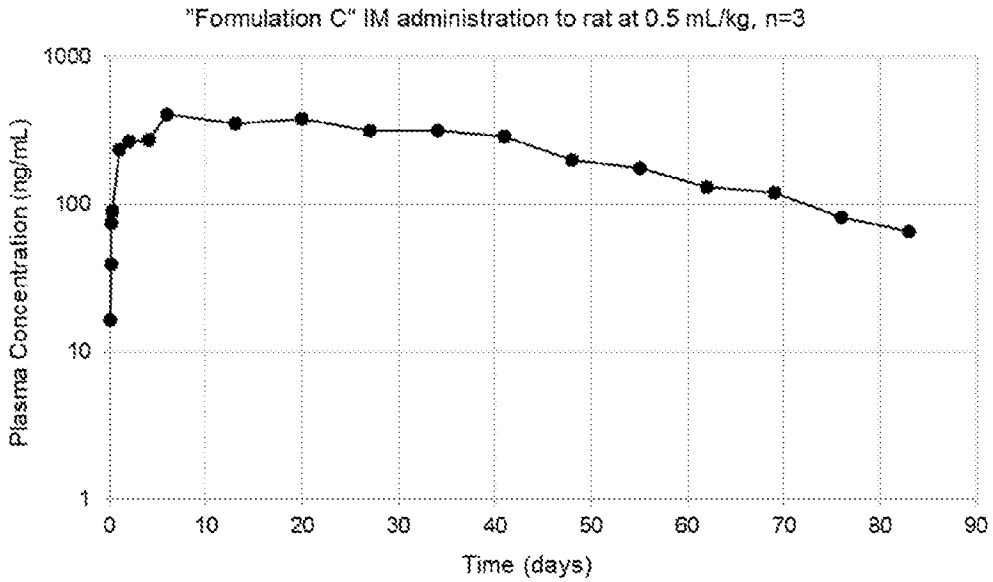

"Formulation C" IM administration to rat at 0.5 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
10
20
30
40
50
60
70
80
90
Time (days)

Figure 10

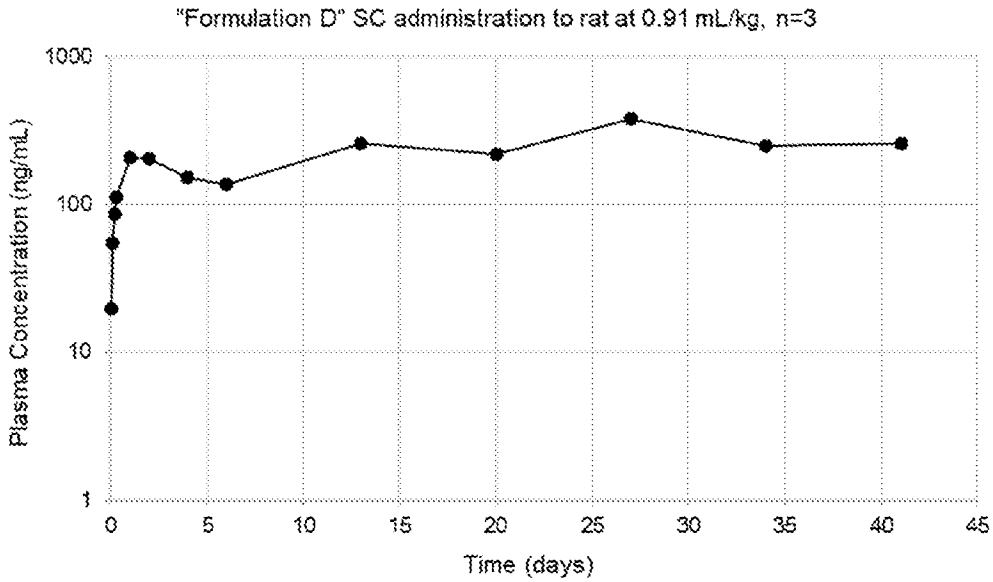

"Formulation D" SC administration to rat at 0.91 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
5
10
15
20
25
30
35
40
45
Time (days)

Figure 11

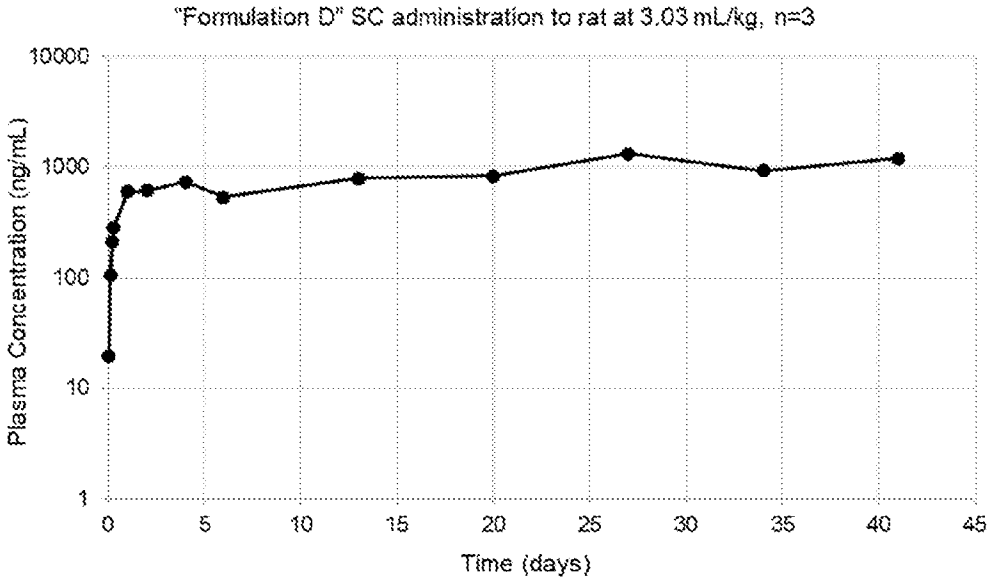

"Formulation D" SC administration to rat at 3.03 mL/kg, n=3
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
5
10
15
20
25
30
35
40
45
Time (days)

Figure 12

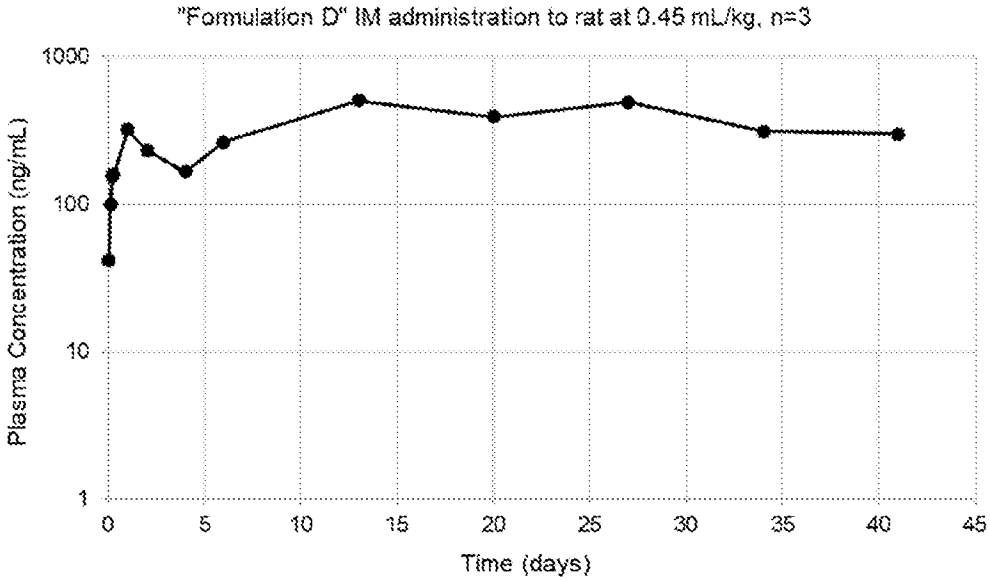

"Formulation D" IM administration to rat at 0.45 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
5
10
15
20
25
30
35
40
45
Time (days)

Figure 13

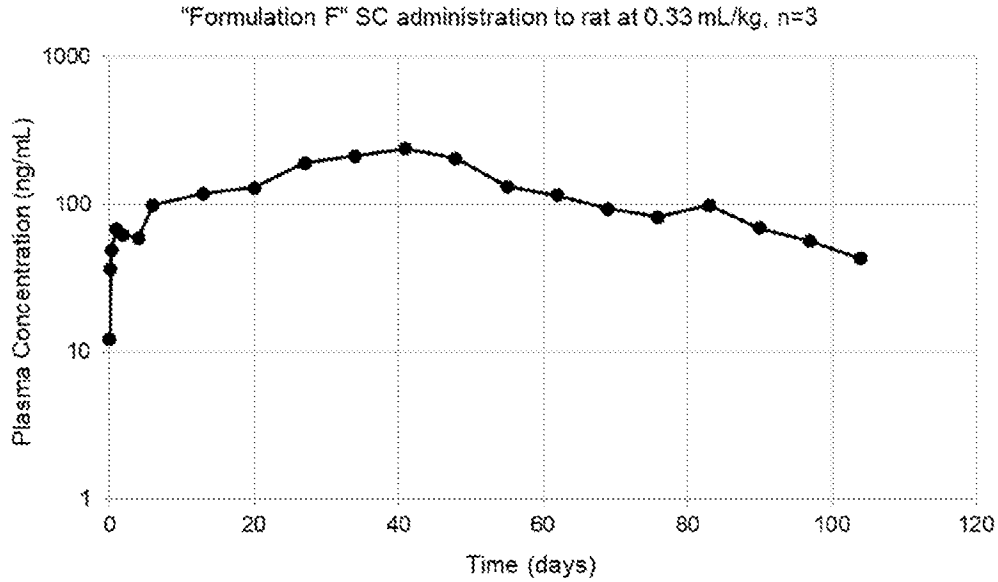

"Formulation F" SC administration to rat at 0.33 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
20
40
60
80
100
120
Time (days)

Figure 14

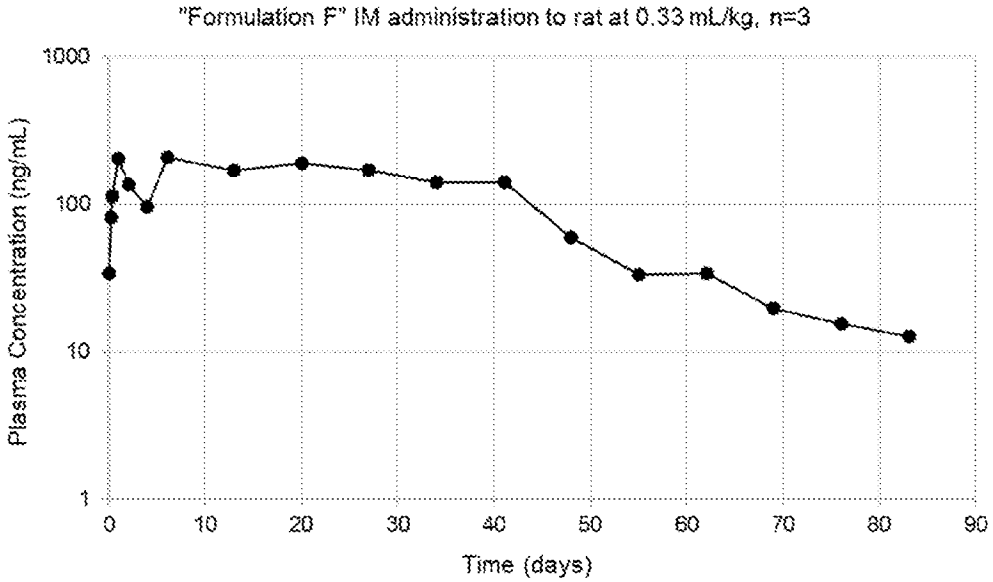

"Formulation F" IM administration to rat at 0.33 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
10
20
30
40
50
60
70
80
90
Time (days)

Figure 15

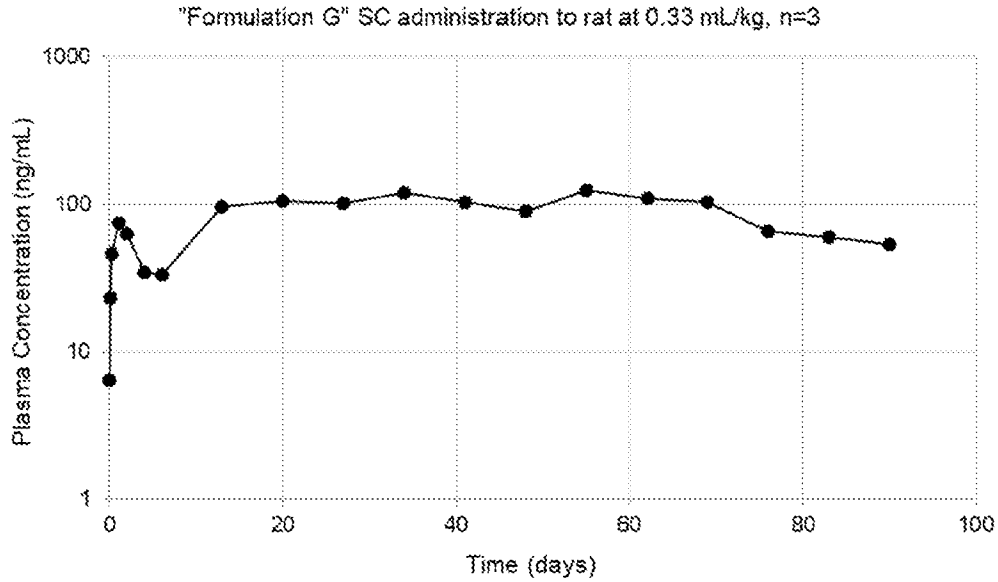

"Formulation G" SC administration to rat at 0.33 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
20
40
60
80
100
Time (days)

Figure 16

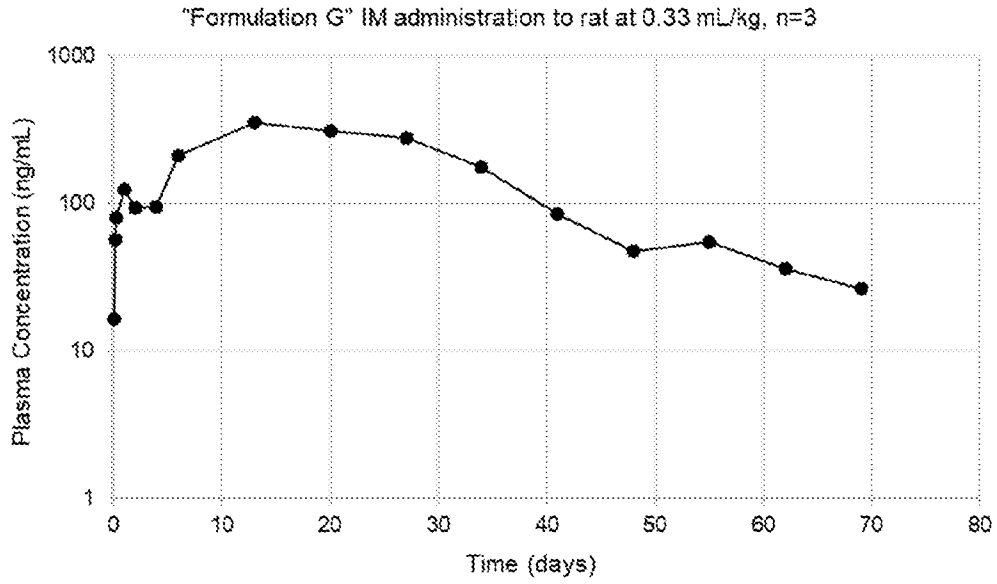

"Formulation G" IM administration to rat at 0.33 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
10
20
30
40
50
60
70
80
Time (days)

Figure 17

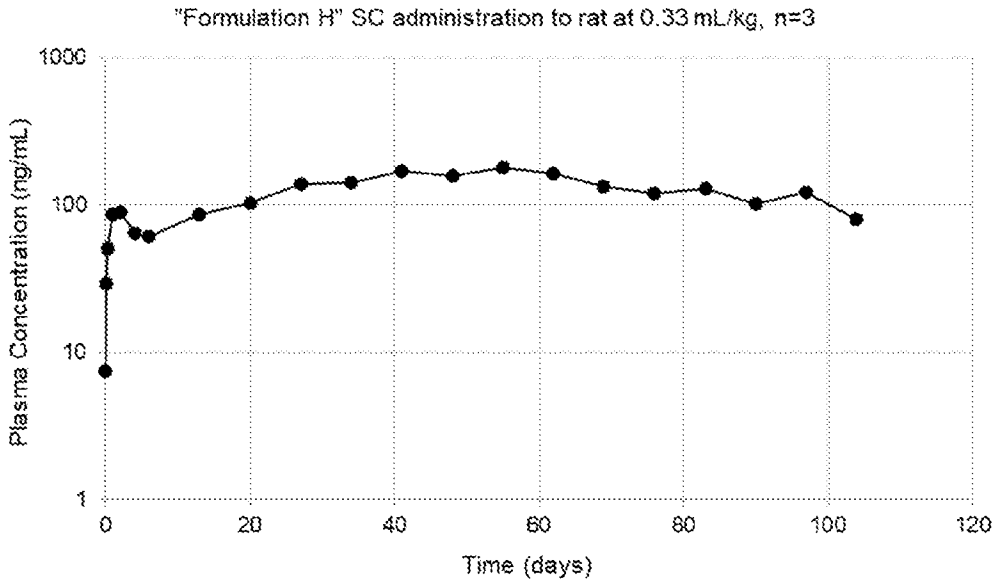

"Formulation H" SC administration to rat at 0.33 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
20
40
60
80
100
120
Time (days)

Figure 18

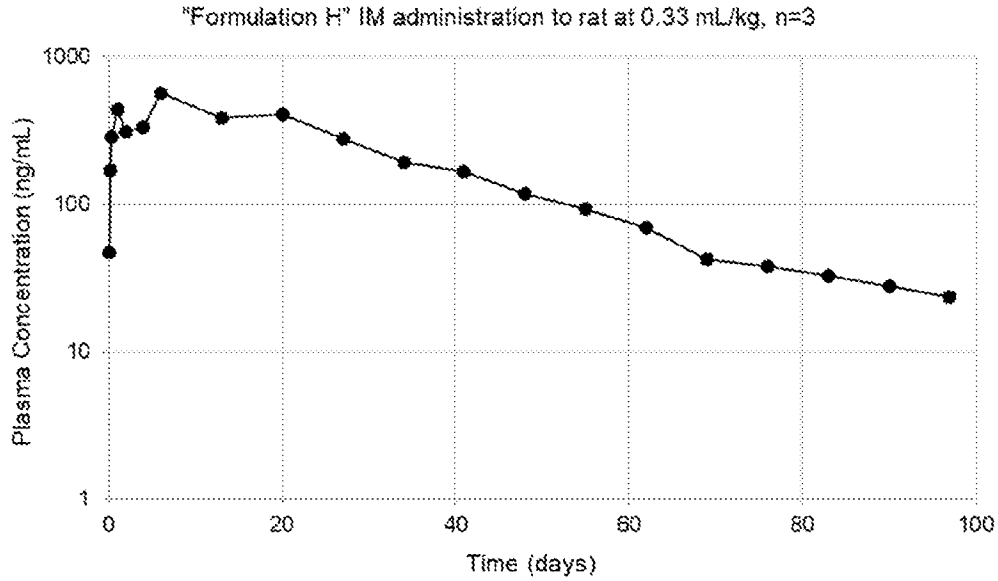

"Formulation H" IM administration to rat at 0.33 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
20
40
60
80
100
Time (days)

Figure 19

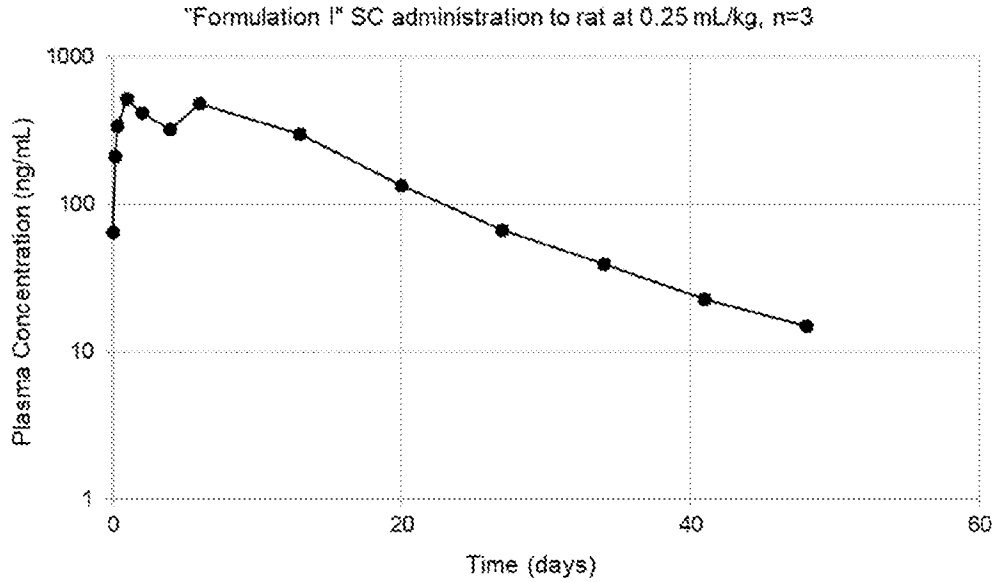

"Formulation I" SC administration to rat at 0.25 mL/kg, n=3
Plasma Concentration (ng/mL)
1000
100
10
1
0
20
40
60
Time (days)

Figure 20

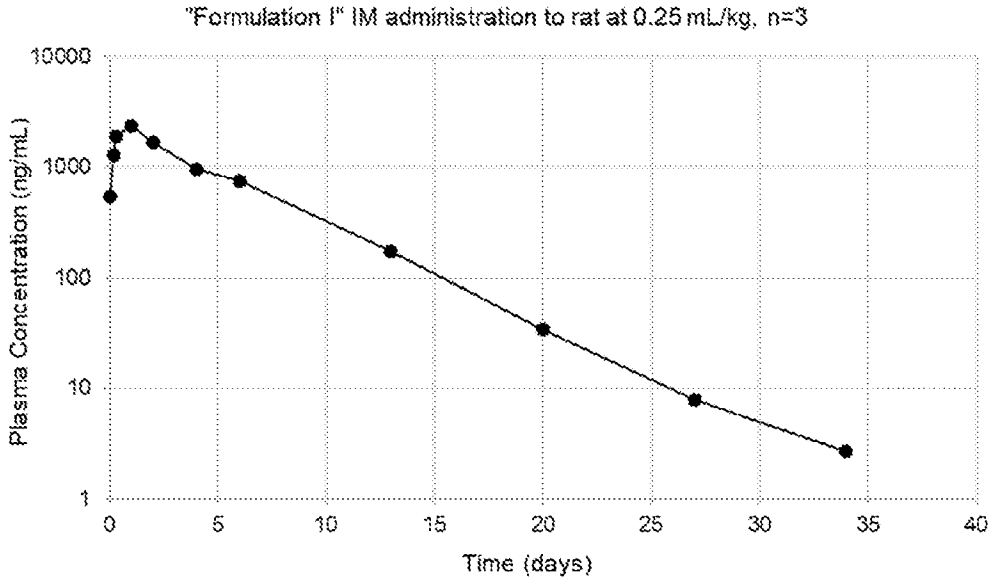

"Formulation I" IM administration to rat at 0.25 mL/kg, n=3
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
5
10
15
20
25
30
35
40
Time (days)

Figure 21

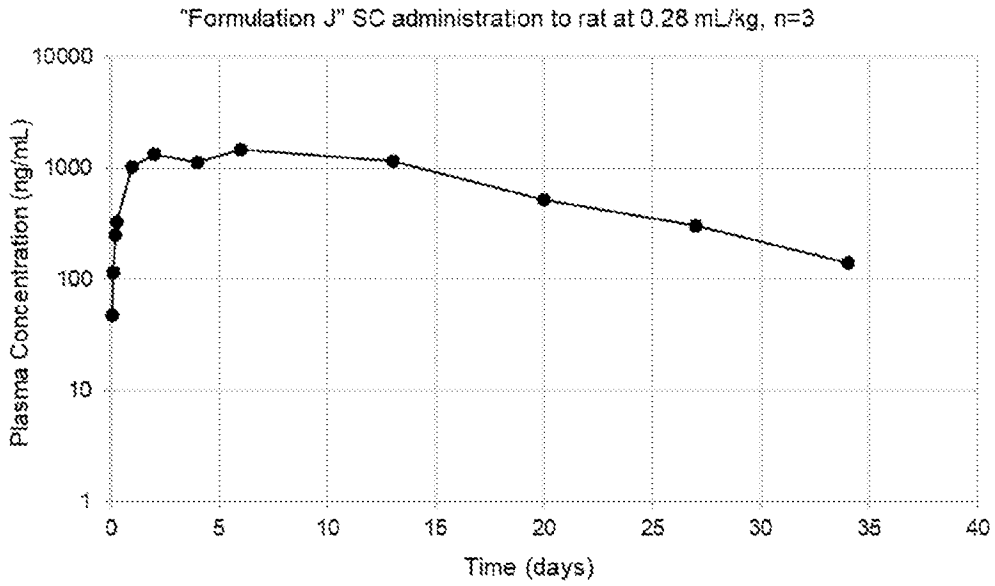
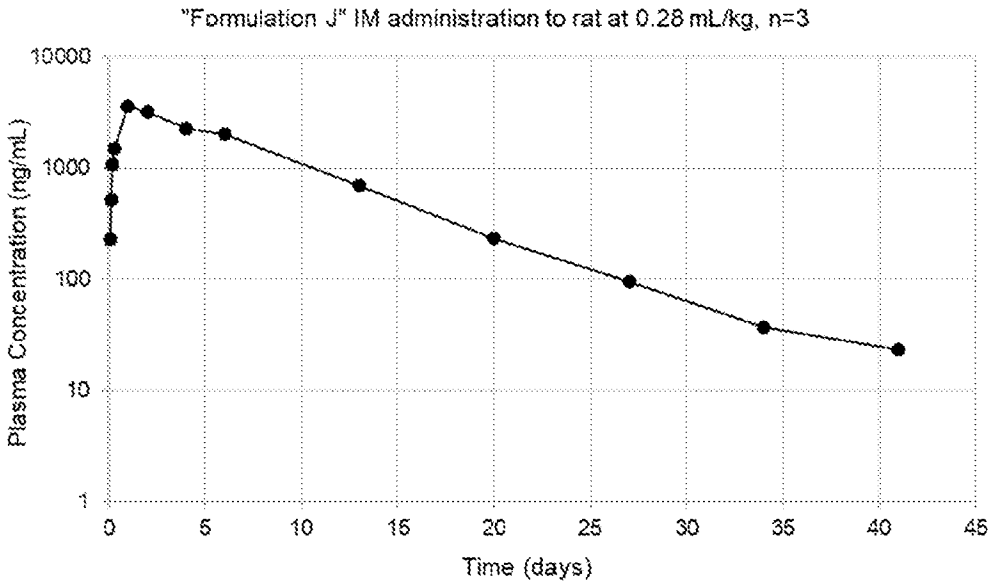

"Formulation J" SC administration to rat at 0.28 mL/kg, n=3
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
5
10
15
20
25
30
35
40
Time (days)

Figure 22


"Formulation J" IM administration to rat at 0.28 mL/kg, n=3
Plasma Concentration (ng/mL)
10000
1000
100
10
1
0
5
10
15
20
25
30
35
40
45
Time (days)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2022/059780

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/10 A61K47/10 A61P1/00
ADD.

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

B. FIELDS SEARCHED

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

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, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/254985 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 24 December 2020 (2020-12-24) cited in the application page 41, lines 1-5; claims 1-15	1-68
X	WO 2020/084492 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 30 April 2020 (2020-04-30) cited in the application claims 1-41	1-68
X	WO 2020/018459 A1 (GILEAD SCIENCES INC [US]) 23 January 2020 (2020-01-23) claims 1-107	1-68

-/--

[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
5 January 2023	16/01/2023

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

1

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2022/059780

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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1

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