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**International Journal of Antimicrobial Agents, Vol. 7, 1996, De Clercq E., "Perspectives for the chemotherapy of respiratory syncytial virus (RSV) infections", pp. 193-202.**

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(72) Inventor(s):
**Graham Heery**
**Yao Da Dong**

(73) Proprietor(s):
**Starpharma Pty Ltd**
**(Incorporated in Australia)**
**4-6 Southampton Crescent, Abbotsford 3067, Victoria, Australia**

(74) Agent and/or Address for Service:
**Mewburn Ellis LLP**
**Aurora Building, Counterslip, Bristol, BS1 6BX, United Kingdom**

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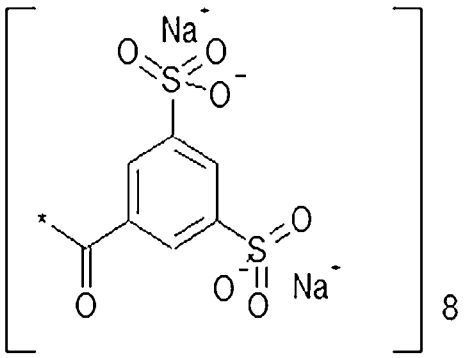
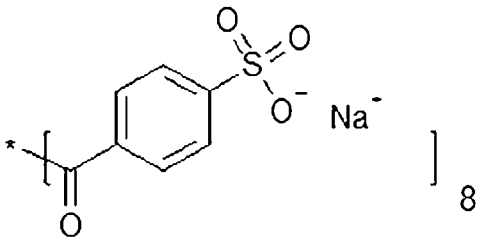
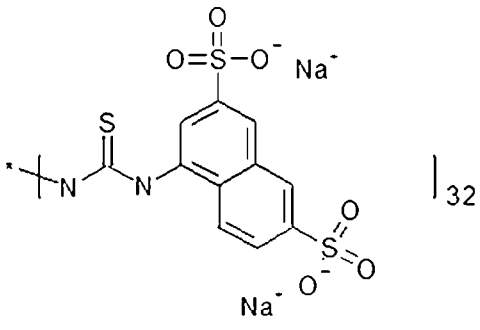
| | Name | Structure |
|---|---|---|
| SPL7674 | [BHAlys] [Lys]16 [CO-Ph-3,5-$(SO_3Na)_2$]32 | |
| SPL7615 | BHALys [Lys]4 [CO-Ph-3,5-$(SO_3Na)$2]8 |  |
| SPL7673 | BHALys [Lys]4 [CO-Ph-4-$(SO_3Na)$]8 |  |
| BRI7021 | (Ac-ile-glu-asp-asn-glu-tyr-thr-ala-arg-glu-gly)8-lys4-lys2-lys-gly-OH | |
| BRI2999 | [BHAlys] [Lys]32 [CSNH-Ph-4-$(SO_3Na)$]64 | |
| BRI2992 | [BHAlys] [Lys]16 [CSNH-Napth-3,6-$(SO_3Na)_2$]32 |  |

**FIGURE 1**

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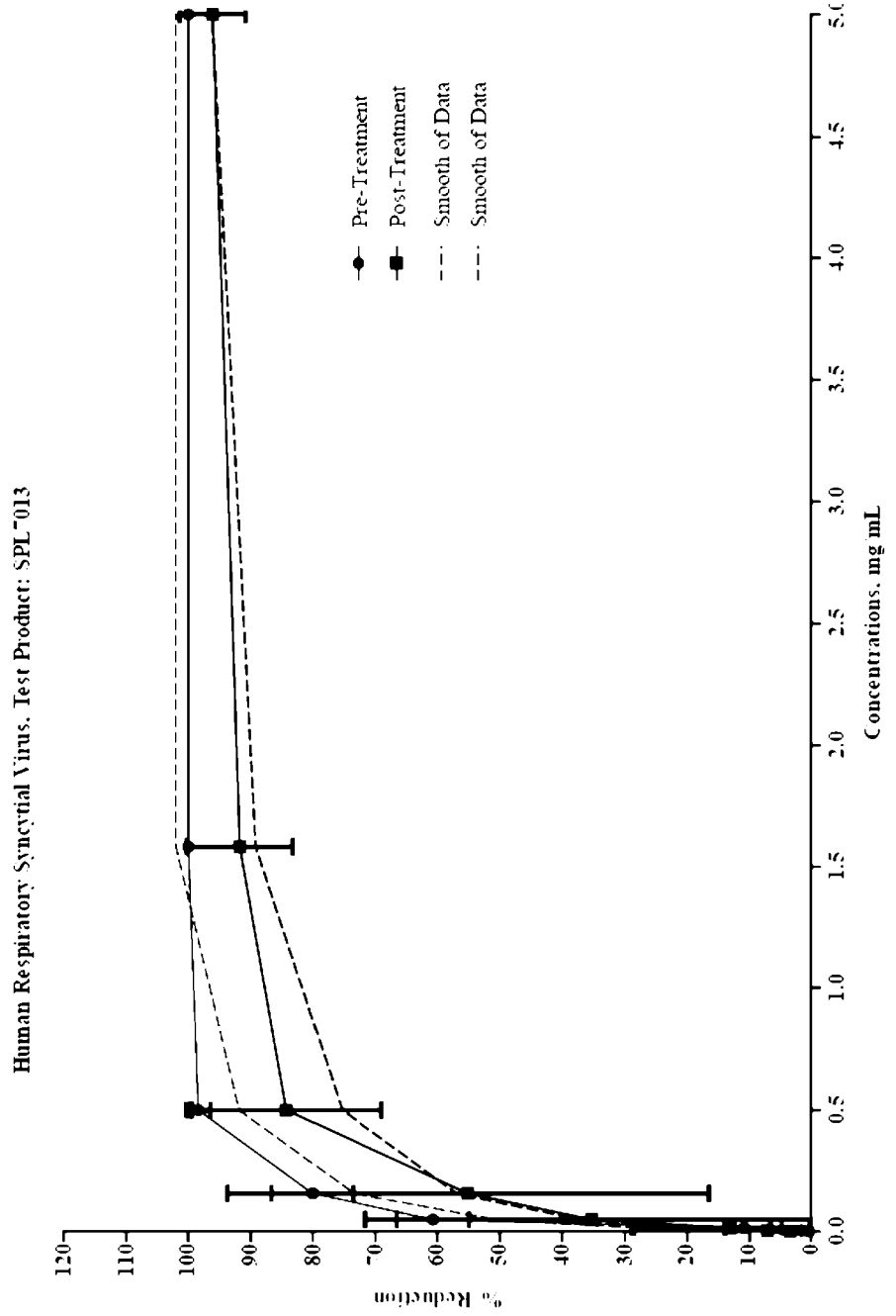



FIGURE 2

The following terms are registered trade marks and should be read as such wherever they occur in this document:

Carbopol

Versamax

# MACROMOLECULE FOR PROPHYLAXIS OF RESPIRATORY SYNCYTIAL VIRUS INFECTION

## Field of the Invention

The present invention relates to methods and compositions for preventing or reducing the likelihood of Respiratory syncytial virus (RSV) infection in an individual, preventing or reducing the likelihood or severity of a symptom associated with an RSV infection in an individual, reducing the severity and/or duration of an RSV infection in an individual, or treating an RSV infection in an individual, preventing or reducing viral shedding in an individual infected with an RSV infection, or reducing transmission of an RSV in a population comprising administering to the individual an effective amount of a macromolecule. The present invention also relates to a device for delivering a composition comprising a macromolecule.

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## Background of the Invention

Viral respiratory tract infections (VRTIs) are some of the most common infections worldwide and represent a major public health concern. Respiratory viruses cause infections in all age groups and are a major contributing factor to morbidity and mortality. Disease severity can range from mild, common cold-like illness to severe, life-threatening respiratory tract infection. The burden of VRTIs is often more pronounced in individuals with chronic co-morbidities or clinical risk factors.

In the past, a significant proportion of respiratory tract disease could not be attributed to a specific pathogen. With the advent of molecular detection and genotyping techniques, there has been a substantial increase in the recognition of several newly identified non-influenza respiratory viruses involved in disease.

These potential pathogens have included coronaviruses, adenovirus, rhinovirus species, human respiratory syncytial virus, and human bocaviruses.

Respiratory syncytial virus (RSV) is a respiratory virus that is a member of the family *Pneumoviridae* and infects most humans by the age of 2. In healthy adults, symptoms are mild but in some individuals symptoms can be severe (particularly in infants and the elderly) resulting in hospitalisation. RSV is responsible for more than

60% of acute respiratory infections in children worldwide. The virus can also make individuals susceptible to secondary bacterial infections like pneumonia or otitis media. In the United States, it is estimated that 11,000 to 17,000 adults die from RSV infection annually, with approximately 10 times that number of patients hospitalized annually. RSV infections in adults are usually not primary infections and are predominantly mild to moderate in severity unless patients have an underlying risk factor such as being immunocompromised, having an underlying chronic pulmonary or circulatory disease, living in a long-term care facility, or being frail. The mortality rate of RSV is as high as 30 to 100% due to RSV infection in solid organ and bone marrow transplant recipients, particularly when infection has occurred within a few days after transplant surgery. Those who are immunosuppressed or otherwise immunocompromised are at enhanced risk of severe RSV infections. RSV is the third greatest cause of influenza-like illness in the elderly. However, it is the second greatest cause of hospitalization.

After many years of research the current therapies for reducing the virus are limited to treating symptoms and an effective vaccine is yet to be developed. One of the challenges is that many candidate cellular receptors have been described for RSV entry, including annexin II, CX3 chemokine receptor 1, epidermal growth factor receptor (EGF), calcium-dependent lectins, Toll-like receptor 4, intercellular adhesion molecule 1 (ICAM-1), and nucleolin. Some receptors like EGF are purportedly used by only certain strains of RSV. Furthermore, RSV is a rapidly evolving virus, making vaccine development difficult, particularly as RSV is known to either evade or suppress B cell memory in humans.

Antiviral dendrimers have been developed with activity against HIV, HPV and HSV in selected animal models, see for example WO02/079299 and WO2007/045009. However, antiviral agents are generally selective in their action against viruses, due primarily to receptor specificity and mode of action. There are no approved broad-spectrum antiviral agents for broad classes of viral agents such as enveloped RNA viruses or negative stranded RNA viruses. Even within a family, such as *Herpes viridae*, agents effective against one virus are not usually effective for others, e.g. treatments against varicella, EBV or HSV are not mutually effective.

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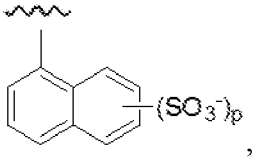
Accordingly, there remains a need for agents capable of preventing or reducing the spread of VRTIs, in particular RSVs. There also remains a need for reducing severity and duration of disease for VRTIs, in particular RSVs.

**Summary of the Invention**

The present inventors have found that the dendrimeric macromolecule, SPL7013, has activity against RSVs *in vitro*. Accordingly, SPL7013 and structurally-related compounds will find utility in reducing the transmission of RSVs, and in preventing or reducing the incidence, severity and duration of associated conditions.

In an aspect, the present invention provides a macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier for use in preventing or reducing the likelihood of Respiratory syncytial virus (RSV) infection in an individual,

wherein the macromolecule comprises a dendrimer of 3 to 5 generations with at least 15 sulfonic acid- or sulfonate-containing moieties attached to one or more surface groups of the dendrimer,

wherein the sulfonic acid- or sulfonate-containing moiety is 

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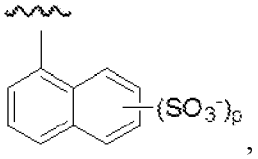
wherein p is an integer of 2, and

wherein the macromolecule comprises a linker wherein the linker is a group -X1-(CH2)q-C(O)-, wherein X1 is the atom which is attached to the sulfonic acid- or sulfonate-containing moiety and is O; q is an integer of 1; and the carbon of the -C(O)- group is attached to the dendrimer.

In an aspect, the present invention provides a macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier for use in treating a Respiratory syncytial virus (RSV) infection in an individual,

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wherein the macromolecule comprises a dendrimer of 3 to 5 generations with at least 15 sulfonic acid- or sulfonate-containing moieties attached to one or more surface groups of the dendrimer,

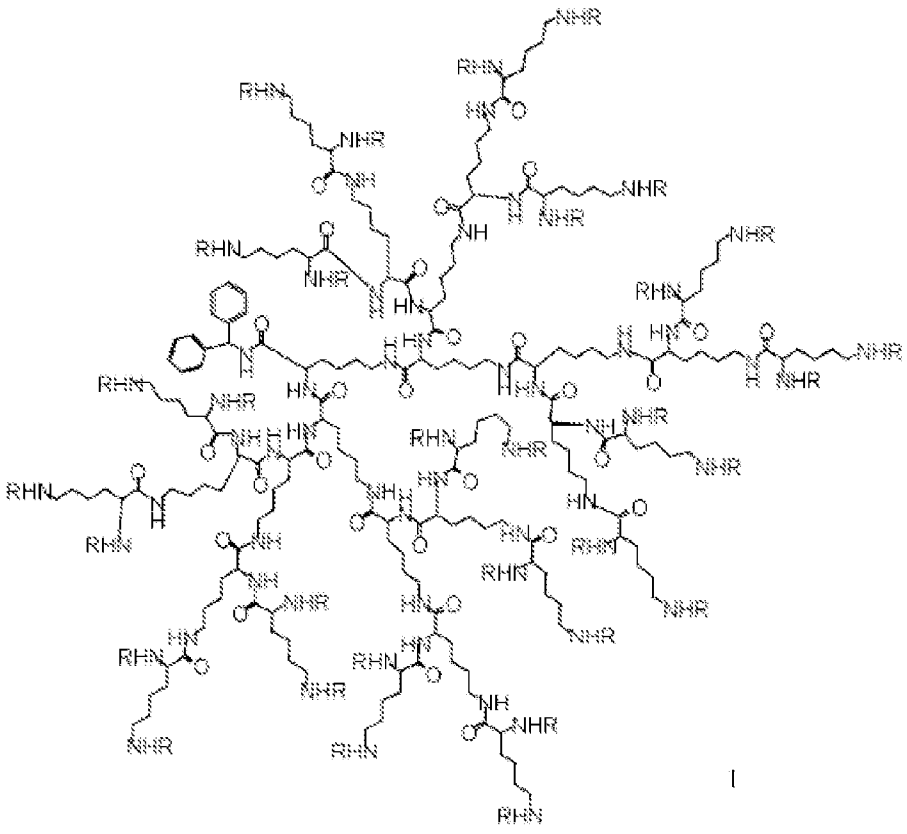
wherein the sulfonic acid- or sulfonate-containing moiety is  ,

wherein p is an integer of 2, and

wherein the macromolecule comprises a linker wherein the linker is a group -X1-(CH2)q-C(O)-, wherein X1 is the atom which is attached to the sulfonic acid- or sulfonate-containing moiety and is O; q is an integer of 1; and the carbon of the -C(O)- group is attached to the dendrimer.

In some embodiments, the RSV is subtype A or subtype B or a subtype or variant thereof. In some embodiments, the RSV is subtype A.

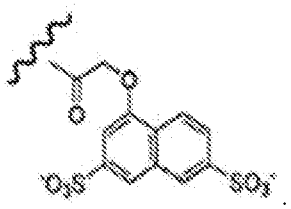
In some embodiments, the dendrimer is



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wherein at least 50% of R is

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In some embodiments, the pharmaceutically acceptable salt is a sodium salt.

In some embodiments, the composition comprises one or more of: Carbopol® 974, hydroxypropylmethyl-cellulose and microcrystalline cellulose /carboxy methyl cellulose.

In some embodiments the composition comprises:

(a) a rheology modifier selected from one or more of: Carbopol$^{RTM}$ 974, hydroxypropylmethyl-cellulose or microcrystalline cellulose /carboxy methyl cellulose;

(b) a preservative selected from one or more of: methyl paraben, propyl paraben, and benzalkonium chloride

(c) an excipient selected from one or more of: glycerine, propylene glycol, ethylenediamine tetraacetic acid; and

(d) a pH modifier.

In some embodiments, the composition comprises a w/w ratio of about 1:20 to about 1:10 of Carpobol 974 or Carbopol 971 to the macromolecule.

In some embodiments, the composition comprises a w/w ratio of about 1:20 to 1:10 of Carbopol® 974 or Carbopol® 971 to the macromolecule.

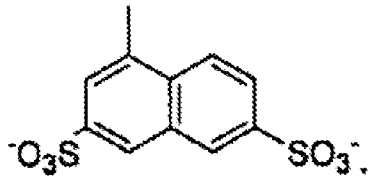
In some embodiments, the composition comprises about 0.05% w/w Carbopol$^{RTM}$ 974 or Carbopol$^{RTM}$ 971 and about 1% w/w of macromolecule.

In some embodiments, the composition comprises: SPL7013, water, Carbopol 974 or Carbopol 971, hydroxypropylmethyl-cellulose, microcrystalline cellulose, glycerin, propylene glycol, methyl paraben, propyl paraben, benzalkonium chloride, and EDTA.

In some embodiments, the macromolecule or pharmaceutically acceptable salt thereof is a dendrimer comprising lysine building units of from 3 to 5 generations, and the sulfonic acid- or sulfonate-containing moieties are napthyldisulfonate moieties.

In some embodiments, the sulfonic acid-containing moiety is

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In some embodiments, the dendrimer is a polylysine dendrimer.

In some embodiments, the macromolecule or a pharmaceutically acceptable salt thereof, or composition is administered topically or administered to the respiratory tract.

In some embodiments, administered to the respiratory tract comprises administration to one or more of: upper respiratory tract, lower respiratory tract, nasal mucosa, nasal cavity, oral cavity, sinuses, throat, pharynx, larynx, nasal turbinates, nasopharynx, oropharynx, trachea, primary bronchi and lungs.

In some embodiments, the composition comprises one or more of the following features:

(a) about 0.5% to about 5% by weight of the macromolecule or pharmaceutically acceptable salt thereof;

(b) about 1% by weight of the macromolecule or pharmaceutically acceptable salt thereof;

I about 0.1 to about 5 mg of the macromolecule or pharmaceutically acceptable salt thereof per dose;

(d) about 1 mg of the macromolecule or pharmaceutically acceptable salt thereof per dose.

In some embodiments, the macromolecule or a pharmaceutically acceptable salt thereof is administered in a nasal spray or an oral spray.

In some embodiments, the macromolecule or a pharmaceutically acceptable salt thereof is administered 1 to 8 times daily.

In some embodiments, the macromolecule or a pharmaceutically acceptable salt thereof is administered for about 1 to about 2 weeks, or about 1 to about 3 weeks, or for less than 30 days.

Any embodiment herein shall be taken to apply *mutatis mutandis* to any other embodiment unless specifically stated otherwise. For instance, as the skilled person

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would understand examples of macromolecules outlined above for the methods of the invention equally apply to compositions of the invention.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally-equivalent products, compositions and methods are clearly within the scope of the invention, as described herein.

Throughout this specification, unless specifically stated otherwise or the context requires otherwise, reference to a single step, composition of matter, group of steps or group of compositions of matter shall be taken to encompass one and a plurality (i.e. one or more) of those steps, compositions of matter, groups of steps or group of compositions of matter.

The invention is hereinafter described by way of the following non-limiting Examples and with reference to the accompanying figures.

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**Brief Description of the Drawings**

**Figure 1** Provides the name and structures of the macromolecules SPL-7674, SPL-7615, SPL-7673, BAI-7021, BRI-2999, and BRI-2992.

**Figure 2 A.** Shows the inhibition of Human respiratory syncytial virus (HRSV) in Hep-2 cells following pre- and post-infection treatment with SPL7013. **B.** Shows the cytotoxicity of HRSV for Hep-2 cells following pre-treatment and post-treatment with SPL7013.

**Description of the Invention**

Definitions

The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or

group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

As used herein, the term "about" refers to a quantity, level, value, dimension, size, or amount that varies by as much as 30%, 25%, 20%, 15%, 10%, 5% or 1% to a reference quantity, level, value, dimension, size, or amount.

As used herein, the term "individual" refers to any individual susceptible to an RSV virus infection. In a particular embodiment, the individual is a human, including fetus, infant, child, early adult and adult. In some embodiments, the individual is a human adult. In one embodiment, the individual is an animal. In an embodiment, the child is one or more of: less than 16 years in age, less than 14 years in age, less than 12 years in age, less than 10 years in age, less than 5 years in age, less than 3 years in age, less than 2 years in age, less than 1 year in age, less than 6 months in age, less than three months in age, and less than one month in age. In an embodiment, the child is 12 years or older. In an embodiment, the infant is a preterm infant. In one embodiment, the adult is an elderly adult. In an embodiment, the adult is one or more of greater than 60 years in age, greater than 65 years in age, greater than 70 years in age, greater than 75 years in age, greater than 80 years in age, greater than 85 years in age, greater than 90 years in age. In some embodiments, the individual is a human. some embodiments, the individual is immunocompromised. In some embodiments, the individual has recently undergone surgery. In some embodiments, the individual is1 day, or 2 days, or 3 days, or 4 days, or 5 days, or 6 days, or 7 days, or 1.5 weeks, or 2 weeks, or three weeks post-surgery. In some embodiments, the individual is or will be a transplant recipient. In some embodiment, the individual is or will be a lung transplant recipient, or bone marrow or stem cell recipient. In some embodiments, the individual has a respiratory condition. In some embodiments, the respiratory condition is selected from one or more of: asthma, chronic obstructive pulmonary disease, sleep apnoea, emphysema, lung cancer, cystic fibrosis, bronchitis, chronic bronchitis, pneumonia, pleural effusion, whooping cough, COVID-19, asbestosis, bronchiectasis, pneumothorax, silicosis, and tuberculosis.

As used herein, the term "prevention" or “prophylaxis” refers to reducing the likelihood of contracting or developing infection or a symptom thereof. Prevention

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need not be complete and does not imply that a subject will not eventually contract or develop the infection or a symptom thereof.

As used herein, the terms "treating" or "treatment" refers to at least partially obtaining a desired therapeutic outcome. In an embodiment, treatment comprises preventing or delaying the appearance of one or more symptoms of an RSV infection. In an embodiment, treatment comprises arresting or reducing the development of one or more symptoms of an RSV infection.

As used herein, the phrase “reducing the severity of an infection”, or similar phrases, includes reducing one or more of the following in an individual: titer of a virus, duration of the virus infection, the harshness or duration of one or more symptoms of a virus infection in an individual. In an embodiment, the virus infection is an RSV virus infection.

As used herein, the phrase “duration of an RSV infection” refers to the time in which an individual has an RSV infection or a symptom caused by an RSV infection.

As used herein, the phrase “macromolecules and pharmaceutically acceptable salts thereof” is used interchangeably with “macromolecules” as the context requires.

As used herein, “SPL7013” refers to astodrimer sodium (INN, USAN), CAS number 676271-69-5. SPL7013 is also known as 2, 6-Bis-{(1-napthalenyl-3,6-disulfonic acid)-oxyacetamido}-2,6-bis-2,6-bis-2,6-bis-(2,6-diamino-hexanoylamino)-2,6-diamino-hexanoic acid (diphenylmethyl)-amide, polysodium salt; or Tetrahexacontasodium N2,N6-bis{N2,N6-bis[N2,N6-bis(N2,N6-bis{N2,N6-bis[(3,6-disulfonatonaphthalen-1-yloxy)acetyl]-l-lysyl}-l-lysyl)-l-lysyl]-l-lysyl}-N1-(diphenylmethyl)-l-lysinamide.

As used herein, “astodrimer” refers to CAS number 1379746-42-5. Also known as 2, 6-Bis-{(1-napthalenyl-3,6-disulfonic acid)-oxyacetamido}-2,6-bis-2,6-bis-2,6-bis-(2,6-diamino-hexanoylamino)-2,6-diamino-hexanoic acid (diphenylmethyl)-amide; or N2,N6-bis{N2,N6-bis[N2,N6-bis(N2,N6-bis{N2,N6-bis[(3,6-disulfonatonaphthalen-1-yloxy)acetyl]-l-lysyl}-l-lysyl)-l-lysyl]-l-lysyl}-N1-(diphenylmethyl)-l-lysinamide.

Macromolecules and pharmaceutically acceptable salts thereof

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The present disclosure involves the use of macromolecules and/or pharmaceutically acceptable salts thereof. Given that the macromolecule may contain multiple sulfonate groups, the pharmaceutically acceptable salts may comprise multiple cations.

The pharmaceutically acceptable salt may be of any suitable type. Examples of suitable salts include, but are not limited to metallic salts (for example, aluminium, calcium, lithium, magnesium, potassium, sodium and zinc salts), organic salts (for example, organic amines such as N,NI-dibenzylethylenediamine, chloroprocaine, diethanolamine, ethylenediamine, dicyclohexylamine, cyclohexylamine, meglumine, (N-methylglucamine) and procaine), quaternary amines (for example, choline), sulphonium salts and phosphonium salts. In particular embodiments, salts are selected from sodium and potassium, especially sodium. In an embodiment, the salt is a sodium salt (e.g. it may be a polysodium salt).

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Those skilled in the art will appreciate that many organic compounds can form complexes in solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates, such as hydrates, exist when the compound incorporates solvent. It will be understood that the macromolecules of the present invention, as well as salts thereof, may be present in the form of solvates. Solvates of the macromolecules which are suitable are those where the associated solvent is pharmaceutically acceptable.

The macromolecules used in the present invention comprise dendrimers of 3 to 5 generations with at least 15 sulfonic acid- or sulfonate-containing moieties attached to one or more surface groups of the dendrimer. The dendrimers useful in the invention may be any suitable dendrimer of 3 to 5 generations that is capable of presenting at least 15 sulfonic acid- or sulfonate-containing moieties on its surface. In some embodiments, the dendrimer is selected from a polylysine, polyglutamate, polyaspartate, polyamidoamine (PAMAM), poly(etherhydroxylamine), polyether, polyester or poly(propyleneimide) (PPI) dendrimer having 3 to 5 generations. In some embodiments, the dendrimer has 3 to 4 generations. In some embodiments, the dendrimer has 4 generations. In some embodiments the dendrimer is an amino acid

dendrimer, selected from the group comprising polylysine, polyglutamate and polyaspartate.

The macromolecule also comprises at least 15 sulfonic acid- or sulfonate-containing moieties attached to the one or more surface functional groups of the outermost generation of the dendrimer. For example, when the dendrimer is a polylysine, polyamidoamine, poly(etherhydroxylamine) or poly(propyleneimide) dendrimer, the surface functional groups are amino groups, and when the dendrimer is a polyglutamate or polyaspartate dendrimer, the surface functional groups are carboxylic acids.

Dendrimers are branched polymeric macromolecules composed of multiple branched monomers radiating from a central core moiety. The number of branch points increases upon moving from the dendrimer core to its surface and is defined by successive layers or "generations" of monomers (or building units). Each generation of building units is numbered to indicate the distance from the core. For example, Generation 1 (G1) is the layer of building units attached to the core, Generation 2 (G2) is the layer of building units attached to Generation 1, Generation 3 (G3) is the layer of building units attached to Generation 2, and so on.

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The outermost generation of building units provides the surface of the dendrimer and presents functional groups, to which the at least one sulfonic acid- or sulfonate-containing moiety is covalently bonded. The sulfonic acid- or sulfonate-containing group may be directly bonded to the surface functional group or may be attached to the surface functional group through a linker.

The dendrimers contemplated herein can be prepared by methods known in the art. For example, they may be prepared in either a convergent manner (where, effectively, the branches are pre-formed and then attached to the core) or a divergent manner (where the layers or generations are successively built outwards from the core). Both these methods would be well understood to the skilled person.

For example, in the case of lysine dendrimers, a divergent synthesis may involve reaction of the amine groups of a layer of lysine residues, with the carboxyl groups of amino-protected lysines, using amidation chemistry, to “grow” the dendrimer and form

the next generation of building units. The protecting groups may then be removed, unveiling the amino groups of the new generation of lysine building units.

The dendrimers may comprise any suitable core. As used herein, "core" refers to the moiety upon which generations of monomers or building units are built (either through a divergent process or a convergent process), and may be any moiety having at least one reactive or functional site from which layers of monomer or building units are successively generated (or to which a pre-formed "branch" is attached).

The core may be formed from a core precursor having reactive groups suitable for reaction with building units, for example the core may be formed from a core precursor having 1, 2, 3 or 4 reactive groups. Some exemplary suitable cores contemplated herein include those formed from core precursors having 1, 2, 3 or 4 reactive groups independently selected from, amino, carboxyl, thiol, alkyl, alkynyl, nitrile, halo, azido, hydroxylamine, carbonyl, maleimide, acrylate or hydroxy groups to which the layers or generations of building units or monomers can be attached.

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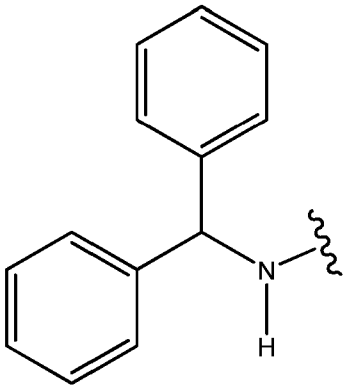
In some embodiments, the core is covalently attached to two building units *via* amide linkages, each amide linkage being formed between a nitrogen atom present in the core and the carbon atom of an acyl group present in a building unit. Accordingly, the core may for example be formed from a core precursor comprising two amino groups.

A core moiety may be the same as a building unit or may be different.

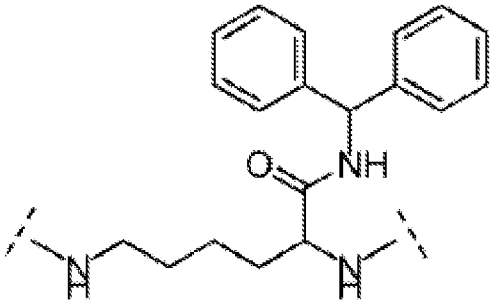
Exemplary cores include polyaminohydrocarbons, disulfide containing polyamines, poly(glycidyl ethers), aminoethanol, ammonia, arylmethylhalides, piperazine, aminoethylpiperazine, poly(ethyleneimine), alkylene/arylene dithiols, 4,4-dithiobutyric acid, mercaptoalkylamines, thioether alkylamines, isocyanurate, heterocycles, macrocycles, polyglycidylmethacrylate, phosphine, porphines, oxiranes, thioranes, oxetanes, aziridines, azetidines, multiazidofunctionalities, siloxanes, oxazolines, carbamates or caprolactones.

Some non-limiting examples of core moieties contemplated herein include ammonia and diamino $C_2$-$C_{12}$ alkanes such as ethylene diamine, 1,4-diaminobutane and 1,6-diaminohexane. However, it will be appreciated that the core is not necessarily a linear moiety with a single reactive group at each end. Non-linear, cyclic or branched

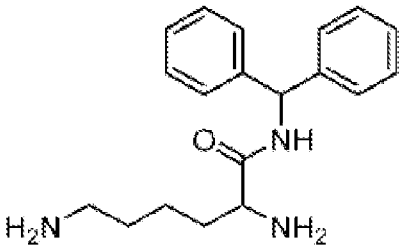
core moieties are also contemplated by the present invention. For example, arylmethylamines such as benzhydrylamine (BHA), are suitable cores. In some embodiments, the core is or comprises a benzhydrylamine (BHA) group:




In some preferred embodiments, the core is a benzyhydrylamine-lysine core (BHALys). A BHALys core has the following structure:




and, in the dendrimers, is covalently attached to building units through two nitrogen atoms. A BHALys core, may, for example, be formed from a core precursor:




having two reactive amino nitrogens.

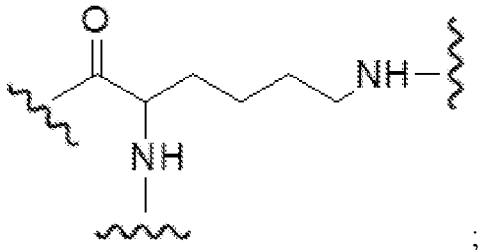
In some preferred embodiments, the core is BHALys core which comprises an L-lysine residue.

In some preferred embodiments, the core is BHALys core which contains an L-lysine residue.

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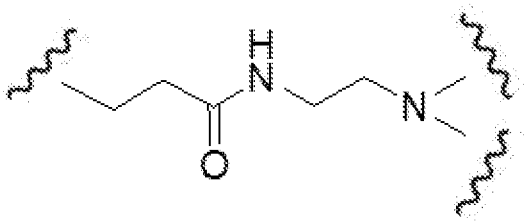
The dendrimers also comprise one or more building units. In some embodiments, the building units of the dendrimer are selected from:

Lysine building units:



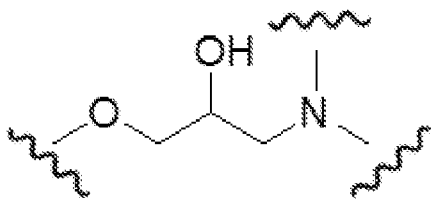
;

Amidoamine building units:



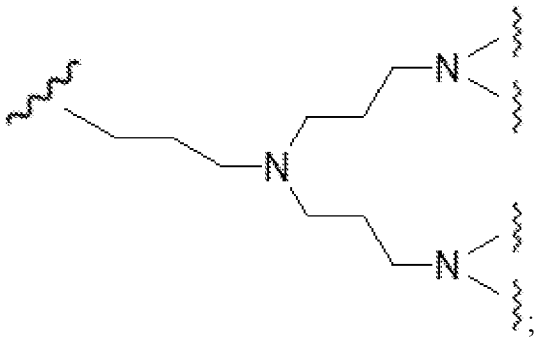
;

Etherhydroxyamine building units:



;

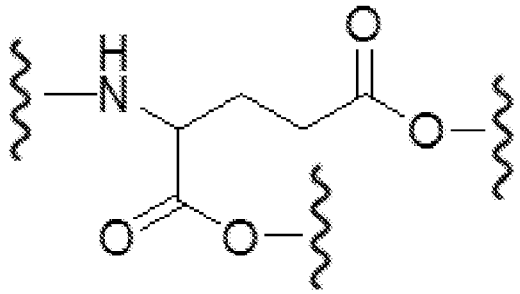
Propyleneimine building units:



;

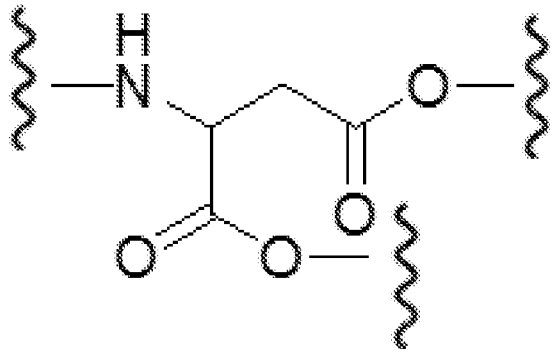
Glutamic acid building units:

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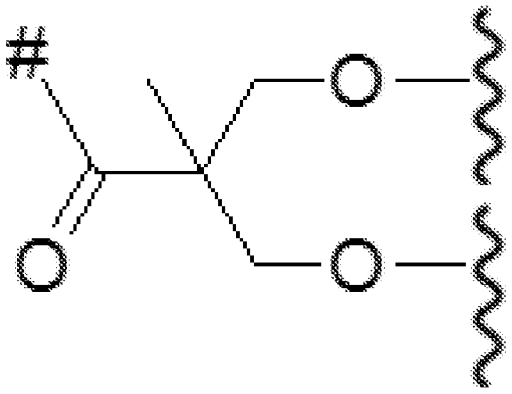
;

Aspartic acid building units:



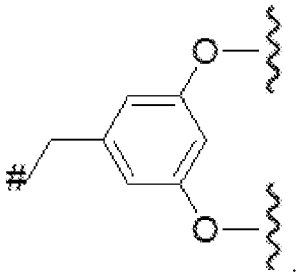
;

Polyester building units:



; and

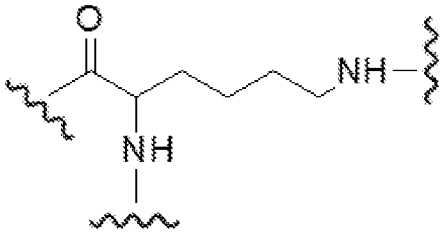
Polyether building units:



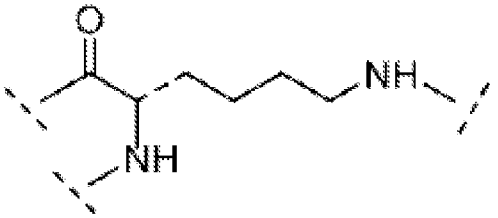
.

In some preferred embodiments, the building units are lysine residues, e.g.:

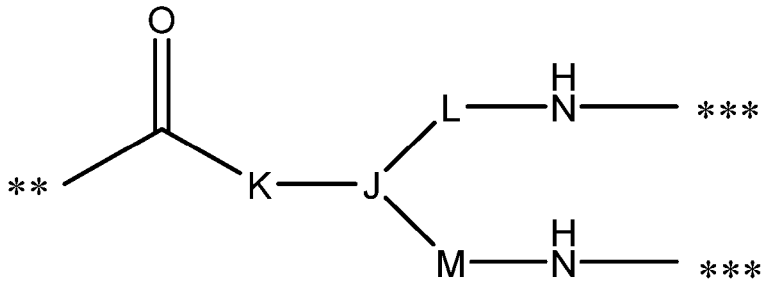
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In some preferred embodiments, the building units are L-lysine residues, e.g.:



In some embodiments, the building unit or building units of the dendrimer are lysine or lysine analogues selected from a compound of the following formula:



wherein K is absent or is selected from –$C_{1-6}$ alkylene-, -$C_{1-6}$ alkyleneNHC(O)-, -$C_{1-6}$ alkyleneC(O)-, -$C_{1-3}$ alkylene-O-$C_{1-3}$ alkylene-, -$C_{1-3}$ alkylene-O-$C_{1-3}$ alkyleneNHC(O)- and -$C_{1-3}$ alkylene-O-$C_{1-3}$ alkyleneC(O)-;

J is selected from CH or N;

L and M are independently absent or is selected from –$C_{1-6}$ alkylene- or -$C_{1-3}$ alkyleneO$C_{1-3}$ alkylene; provided that when L and/or M are absent, J is CH;

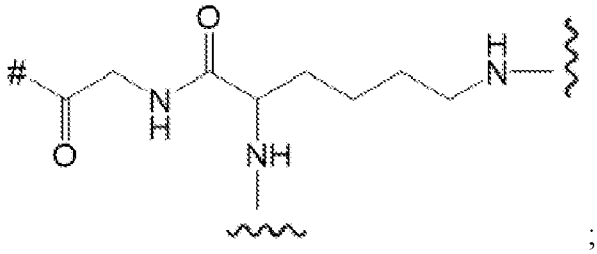
** indicates the linkage between the lysine or lysine analogue and the core of the dendrimer or the previous generation of building units; and

*** indicates the linkage between the lysine or lysine analogue and the subsequent generation of lysine or lysine analogues or forms the surface amino groups of the dendrimer.

Exemplary lysine analogue building units including the following:

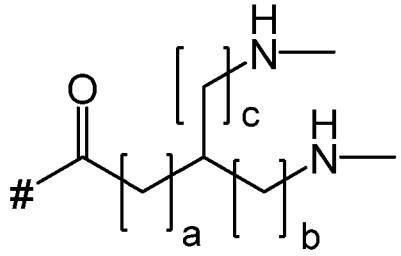
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Glycyl-Lysine **1** having the structure:



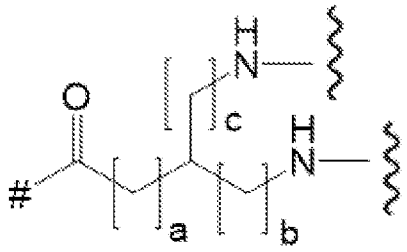
;

Analogue **2**, having the structure below, where a is an integer 1 or 2; and b and c are independently integers 1, 2, 3 or 4:



;

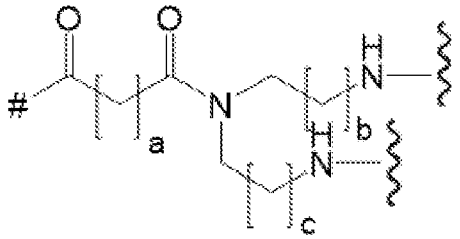
Analogue **3**, having the structure below, where a is an integer 0, 1 or 2; and b and c are independently integers 2, 3, 4, 5 or 6:



; and

Analogue **4**, having the structure below, where a is an integer 0, 1, 2, 3, 4 or 5; and b and c are independently integers 1, 2, 3, 4 or 5:

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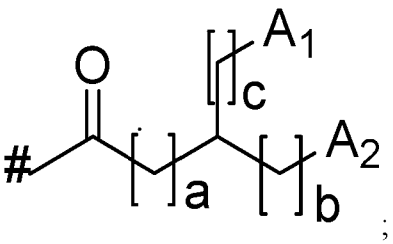


;

wherein each # denotes the carbonyl residue of the carboxyl group which forms an amide bond with a nitrogen atom of the core or a nitrogen atom of a previous generation of building units; and wherein any methylene group of the building units may be replaced by a methyleneoxy ($CH_2$-O) or ethyleneoxy ($CH_2$-$CH_2$-O) group, provided that this does not result in the formation of a carbonate (-O-C(O)-O-) or carbamate (-O-C(O)-N-) moiety within the building unit.

Other suitable building units/building unit precursors include:

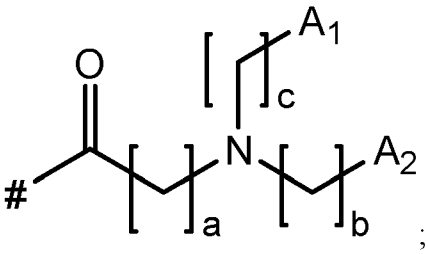
Analogue **5**, having the structure below, where a is an integer of 0 to 2; b and c are the same or different and are integers of 1 to 4; $A_1$ and $A_2$ are the same or different and selected from $NH_2$, $CO_2H$, OH, SH, X, Allyl-X, epoxide, aziridine, $N_3$ or alkyne, where X is F, Cl, Br or I,



;

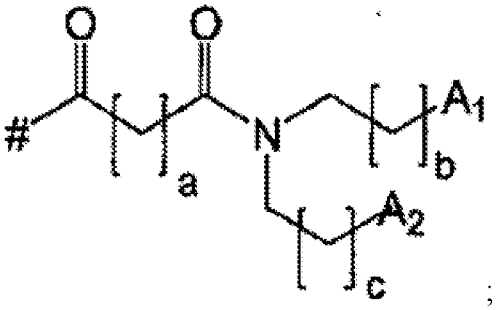
Analogue **6**, having the structure below, where a is an integer of 0 to 2; b and c are the same or different and are integers of 2 to 6; $A_1$ and $A_2$ are the same or different and selected from $NH_2$, $CO_2H$, OH, SH, X, Allyl-X, epoxide, aziridine, $N_3$ or alkyne, where X is F, Cl, Br or I,

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; and

Analogue 7, having the structure below, where a is an integer of 0 to 5; b and c are the same or different and are integers of 1 to 5; $A_1$ and $A_2$ are the same or different and selected from $NH_2$, $CO_2H$, OH, SH, X, Allyl-X, epoxide, aziridine, $N_3$ or alkyne, where X is F, Cl, Br or I,



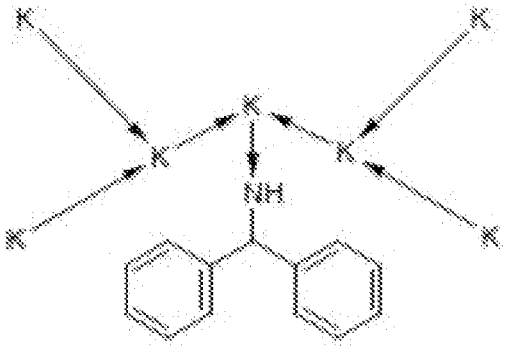

;

wherein each # denotes the carbonyl residue of the carboxyl group which forms an amide bond with a nitrogen atom of the core or a nitrogen atom of a previous generation of building units;

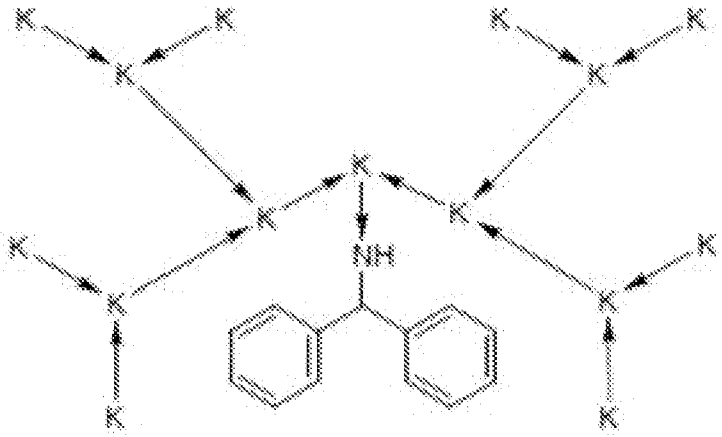
and wherein any methylene group of the building units may be replaced by a methyleneoxy ($CH_2$-O) or ethyleneoxy ($CH_2$-$CH_2$-O) group, provided that this does not result in the formation of a carbonate (-O-C(O)-O-) or carbamate (-O-C(O)-N-) moiety within the building unit.

In some embodiments, the macromolecule is a polylysine dendrimer having lysine building units, especially a polylysine dendrimer with a benzhydrylamine group, e.g. a dendrimer as shown below:

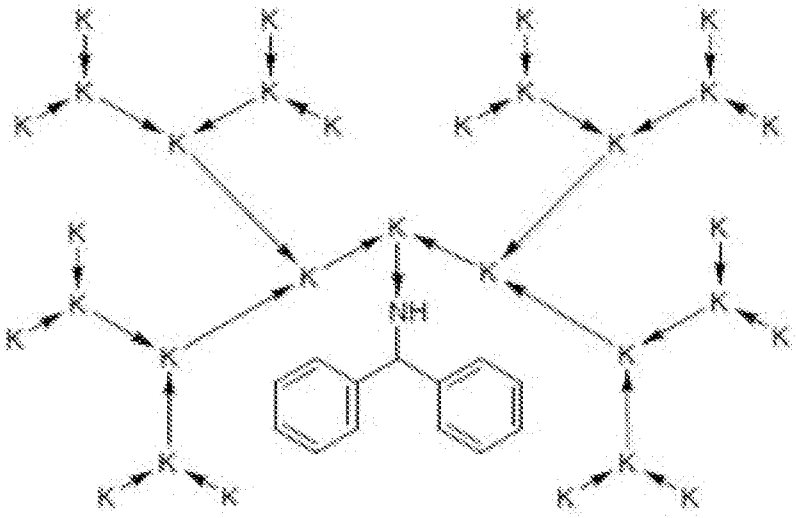
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;



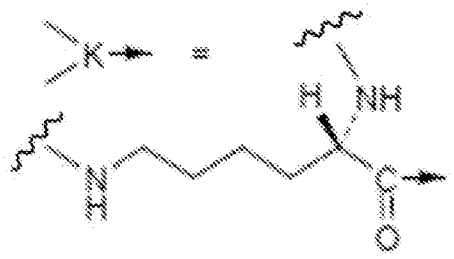

; or




;

wherein

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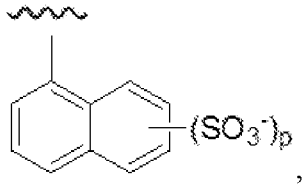
In some aspects the dendrimer contains 3 to 5 generations of building units, e.g. in some embodiments it comprises a core and 3 to 5 generation is of building units. In some embodiments, the dendrimer comprises a BHALys core and 3 to 5 generations of lysine building units. In some embodiments, the dendrimer provides 16, 32 or 64 nitrogen atoms on the surface layer of building units for attachment to sulfonic acid or sulfonate-containing moieties (either directly or via a linker). In some embodiments, the dendrimer provides 32 nitrogen atoms on the surface layer of building units for attachment to sulfonic acid or sulfonate-containing moieties (either directly or via a linker).

The sulfonic acid-containing or sulfonate-containing moiety is a moiety that is able to present the sulfonic acid or sulfonate group on the surface of the dendrimer. In some embodiments, the sulfonic acid- or sulfonate-containing moiety has one sulfonic acid or sulfonate group. In other embodiments, the sulfonic acid- or sulfonate-containing moiety has more than one sulfonic acid or sulfonate group, for example 2 or 3 sulfonic acid or sulfonate groups, especially 2 sulfonic acid or sulfonate groups. In some embodiments, the sulfonic acid- or sulfonate-containing moiety comprises an aryl group, such as a phenyl group or naphthyl group, especially a naphthyl group. In some embodiments, the sulfonic acid- or sulfonate-containing moiety comprises a naphthyl group substituted by two sulfonic acid or sulfonate moieties (also referred to as a napthyldisulfonate moiety), for example a 3,6-disulfonatonapthyl moiety. In some embodiments, a 3,6-disulfonatonapthyl moiety which is connected to the dendrimer through the 1-position of the naphthalene is used.

When the sulfonate-containing moiety is present, the moiety may be present in ionic form ($-SO_3^-$) or in the form of a salt, for example, the sodium salt ($-SO_3Na$).

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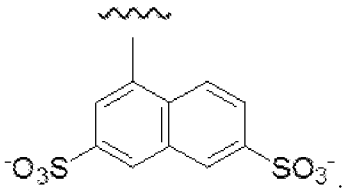
The sulfonic acid or sulfonate-containing moiety is



,

in which p is an integer of 2.

In some embodiments, the sulfonic acid- or sulfonate-containing moiety is:



.

At least 15 sulfonic acid- or sulfonate-containing moieties are present on the surface of the dendrimer. In some embodiments at least 30 sulfonic acid- or sulfonate-containing moieties are present on the surface of the dendrimer. In some embodiments, 32 sulfonic acid- or sulfonate-containing moieties are present on the surface of the dendrimer.

The sulfonic acid- or sulfonate-containing moiety is attached to the surface amino group of the dendrimer through a linker group.

The linker is a group $-X_1-(CH_2)_q-C(O)-$, wherein $X_1$ is the atom which is attached to the sulfonic acid- or sulfonate-containing moiety and is O; q is an integer of 1; and the carbon of the -C(O)- group is attached to the surface amino group of the dendrimer.

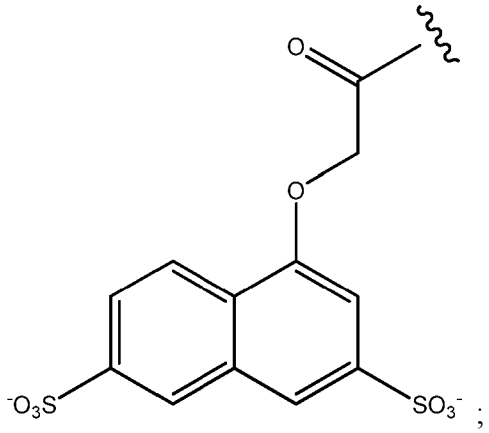
The linker is

$$\#\text{-}O\text{-}CH_2\text{-}C(O)\text{-}*$$

in which # designates attachment to the sulfonic acid-containing moiety and * designates attachment to the surface amino group of the dendrimer.

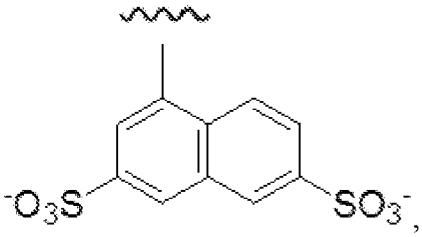
In some embodiments, the sulfonic acid- or sulfonate-containing moiety is attached to the surface amino group of the dendrimer through a linker group, and the linker-sulfonic acid/sulfonate moiety is:

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or a pharmaceutically acceptable salt thereof.

In some embodiments, the sulfonic acid- or sulfonate-containing moiety is



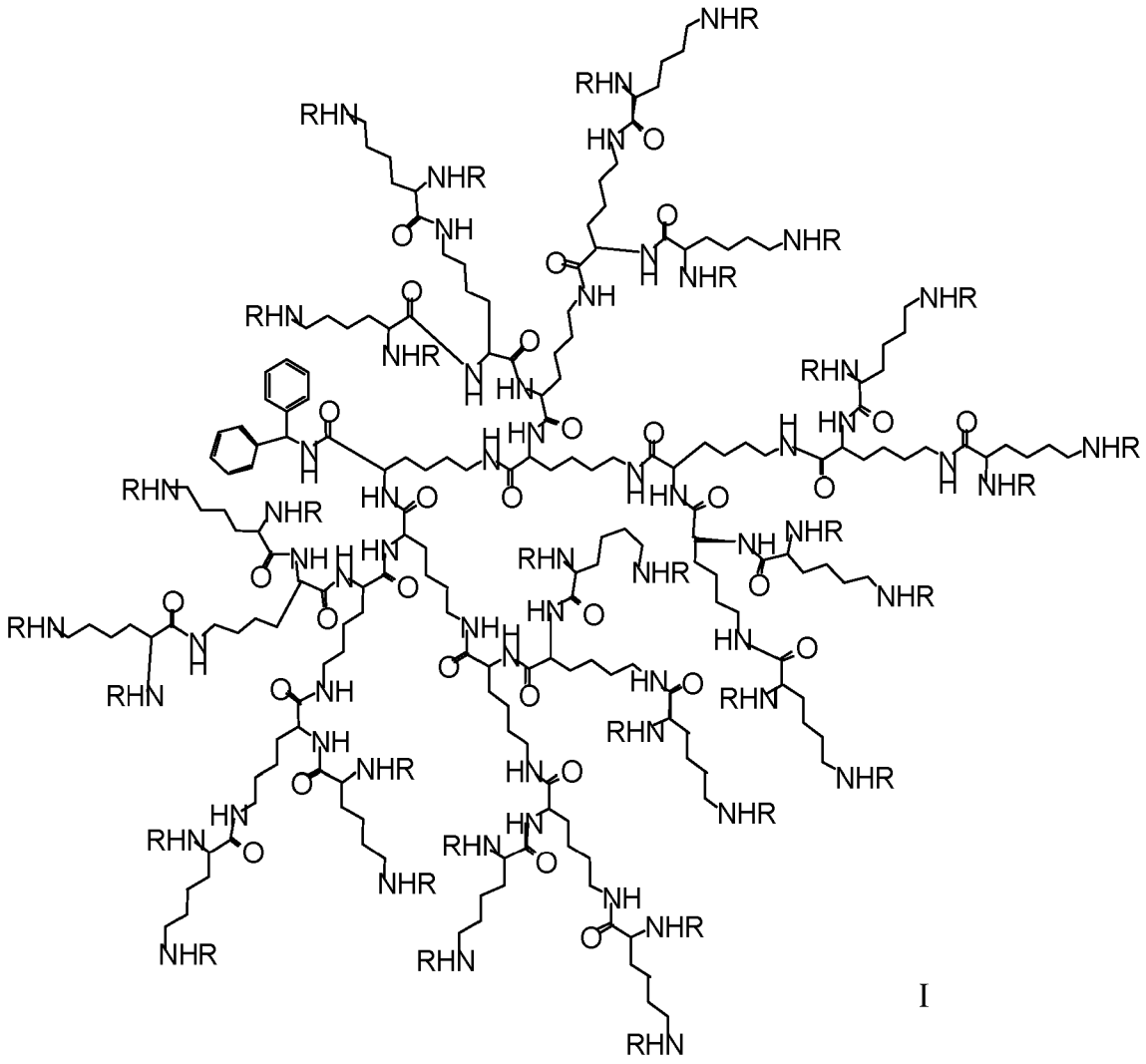
, and the linker is

#-O-$(CH_2)_q$-C(O)-*

wherein q is an integer of 1, and in which # designates attachment to the sulfonic acid-containing moiety and * designates attachment to the surface amino group of the dendrimer.

Exemplary dendrimers useful in the invention include those of formulae I, II and III:

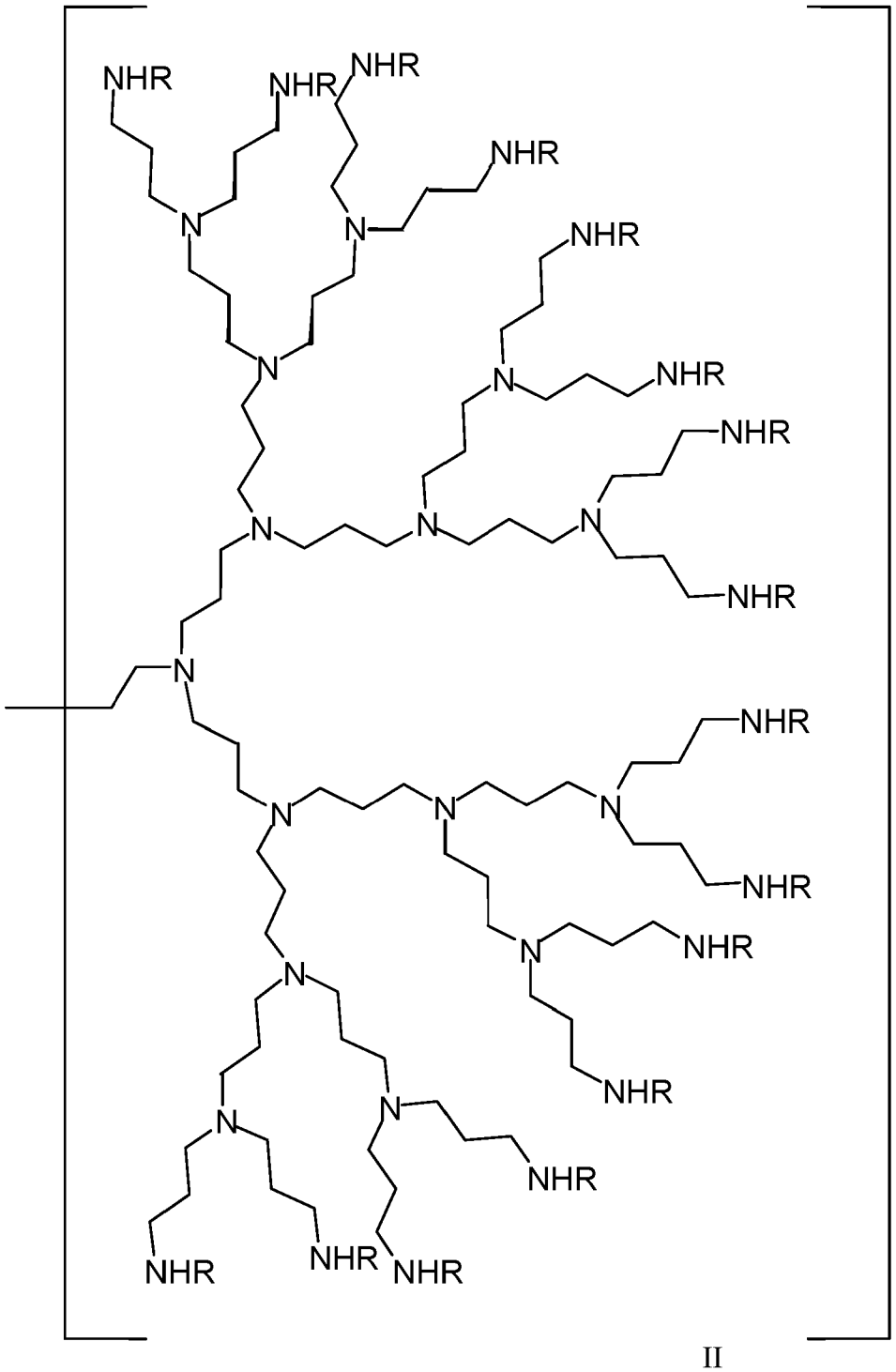
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I

;

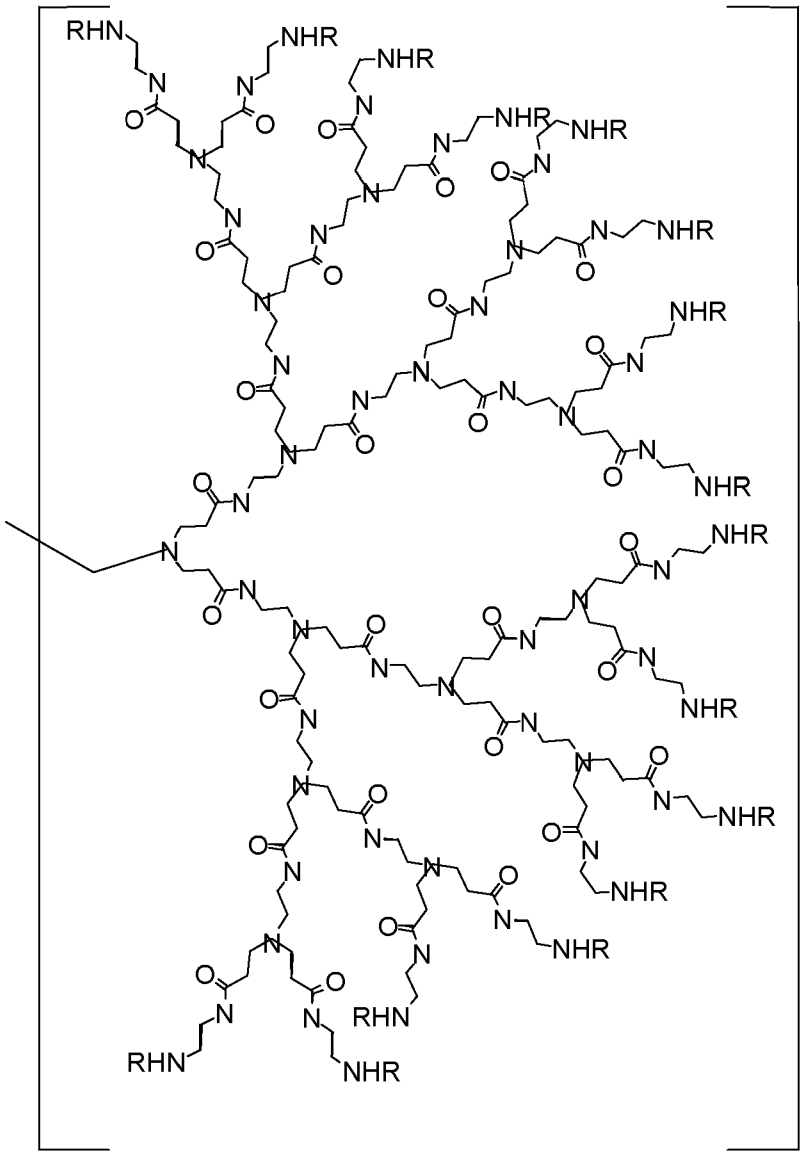
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II

;

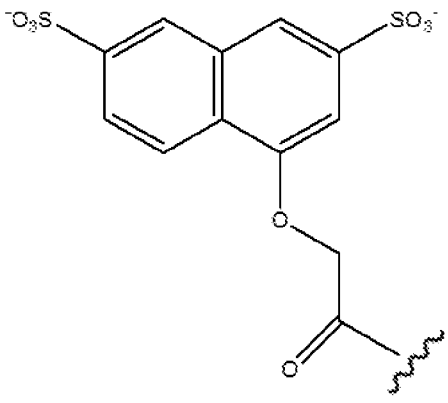
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III

;

in which each R group is represented by a group of formula IV or hydrogen:




IV;

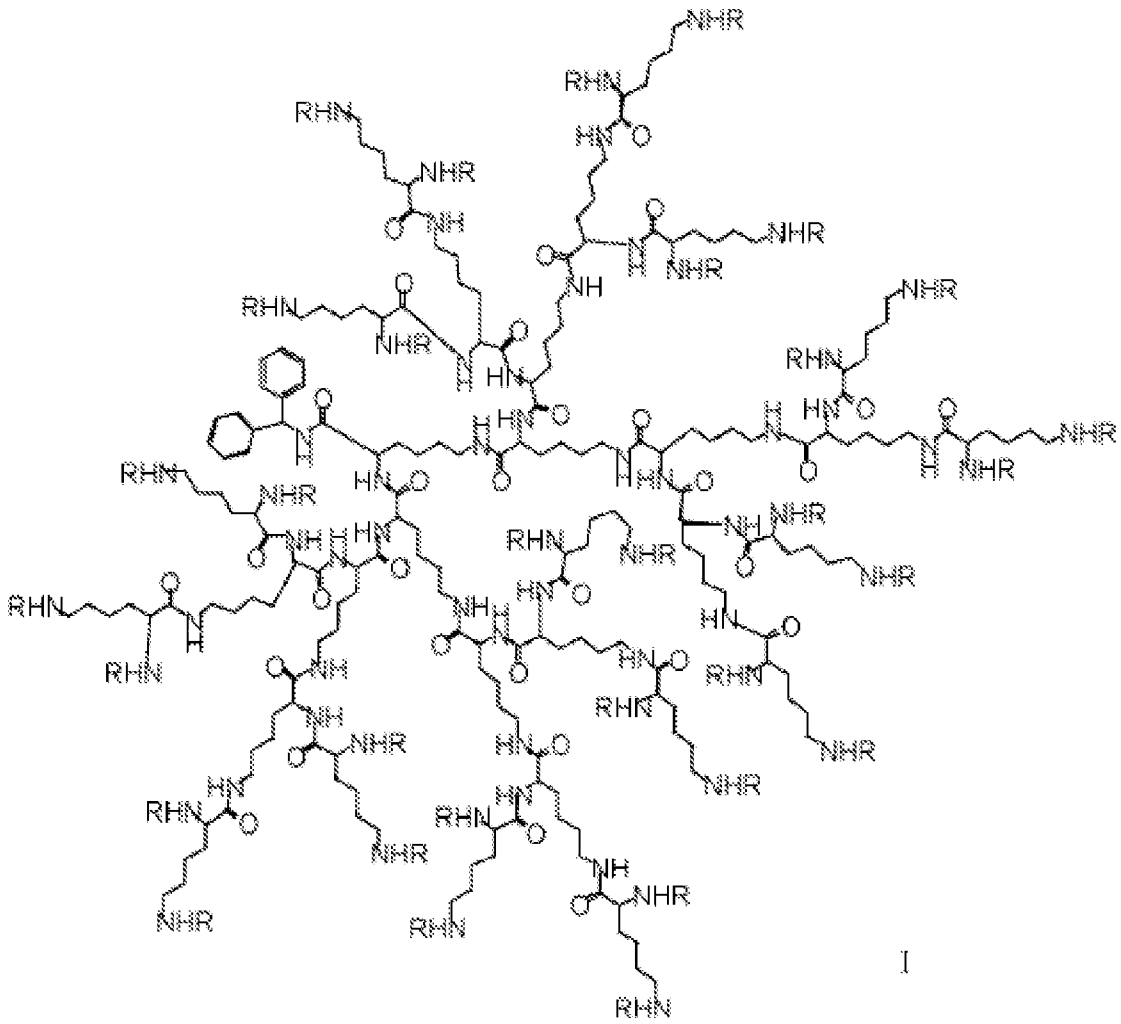
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provided that at least one R group is a group of formula IV;

or a pharmaceutically acceptable salt thereof.

In particular embodiments, more than one R group is a group of formula IV, for example in some embodiments at least 10 of the R groups are groups of formula IV, at least 15 of the R groups are groups of formula IV, at least 20 of the R groups are groups of formula IV, at least 25 of the R groups are groups of formula IV or at least 30 of the R groups are groups of formula IV. In some embodiments, all of the R groups are groups of formula IV.

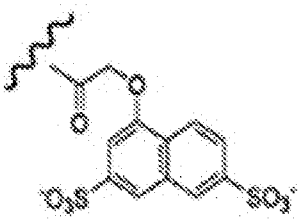
In some embodiments, the dendrimer is



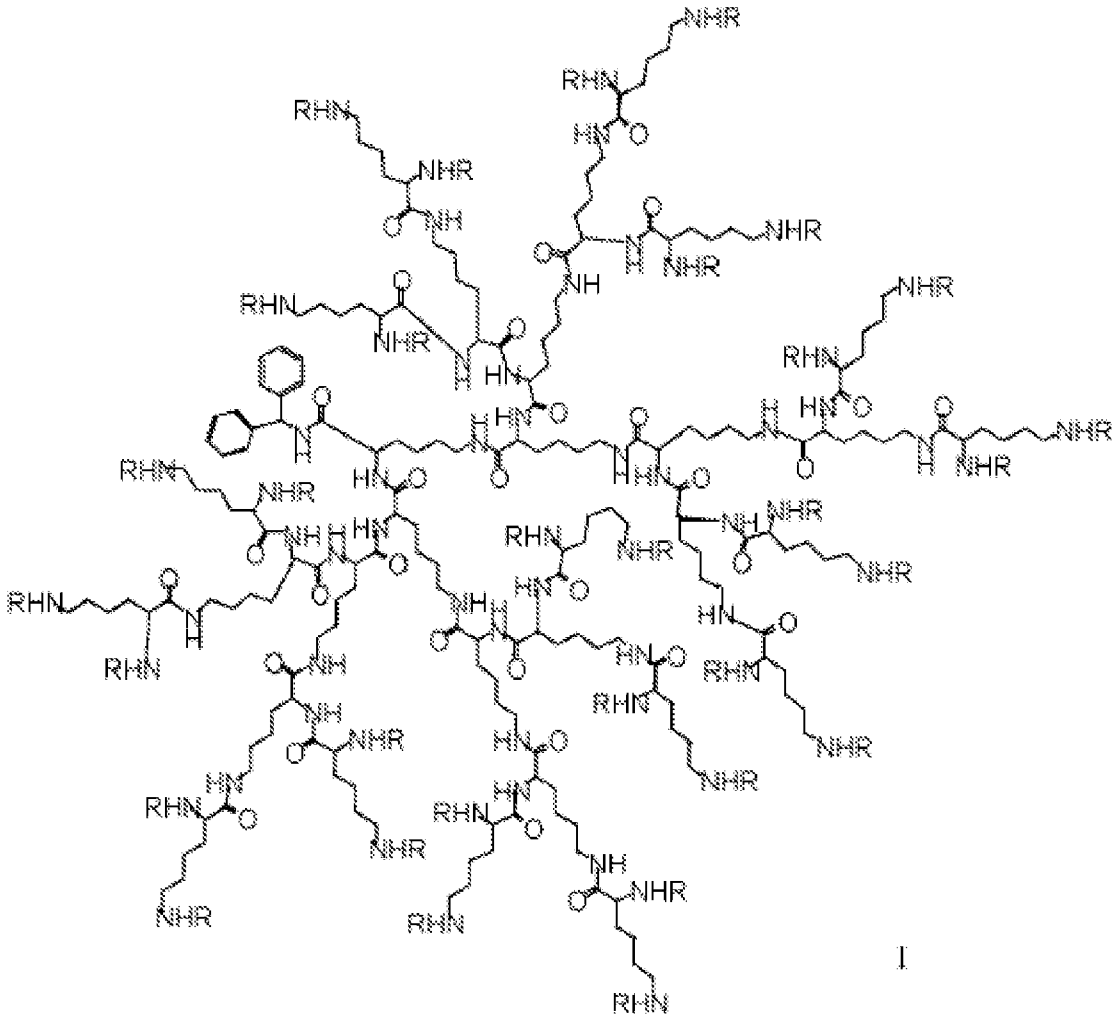
I

wherein at least 25% of R is

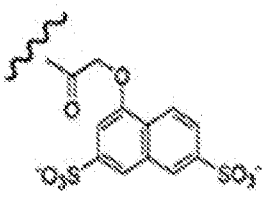
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 , and wherein the pharmaceutically acceptable salt is a sodium salt.

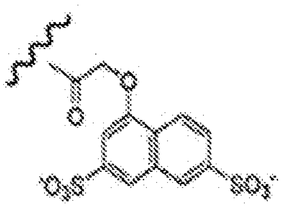
In some embodiments, the dendrimer is



I

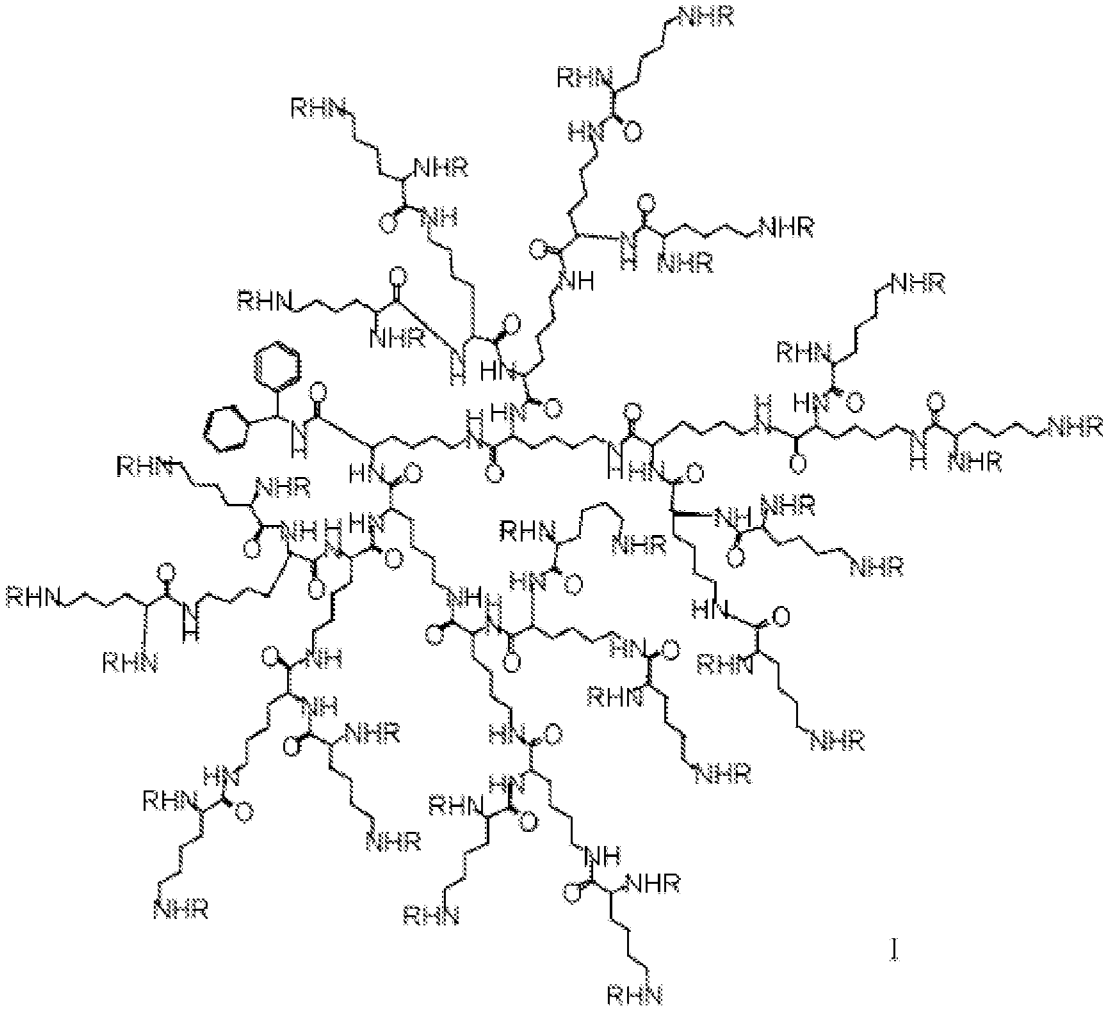
 , and wherein at least 25%, at least 50%, at least 75%, or at least 90% of R is

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, and wherein the pharmaceutically acceptable salt is a sodium salt.

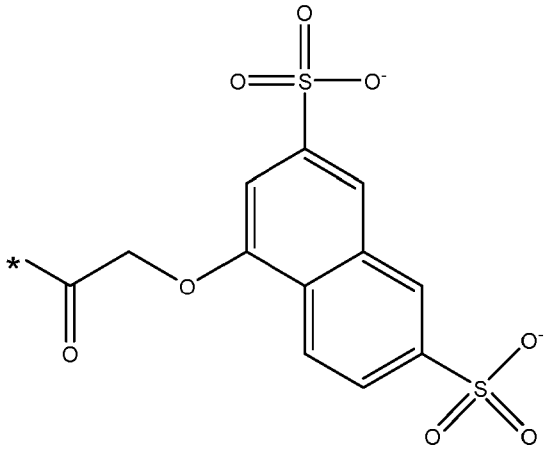
In some embodiments, the macromolecule is a dendrimer of formula I:



I

where R represents a group of the formula IV:

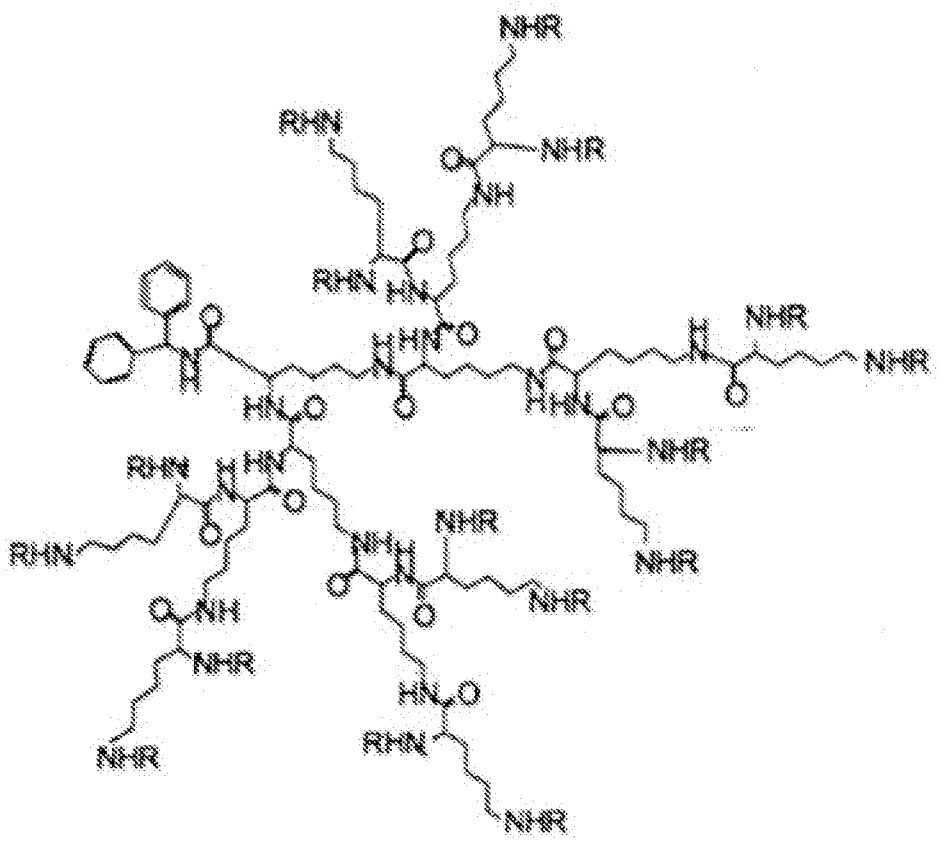
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(IV);

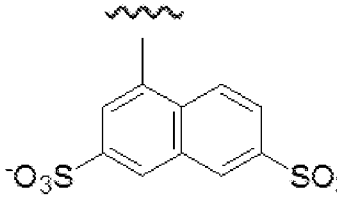
wherein * represents the attachment point to the surface amino group of the dendrimer, and wherein the pharmaceutically acceptable salt is sodium.

In some embodiments, the dendrimer is



wherein R is hydrogen or a group R′,

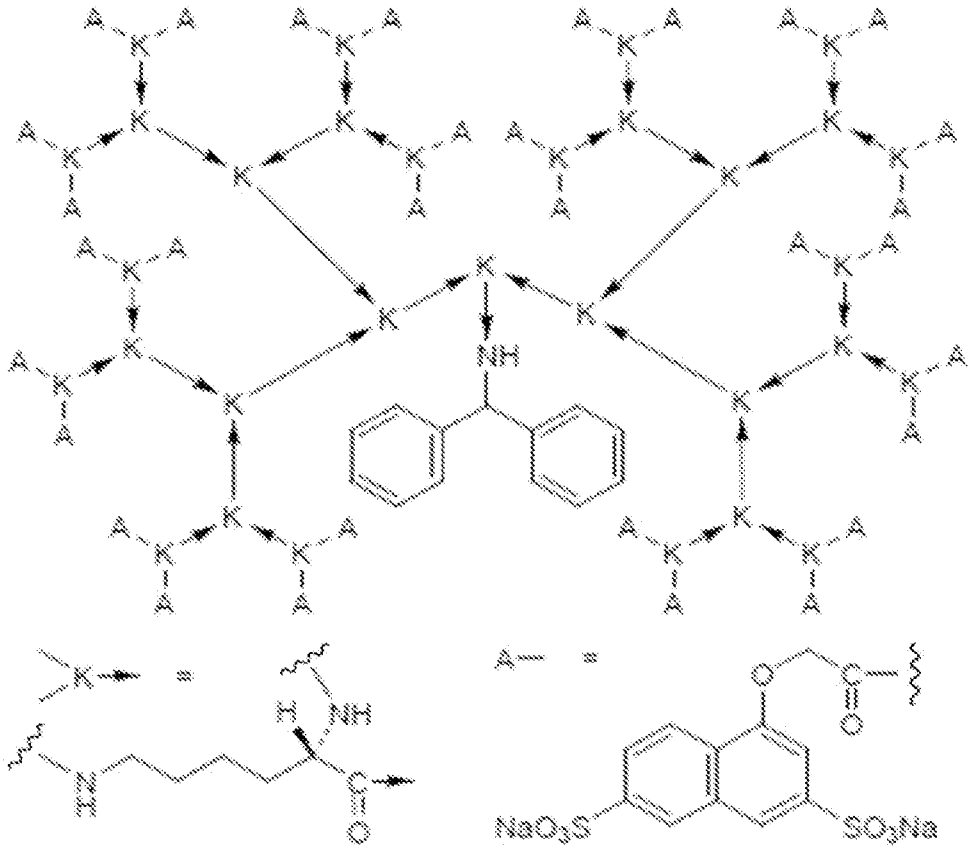
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R′ is a linked sulfonic acid- or sulfonate-containing moiety, in which the sulfonic acid- or sulfonate-containing moiety is  , and the linker is

#-O-$(CH_2)_q$-C(O)-*

wherein q is an integer of 1, and in which # designates attachment to the sulfonic acid- or sulfonate-containing moiety and * designates attachment to the surface amino group of the dendrimer, and wherein at least 25%, at least 50%, at least 75%, or at least 90%, or all, of R is R', and wherein the pharmaceutically acceptable salt is a sodium salt.

A particular dendrimer of formula I has all R groups as groups of formula IV (SPL7013). SPL7013, also known as astodrimer sodium, has the structure:



In some embodiments, the macromolecule is astodrimer. In some embodiments, the macromolecule is a pharmaceutically acceptable salt of astodrimer. In some

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embodiments, the pharmaceutically acceptable salt thereof is SPL7013 (astodrimer sodium).

A particular dendrimer of formula II has all R groups as groups of formula IV (SPL7320). A particular dendrimer of formula III has all R groups as groups of formula IV (SPL7304).

The synthesis of dendrimers of Formulae I, II and III is described in WO02/079299.

The macromolecule is not SPL-7674, SPL-7615, SPL-7673, BAI-7021, BRI-2999, and BRI-2992. The structures of these molecules are shown in Figure 1.

Respiratory syncytial virus

As used herein, "*Orthopneumovirus*", known by the common name of "Respiratory syncytial virus" or "RSV" are negative-sense, single-stranded RNA viruses. RSV is a member of the *Pneumoviridae* family. RSV primarily infects respiratory epithelial cells. There is a single RSV serotype with two major antigenic subgroups, A and B as outlined in Borchers et al (2013). The subtypes can be determined based on the reactivity of the F and G surface proteins to monoclonal antibodies. RSV infections cause can cause symptoms in primates, humans, rats, mice, cows, guinea pigs, ferrets, and hamsters.

In one embodiment, the RSV is a human RSV (HRSV). In one embodiment, the HRSV is HRSV long.

In one embodiment, the RSV is selected from RSV subtype A (RSVA) or RSV subtype B (RSVB).

In an embodiment, the RSVA is selected from GA1, GA2, GA3, GA4, GA5, GA6, and GA7 clades as described in Melero et al (2013). In an embodiment, the RSVA is selected from GA2 and GA5. In an embodiment, GA2 clade includes NA1, NA2, CB-A, and ON1 genotypes. In an embodiment, the RSVB is one or more of GB1, GB2, GB3/SAB3, GB4, and BA. In an embodiment, the RSVB is BA clade.

In an embodiment, the RSVA is a member of one of the twenty-three genotypes identified in Ramaekers et al 2020. In an embodiment, the RSVA is selected from genotype A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16,

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A17, A18, A19, A20, A21, A22 and A23. In an embodiment, the RSVB is a member of one of the six RSVB genotypes identified in Ramaekers et al 2020. In an embodiment, the RSVB is selected from genotype B1, B2, B3, B4, B5 and B6.

In an embodiment, the RSV infection causes one or more of the following symptoms: congested or runny nose, decrease in appetite, coughing, mucus when coughing (yellow, green, or gray mucus), sneezing, sore throat, mild headache, fever, wheezing, rapid breathing or difficulty breathing, bluish colour of the skin (cyanosis), severe asthma symptoms in individuals with asthma, acute bronchitis, severe bronchitis, airway inflammation, airway congestion, chronic obstructive pulmonary disease, heart congestion, bacteremia, pneumonia, acute otitis media, and recurrent otitis media.

RSV infections can result in secondary infections such as for example bacteremia, pneumonia, acute otitis media, and recurrent otitis media.

RSV can be transmitted from one individual to another through contact of viral droplets with mucosa. Typically, viral droplets are airborne and inhaled via the respiratory tract including the nasal airway. Typically, the individual is a human individual. In some embodiments, the individual is a live stock or domestic animal. In an embodiment, the livestock is a cow. Typically, during an infection, RSV can be found in the upper respiratory tract, for example the nasal passages. In some examples, RSV can be found in the lower respiratory tract, for example the bronchi and/or alveoli.

In an embodiment, the macromolecule or pharmaceutically acceptable salt thereof reduces the viral load of the individual. A person skilled in the art will appreciate that viral load can be measured by any method known to a person skilled in the art including for example, measurement by Quantitative reverse transcription PCR (RT-qPCR) to the relevant viral nucleotide sequences. In one embodiment, viral load is reduced to above 20CT (cycle threshold), or reduced to above 30CT, or reduced to above 35CT, or reduced to above 40CT.

In one embodiment, the macromolecule reduces the RSV antibody titre of the individual. In one embodiment, the IgA, IgG, IgM and/or IgE antibody titre is measured by ELISA, and is reduced to below detectable levels. In some embodiments,

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the sample tested is taken from oral swabs, nasal swabs, blood sample, throat swabs or lung fluid.

In some embodiments, the macromolecule is retained within the lung and does not leach into the systemic circulation.

In some embodiments, the percentage of macromolecule that reaches the systemic circulation is less than 10%, less than 25%, less than 50% and less than 70%. Systemic delivery refers to the delivery of the drug pharmaceutically active agent to the blood from the lungs, either directly via absorption into lung capillaries or after absorption into pulmonary lymphatic capillaries.

Treatment of RSV can include one or more of the following: hospitalisation, intensive care treatment, ICU admission, intubation and supplemental oxygen.

Methods and uses

Described herein are methods and uses for preventing or reducing the likelihood an RSV infection in an individual, preventing or reducing the likelihood of a symptom associated with an RSV infection in an individual, reducing the severity and/or duration of an infection in an individual, treating an RSV infection in an individual, preventing or reducing viral shedding in an individual infected with an RSV infection, or reducing transmission of an RSV in a population, comprising administering to the individual an effective amount of a macromolecule as described herein.

In one embodiment, the macromolecule as described herein is intended for administration to the respiratory tract. As used herein, the term "respiratory tract" refers to the passage formed by the mouth, nose, throat, and lungs, through which air passes during breathing. A reference to the respiratory tract includes both the upper respiratory tract and/or lower respiratory tract. In one embodiment, the macromolecule as described herein is intended for administration to the upper respiratory tract. In one embodiment, the macromolecule as described herein is intended for administration to the lower respiratory tract. A person skilled in the art will appreciate that the upper respiratory tract comprises one or more of the: nasal cavity, oral cavity, sinuses, throat, pharynx and larynx. A person skilled in the art will appreciate that the nasal cavity comprises one or more of the: vestibular area, olfactory area, superior turbinate, middle

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turbinate, inferior turbinate and the nasopharynx. A person skilled in the art will appreciate that the lower respiratory tract comprises one or more of the: trachea, primary bronchi and lungs. In some embodiments, the macromolecule is delivered nasally. In an embodiment, administering a macromolecule comprises administering to the mucosa of one or more areas of the respiratory tract. In an embodiment, the macromolecule is administered to the nasal cavity. In an embodiment, the macromolecule as described herein is administered to the nasal mucosa. In an embodiment, the macromolecule is administered to one or more of the nasal turbinates, nasopharynx, and/or oropharynx. In an embodiment, the macromolecule as described herein is administered to the oral mucosa. In an embodiment, the macromolecule as described herein is administered to the mucosa of the primary bronchi. In an embodiment, the macromolecule as described herein is administered to the mucosa of the lungs.

The lung is known to be a particularly harsh environment for stability of active agents. Small molecules quickly pass through the lung epithelium and are cleared into the vascular system. Particle size is important to reach the relevant diseased structures within the lung. Another difficulty encountered in delivery of large particles to the lung is that the action of cilia in the lung will tend to quickly remove agents delivered to the lung, and result in excretion via the faeces. Thus, a particular advantage of some embodiments, of the present invention is that the dendrimer is not degraded or rapidly expelled by the cilia after administration to the lung environment. In some embodiments, the macromolecule is retained within the lung for an extended period of time. In some embodiments, the macromolecule is retained within the lung for up to a month, a week or a day.

In some embodiments, the macromolecule is administered topically. In an embodiment the macromolecule is administered topically to the epidermis or the eye. In some embodiments, topical administration does not cover administration to the respiratory tract.

In some embodiments, the macromolecule is administered dermally. For example, the macromolecule may be administered dermally to one or more of a hand, wrist, forearm, face and neck.

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In some embodiments, the macromolecule is delivered via a parenteral routes (e.g. intravenous, subcutaneous or intramuscular) for systemic delivery. In some embodiments, the macromolecule is delivered by bolus or infusion. In some embodiments, the macromolecule is delivered via injection. In some embodiment, the macromolecule is delivered intravenously.

In some embodiments, the macromolecule is applied to a surface. In some embodiments, the macromolecule is applied to surfaces, including metal, polymers such as paint, plastic and rubber, fabric, polymers, wood, ceramics, glass, concrete, skin, human tissues, mucosa and bone. In some embodiments, the macromolecule is applied to personal protective equipment (PPE), including gloves, masks, gowns and scrubs. In some embodiments, the macromolecule is applied to wipes and tissues. In some embodiments, the macromolecule is applied to the surgical/medical field including the patient, the table, and equipment. The surgical/medical field may be for human or veterinary use.

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Compositions

In some embodiments, a composition comprising the macromolecule and a pharmaceutically acceptable carrier is used. The compositions as described herein are suitable for e.g. respiratory administration via nasal, pulmonary, ocular administration, dermal administration and/or parenteral administration.

The pharmaceutical composition may also include polymeric excipients/additives or carriers, e.g., polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, microcrystalline cellulose /carboxy methyl cellulose, Ficolls (a polymeric sugar), hydroxyethylstarch (HES), dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin), dextrans, PVP, inulin, polyethylene glycols, and pectin. The pharmaceutical composition may also include amino acid or sugar carriers, e.g., glycine, leucine, alanine, mannitol and trehalose. The compositions may further include diluents, buffers, binders, disintegrants, thickeners, lubricants, preservatives (including antioxidants), flavoring agents, taste-masking agents, inorganic salts (e.g., sodium chloride), antimicrobial agents (e.g., benzalkonium

chloride), sweeteners, antistatic agents, sorbitan esters, lipids (e.g., phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines, fatty acids and fatty esters, steroids (e.g., cholesterol)), and chelating agents (e.g., EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the invention are listed in "Remington: The Science & Practice of Pharmacy", 19.sup.th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52.sup.nd ed., Medical Economics, Montvale, N.J. (1998), and in "Handbook of Pharmaceutical Excipients", Third Ed., Ed. A. H. Kibbe, Pharmaceutical Press, 2000.

The carrier, excipient or diluent may include one or more of any and all conventional solvents, dispersion media, fillers, solid carriers, aqueous solutions, coatings, viscosity modifying agents, isotonic agents, and absorption enhancing or delaying agents, activity enhancing or delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art, and it is described, by way of example, in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, Pennsylvania, USA. Except insofar as any conventional carrier and/or diluent is incompatible with the active ingredient, use thereof in the compositions of the present invention is contemplated.

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In some embodiments, the composition of macromolecule comprises a rheology modifying agent, especially a polyacrylic acid (carbomer), for example, Carbopol® polymer such as Carbopol® 971P, 974P or 71G or Noveon Polycarbophil, from Lubrizol or their equivalent. In some embodiment, the rheology modifying agent is Carbopol®974P. They may be homopolymers of acrylic acid, or crosslinked with an allyl ether of pentaerythritol, allyl ether of sucrose, or allyl ether of propylene. In an embodiment, it is a carbomer. In an embodiment, it is a carboxypolymethylene. In an embodiment, it is an acrylic acid polymer. It will be appreciated by a person skilled in the art that chains can have different lengths, different degrees of cross-linking, molecular weight and the like and can be of different grades for specific uses (such as pharmaceutical which is designated by a P). In some embodiments the Carbopol polymer is a NF (national formulatory) version. A person skilled the art will be aware of when it is suitable to use pharmaceutical and non-pharmaceutical grades. The

rheology modifier may be present in an amount of 1-10% w/w, especially about 2 to 5% w/w, or 0.01 to 0.1% w/w. In some embodiments, the rheology modifier is carbopol. The carbopol rheology modifier is present in an amount such as 0.01% to 1% w/w, or about 0.01 to 0.1%, especially 0.05% to 0.1%, especially 0.05% w/w. In some embodiments, the carbopol is Carbopol 974. In some embodiment, Carbopol 974 is present in an amount such as 0.05% w/w to about 5% w/w, or about 0.05% w/w to about 3% w/w, or about 0.05% w/w to about 2% w/w, or about 0.05% w/w to about 1% w/w, or about 1%, or about 0.05% w/w Carbopol 974. In some embodiments, the carbopol is Carbopol 971. In some embodiment, Carbopol 971 is present in an amount such as 0.05% w/w to about 1% w/w, or about 0.05% w/w to about 1.5% w/w, or about 0.05% w/w to about 1.8% Carbopol 971. In some embodiments, the rheology modifying agent is a cellulose, for example, hydroxypropylmethyl-cellulose or microcrystalline cellulose /carboxy methyl cellulose. In some embodiment, the rheology modifying agent is hydroxypropylmethyl-cellulose. In some embodiments, hydroxypropylmethyl-cellulose is present in an amount, such as 0.01% to 1% w/w, or about 0.05 to 0.5% w/w, especially about 0.1%. In some embodiment, the rheology modifying agent is microcrystalline cellulose /carboxy methyl cellulose. In some embodiments, microcrystalline cellulose /carboxy methyl cellulose is present in an amount, such as 0.5% to 5% w/w, or about 1% to 3% w/w, especially about 2% w/w. The rheology modifier aids the composition in having bioadhesive/mucoadhesive properties.

The composition of macromolecule may also include a chelating agent, such as a polyaminocarboxylic acid. A particularly useful chelating agent is ethylenediamine tetraacetic acid (EDTA) and its salts. Suitable amounts of chelating agent are in the range of 0.001% to 2% w/w, especially 0.005% to 1% w/w. In some embodiments, the chelating agent is present in a low amount, such as 0.001% to 0.1% w/w, especially about 0.005%. Other ingredients that may be included in the gel composition include preservatives such as parabens in an amount of up to 1% w/w, for example methylparaben and propylparaben or mixtures thereof. Suitable amounts of parabens are in the range of 0.01% to 0.5% w/w, especially 0.01% to 0.2% w/w. In some embodiments, methyl paraben is present in an amount, such as 0.05% to 0.2% w/w,

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especially about 0.18%. In some embodiments, methyl paraben is present in an amount, such as 0.14% to 0.23% w/w. In some embodiments, propyl paraben is present in an amount, such as 0.01% to 0.05% w/w, especially about 0.02%. In some embodiments, propyl paraben is present in an amount, such as 0.015% to 0.0025% w/w. In some embodiments, benzalkonium chloride is present in an amount, in the range of 0.01% to 0.1%w/w, especially about 0.05%.

Other ingredients that may be included in the composition include, for example, solvents such as water, pH adjusting agents such as hydroxide and or hydrocholic acid, and emollients and humectants such as glycerin and propylene glycol, in an amount of up to 5%. In some embodiment, glycerin (glycerol) is present. In some embodiments, glycerin is present in an amount, such as 0.1% to 5% w/w, 0.5 % to 2% w/w, especially about 1% w/w. In some embodiments, propylene glycol is present. In some embodiments, propylene glycol is present in an amount, such as 0.1% to 5%w/w, 0.5 % to 2%w/w, especially about 1%w/w.

In an embodiment, the composition, when delivered by a nasal spray device as described herein, creates a moisturizing and protective barrier in the nasal cavity. In an embodiment, the composition, when delivered by a nasal spray device as described herein, creates a moisturizing and protective barrier on the nasal mucosa.

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*Respiratory compositions (nasal and oral)*

In some embodiments, administering the macromolecule to the respiratory tract may include delivering the macromolecule to the diseased lung by an oral or nasal route; to the upper respiratory tract via the nasal route; or to the nasal cavity and/or the nasal mucosa via the nasal route. For example, in some embodiments, the macromolecule may be delivered by inhalation, such as inhalation via the mouth and/or nose. In some embodiments, the macromolecule may be delivered by intratracheal instillation or insufflation. As such, the macromolecule may be delivered to the respiratory tract without the need for a separate targeting agent that targets the pharmaceutically active agent to the diseased tissue or cells.

For example, in some embodiments, pharmaceutical compositions may be aerosol compositions, nebulized compositions, dry powder compositions, aqueous

compositions or insufflation compositions. In some embodiments, pharmaceutical compositions may be included in pressurized metered dose inhalers, dry powder inhalers, nebulizers, sprays and the like. In an embodiment, the composition is suitable for administration in a nasal spray, an oral spray, an inhaler or a nebuliser. For additional discussion, see Zarogoulidis et al (2012).

In some embodiments, the macromolecule is formulated for nasal delivery. In some embodiments, the macromolecule is formulated for delivery to the nasal cavity. In some embodiments, the macromolecule is formulated for delivery to the nasal mucosa. In some embodiment, the composition is formulated for delivery to one or more of nasal turbinates, nasopharynx, and/or oropharynx.

In some embodiments, the pharmaceutical composition may be suitable for intra nasal delivery, such as an aqueous nasal spray composition or a dry powder nasal spray. Nasal spray compositions may include purified aqueous solutions of the active agent with preservative agents and isotonic agents. Such compositions may be adjusted to a pH and isotonic state compatible with the nasal mucous membranes. In some embodiments, the macromolecule is delivered as a powder, a gel, a liquid, an aerosol or an emulsion. In some embodiments, the pH of the composition is about 4.5 to about 7.42. In some embodiments, the pH of the composition is about 5 to about 7. In some embodiments, the pH of the composition is about 5 to about 6.5. In some embodiments, the pH is about 5.5 to about 6.5. In other embodiments, the pH is about 7.4.

In some embodiments, the osmolality of the composition is about 200 to about 700 Osmol/kg. In some embodiments, the osmolality of the composition is about 300 to about 600 Osmol/kg. In some embodiments, the osmolality of the composition is about 300 to about 700 Osmol/kg. In some embodiments, the osmolality of the composition is about 200 to about 400 Osmol/kg, more preferably about 280 Osmol/Kg. Osmolality regulators include NaCl, lysine, $CaCl_2$, sodium citrate and pH regulators include $H_2SO_4$, NaOH, tromethamine, HCl. In some embodiments, the osmolality of the composition is about 200 to about 400mOsmol.

In some embodiments, the composition comprises methylparaben at about 0.14% to about 0.23%.

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In some embodiment, the composition comprises propylparaben at a concentration of about 0.015% to about 0.025%.

In an embodiment, the nasal spray composition has antiviral activity against a RSV virus. In an embodiment, the nasal spray composition inactivates more than 90%, or more than 92%, or more than 95%, or more than 99%, or more than 99.9% of RSV. In an embodiment, inactivation is after at least 1 minute of exposure to a composition as described herein. In an embodiment, the nasal spray composition provides a moisture layer to help keep nasal tissue hydrated. Hydration of the nasal tissue protects it from dryness and damage making it more difficult for viral penetration.

In some embodiments, the macromolecule is formulated for delivery to the lung. Neutral pH and tonicity are important factors for lower respiratory delivery to avoid bronchoconstriction in patients with respiratory impairment, as the lungs are poorly buffered.

In some embodiments, the pharmaceutical composition may be a dry powder with particle sizes greater than 0.5 μm and less than 50 μm. In some embodiments, the particle size is less than 5um, greater than 1um.

In some embodiments, the macromolecule may have a particulate size of less than about 100 nm. In other embodiments, macromolecule may have a particulate size between about 1 and about 10 nm, between about 2 and about 8 nm, and between about 3 and about 6 nm by DLS. In some embodiments, the macromolecules may have a mean size of about 5 nm by DLS (at 1 mg/ml in 10−2M NaCl). In some embodiments, the macromolecule may have a molecular weight of less than 30 kDa, between about 10 to about 30 kDa, and between about 10 to about 20 kDa.

Examples of ingredients suitable for nasal or oral delivery include are provided below in Table 1.

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**Table 1. Suitable ingredients for nasal delivery.**

| Ingredients | IIG for nasal route, %w/w | Function |
|---|---|---|
| Alcohol (ethanol), 200 proof | 2 | Co-solvent |

| | | |
|---|---|---|
| Anhydrous dextrose | 0.5 | tonicity |
| Anhydrous trisodiumcitrate | 0.0006 | buffer |
| Benzyl alcohol | 0.0366 | preservative |
| Benzalkonium chloride | 0.119 | preservative |
| Butylated hydroxyanisole | 0.0002 | antioxidant |
| Cellulose microcrystalline | 2 | Suspending agent, stabilizer |
| Chlorobutanol | 0.5 | preservative |
| Carboxymethyl cellulose Na | 0.15 | Suspending agent |
| Hydroxypropyl methylcellulose | (4- topical) | |
| Edetate disodium | 0.5 | Chelator, antioxidant |
| Hydrochloric acid | Not reported | pH adjustment |
| Methylparaben | 0.7 | preservative |
| Oleic acid | 0.132 | Penetration enhancer |
| PEG400 | 20 | Surfactant, co-solvent |
| PEG3500 | 1.5 | surfactant |
| Phenylethyl alcohol | 0.254 | Preservative, masking agent |
| Polyoxyl 400 stearate | 15 | surfactant |
| Polysorbate 20 | 2.5 | surfactant |
| Polysorbate 80 | 10 | surfactant |
| Propylene glycol | 20 | Co-solvent |
| Propylparaben | 0.3 | Preservative |
| Sodium chloride | 1.9 | tonicity |
| Sodium hydroxide | 0.004 | pH adjustment |
| Sulfuric acid | 0.4 | pH adjustment |
| Succinic Acid | | |

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| | | |
|---|---|---|
| Disodium Succinate | | |
| Zinc Acetate | | |
| Sugars, or flavouring agents e.g. Sodium Saccharin | | |

The rapid mucociliary clearance in the nasal cavity and presence of nasal lysozymes and macrophage can present challenges to mucosal delivery. Mucoadhesive excipients may be required. Depending on the intended mode of administration, the compositions may comprise a bioadhesive agent. In an embodiment, the bioadhesive is a mucoadhesive polymer. A bioadhesive agent may alter the viscosity, rheology and/or the ciliary beating frequency (CBF). Examples of mucoadhesive polymers include poly(acrylates), chitosan, cellulose and derivatives including carboxymethylcellulose and hydroxypropyl cellulose, hyaluronic acid derivatives, pectin, traganth, starch, poly(ethylene glycol), sulfated polysaccharides, carrageenan, sodium alginate, polyvinyl alcohol, polyvinylpyrrolidone, acacia gum, alginic acid, and gelatine. In an embodiment, the composition may comprise a nasal mucoadhesive component.

However, viscosity should not impede airflow. In some embodiments, viscosity of the composition is between 1 and 10000 cP, or between 1 and 1000cP, or between 100 and 1000cP, or between 100 and 500cP, or between 100 and 400cP, or between 150 and 300cP, or between 150 and 250cP, or between 1 and 200cP, or between 1 and 100cP, or between 1 and 50cP, or between 1 and 25cP, or between 1 and 10 cP. In a preferred embodiment, the viscosity of the composition is about 1 to about 10cP (in comparison, SPL7013 gel for vaginal use has a viscosity of 20,000 to 60,000cP). In some embodiments, the kinematic viscosity of the solution is below 1000, or below $500mm^2s^{-1}$.

For lung delivery, viscosity should be low. In some embodiments, the viscosity is less than 200cP. In some embodiments, the viscosity is less than 100cP.

For nasal delivery, viscosity should be low. In some embodiments, the viscosity is less than 100cP. In some embodiments, the viscosity is less than 50cP. In some embodiments, the viscosity is less than 20cP. In some embodiments, the viscosity is less than 15cP. In some embodiments, the viscosity is less than 10cP.

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In one embodiment, the nasal composition comprises the formulation as shown in Table 2.

**Table 2. Provides an example of the nasal or oral composition as described herein comprising SPL7013.**

| Component | % w/w |
|---|---|
| SPL7013 | 0.5 to 5.0 |
| Purified Water | qs to 100 |
| Glycerin | 0 to 1.0 |
| Propylene Glycol | 0 to 2.0 |
| Methylparaben | 0 to 0.5 |
| Propylparaben | 0 to 0.05 |
| Disodium EDTA | 0.005 to 0.1 |
| Citric acid | 0 to 5.0 |
| Carbomer 971P or 934P, 974P or other viscosity/rheology modifier, e.g. cellulose | 0.1 to 5.0 and 0.05 to 0.1 |
| Benzalkonium chloride | 0 to 0.1 |
| Sodium Hydroxide or other pH modifier | qs to pH 4.5 to 7 |

In some embodiments, the pharmaceutical composition may also include any other therapeutic ingredients, surfactants, propellants, stabilizers, or the like. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the composition and not unduly deleterious to the recipient thereof.

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In some embodiments, the pharmaceutical composition may produce particle sizes greater than 0.5 μm and less than 50 μm. In some embodiments, the particle size is less than 5 μm, less than 1 μm, or less than 10 μm.

In one embodiment, the mean particle size is from about 0.21 to about -200 μm. In one embodiment, the mean particle size is from about 1 to about 200 μm. In one embodiment, the mean particle size is from about 1 to about 50 μm. In one embodiment, the mean particle size is from about 1 to about 20 μm. In one embodiment, the mean particle size is from about 1 to about 5 μm.

In some embodiments, a particle diameter of 1 to about 5 μm is good for delivery to the lower airway; from 5 to 10 μm particles deposit mostly in the trachea and bronchi, while diameter > 10 μm particles deposit mostly in the nose. Usually particles less than 10 μm median aerodynamic diameter, can reach the lower airways during nasal breathing. The composition may be a liquid, gel or powder.

In some embodiments, suitable for lower airway delivery the Dv90 is about 5 to 20 μm. In some embodiments, suitable for lower airway delivery the Dv50 is about 5 to 10 μm. In some embodiments, suitable for lower airway delivery the Dv10 is about 1 to 5 μm. In some embodiments, suitable for nasal delivery the Dv10 is greater than about 10, 15 or 20 μm.

In some embodiments suitable for nasal delivery, the Dv50 is greater than about 20, 40 or 60 μm. In some embodiments suitable for nasal delivery, the Dv90 is greater than about 60, 80 or 1000 μm.

In some embodiments suitable for nasal delivery, about 10% to about 0.5% of the particles are about 10 μm or less. In some embodiments suitable for nasal delivery, about 10% to about 0.5% of the particles are about 10 μm or less. In some embodiments suitable for nasal delivery, about 7% to about 0.5% of the particles are about 10 μm or less. In some embodiments suitable for nasal delivery, about 5% to about 0.5% of the particles are about 10 μm or less. In some embodiments suitable for nasal delivery, about 10% to about 0.5% of the particles are about 5 μm or less. In some embodiments suitable for nasal delivery, about 7% to about 0.5% of the particles are about 5 μm or less. In some embodiments suitable for nasal delivery, about 6% to about 0.5% of the particles are about 5 μm or less. In some embodiments suitable for

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nasal delivery, about 5% to about 0.5% of the particles are about 5 μm or less. In some embodiments suitable for nasal delivery, less than about 10% of the particles are about 6 μm or less. In some embodiments suitable for nasal delivery, less than about 10% of the particles are about 5 μm or less. In some embodiments suitable for nasal delivery, less than about 5% of the particles are about 5 μm or less. In some embodiments suitable for nasal delivery, less than about 5% of the particles are about 5 μm or less.

*Ocular compositions*

The macromolecule of the invention may be delivered in any composition suitable for application to the eye, for example, solutions, ointments, gels, lotions, in slow release polymers or coated, on bound to or impregnated in contact lenses. In an embodiment, the composition can be delivered to the eye in eye drops. In an embodiment, the composition can be delivered to the eye in a spray

By "suitable for application to the eye" is meant that any component of the composition does not cause a long-lasting deleterious effect on the eye or the subject being treated. Transient effects such as minor irritation or "stinging" upon administration may occur without long-lasting deleterious effect. The macromolecule may be formulated as a simple aqueous solution. Alternatively, the macromolecule may be formulated to have one or more of physiologically compatible osmolality and pH, for example, by including salts and buffering agents, and other components such as preservatives, gelling agents, viscosity control agents, ophthalmic lubricating agents, mucoadhesive polymers, surfactants, antioxidants and the like in a solution, gel, lotion or ointment.

The macromolecules of the present invention are retained on or in the epithelium for a period of time, allowing the macromolecule to diffuse out of epithelium. Such diffusion provides slow release of drug into the ocular environment, enabling the anti-viral activity of the macromolecule to be delivered over a period and not be quickly washed away by the ocular fluids and physical cleansing. The macromolecule may be released from the epithelium over a period of greater than 10 minutes, more especially over a period greater than 1 hour, and more especially over a period of more than 6 hours.

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In some embodiment, the invention provides a composition comprising a macromolecule as described herein and at least one pharmaceutically acceptable carrier that provides a pH and osmolality compatible with the eye.

Suitable ophthalmically acceptable salts that may be used as osmolality agents include salts having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite ions. Examples of suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfate and ammonium sulfate.

Suitable ophthalmically acceptable pH adjusting agents and/or buffering agents include acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids, bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and trishydroxymethylaminomethane, and buffers such as citrate-dextrose, sodium bicarbonate and ammonium chloride.

Suitable preservatives include stabilized ammonium compounds such as benzalkonium chloride, cetyhrimethylammonium chloride and cetylpyridinium chloride, mucuric compounds such as phenyl mercuric acetate, imidazolidinyl urea, parabens such as methyl paraben, ethyl parnben, propyl paraben or butyl paraben; phenoxyethanol, chlorophenoxyethanol, phenoxypropanol, chlorobutanol, chlorocresol, phenylethyl alcohol, ethylenediamine tetraacetic acid, sorbic acid and salts thereof.

Suitable gelling agents or viscosity control agents include gelling agents that increase viscosity when they come into contact with lacrimal fluid, for example, lacrimation caused by blinking or tears. Such gelling agents may he used to reduce loss of the macromolecule by lacrimal drainage and allow the macromolecule to have increased residence time and therefore absorption in the eye or epithelial layer of the eyelids. Suitable gelling agents include gellan gum, especially low acetylated gellan gum, alginate gum or chitosan. The viscosity adjusting agent may also include a film-frmning polymer such as an alkylcellulose such as methyl cellulose or ethylcellulose, a hydroxyalkylcellulose such as hydroxyethyl cellulose or hydroxypropyl methylcellulose, hyaluronic acid or its salts, chondroitin sulfate or its salts, polydextrose, cyclodexirin, polydextrin, maltodextrin, dextrin, gelatine, collagen, polygalacturonic acid derivatives such as pectin, natural gums such as xanthan, locust

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bean, acacia, trngacanth and carageenan, agar, polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, polymers of acrylamide, acrylic acid and polycyano acryiates and polymers of methylmethacrylate and 2-hydroxy-ethyl methacrylate. The viscosity control agent or gelling agent may be present in an amount of 0.1 % to about 6.5%, w/w of the composition, especially about 0.5% to 4.5% w/w of the composition.

Suitable lubricating agents include polyvinyl alcohol, methyl cellulose, hydroxypropyl methylcellulose and polyviny lpytrnlidone.

Suitable mucoadhesive polymers include hydroxypropyl methylcellulose, carboxymethylcellulose, poly(methylmethacrylate), polyacrylamide, polycarbophil, polyethylene oxide, sodium alginate and dextrin.

Suitable ophthalmically acceptable surfactants include non-10mc surfactants such as polyoxyethylene fatty acid glycerides and vegetable oils including polyoxyethylene (60) hydrogenated castor oil, polyoxyethylene alkylethers and alkylphenyl ethers such as octoxynol 10 and octoxynol 40.

Suitable antioxidants include ascorbic acid and sodium metabisulfate.

Ophthalmic ointments may also include one or more of thickeners such as liquid paraffin, yellow soft paraffin, hard paraffin, and/or wool fat.

In an embodiment, the ocular compositions as described herein are suitable for treating and or preventing a RSV infection. In an embodiment, the ocular compositions are described herein are suitable for preventing, reducing or sequestering RSV viral shedding in an individual with a RSV infection.

While it is possible that the composition of the invention may be formulated with carriers, diluents and excipients commonly used in the art as discussed above in topical eye compositions, it is well known that a number of commonly used preservatives have drawbacks when used in topical eye compositions. For example, some preservatives cause eye irritation and if used for long term therapy, they may cause damage to the eye. Furthermore, some preservatives are not effective against some strains of bacteria causing spoilage of the compositions. Parabens are generally regarded as unsuitable for ophthalmic compositions because of their irritant nature. In some cases eye drop compositions are formulated without preservative to reduce

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irritancy. However, such compositions must be packaged for single use or refrigerated once they are opened.

In some embodiments, the ocular composition as described herein consists of an aqueous solution of the macromolecule together with at least one pharmaceutically acceptable excipient, wherein the at least one excipient provides a pH of 7.0 to 7.6 and osmolality of 240 to 310 mOsm/kg, especially an osmolality that is isotonic with tears. In other embodiments, the composition comprises an aqueous solution of the macromolecule together with at least one pharmaceutically acceptable excipient, wherein the at least one excipient provides a pH of 7.0 to 7.5 and osmolality of 240 to 310 mOsm/kg but preservatives other than the macromolecule is excluded.

*Other compositions*

In an embodiment, the compositions as described herein are suitable for dermal administration and may be formulated in an aqueous, gel or cream composition.

In an embodiment, the compositions as described herein are suitable for use as a surface spray, wash or wipe, including hand wash, surgical field preparation.

In an embodiment, the compositions as described here are imbedded in, or applied, or conjugated to personal protective equipment (PPE), for example a mask, glove or surgical gown or filters for masks.

In some embodiments, the macromolecules as described herein are formulated in a composition suitable for parenteral delivery. For example, for intravenous delivery, the composition may be an aqueous composition, for example ringers, saline, water or dextrose solution, or may be diluted in 0.9% saline or 5% dextrose for use.

In some embodiments, the compositions are formulated as a lozenge or a throat gargle. Lozenge compositions are described for example in Umashankar et al (2016) and Vera et al (2014).

The compositions as described herein may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated; each unit containing a predetermined

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quantity of active ingredient calculated to produce the desired prophylactic or therapeutic effect in association with the required pharmaceutical carrier and/or diluent.

All methods include the step of bringing the macromolecule into association with a carrier that constitutes one or more accessory ingredients. In general, the compositions may be prepared by bringing the macromolecule into association with a liquid carrier to form a solution or a suspension. Such dosage forms are contemplated to be administered as an over a period of time (e.g., for an inhaled dose from about a few seconds to about 2-6 hours, for a parenteral dose, from a few seconds for a bolus, to 24 hours for an infusion).

Effective amount

The methods of the present disclosure require administration of an effective amount of macromolecule, or of compositions comprising the macromolecule. An "effective amount" means an amount necessary to at least partially attain the desired response, or to delay the onset of, inhibit the progression of or halt altogether infection. An effective amount for a human patient may, for example, fall within the range of about 0.5 mg to about 5 mg. An effect amount for a human patient may, for example, fall within the range of about 0.5 mg to about 5 mg per actuation per nostril.

In some embodiments, the effective amount is in the range of about 0.04 mg to about 1g, about 10mg to about 500mg, about 10mg to about 100mg, or about 100mg to about 500mg. In some embodiments, the effective amount is in the range of about 0.5 to 5 mg. In some embodiments, the effective amount is in the range of about 0.5 to 1.5mg. In some embodiments, the effective amount is about 1 mg. In some embodiments, the effective amount is about 0.5mg.

In some embodiments, the effective amount is in the range of about 0.1 mg to about $1g/m^2$, about 1 mg to about $100mg/m^2$, about 10 mg to about $100mg/m^2$, or about 10 mg to about $500g/m^2$.

In some embodiments, the macromolecule is delivered at 0.1 to 10mg/kg/daily. In another embodiment, the macromolecule is delivered at 1 to 10 mg/kg daily. In another embodiment, the macromolecule is delivered at 0.1 to 1 mg/kg daily.

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In some embodiments, the macromolecule is delivered via an infusion of 0.01 to 5g/day. In another embodiment, the macromolecule is delivered via an infusion of 0.1 to 2g/day. In some embodiments, the macromolecule is delivered via an infusion of 1 to 2g/day. In some embodiments, the macromolecule is delivered via an infusion of 0.5 to 1g/day.

In some embodiments, the composition containing the macromolecule is formulated to contain an amount of macromolecule effective to establish an *in vivo* concentration of macromolecule in the range of from about 0.050 to about 25 μM. An *in vivo* concentration is a blood plasma concentration or a lung fluid concentration, or a tissue concentration such as a lung tissue concentration. In some embodiments, the composition containing the macromolecule is formulated to contain an amount of macromolecule effective to establish an *in vivo* concentration of macromolecule of about 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, or about 15μM. In some embodiments, the composition containing the macromolecule is formulated to contain an amount of macromolecule effective to establish an *in vivo* concentration of macromolecule of at least 0.5 μM, at least 0.75 μM, at least 1 μM, or at least 2 μM. Each such value may be combined to form a range with an upper value of about 20 μM, about 17 μM or about 15 μM. In some embodiments, the composition containing the macromolecule is formulated to contain an amount of macromolecule effective to establish an *in vivo* concentration of macromolecule in the range of from about 0.1 to about 100μM, from about 0.5 to about 50μM, or from about 1 to about 25μM.

In some embodiments, a single dose of 10 to 50 mg/kg would achieve an effective concentration. In another embodiment, a single dose of 20 to 40 mg/kg would achieve an effective concentration. In another embodiment, a single dose of 30 mg/kg would achieve an effective concentration.

Typically, when infused, the macromolecule will be infused at a rate so as to establish and/or maintain an *in vivo* concentration of macromolecule which is greater than the $EC_{50}$, preferably greater than the $EC_{90}$, and which avoids undue side effects.

In some embodiments, the macromolecule is infused at a rate so as to establish and/or maintain an *in vivo* concentration of macromolecule of at least 0.08μM, at least 0.9, at least 0.75 μM, at least 1 μM, at least 2 μM, at least 3 μM, at least 4 μM, at least

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5 μM, at least 10 μM, or at least 20 μM. In some embodiments, the macromolecule is infused at a rate so as to establish and/or maintain an *in vivo* concentration of macromolecule of at least 0.001mg/ml, at least 0.005mg/ml, at least 0.01mg/ml, at least 0.02 mg/ml, at least 0.03 mg/ml, at least 0.04 mg/ml, at least 0.05 mg/ml, at least 0.1 mg/ml, at least 0.2 mg/ml, at least 0.3 mg/ml.

In some embodiments, the macromolecule is infused at a rate so as to establish and/or maintain an *in vivo* concentration of macromolecule in the range of from about 0.01 to about 100μM, from about 0.5 to about 50 μM, from about 1 to about 50 μM, from about 2 to about 50 μM, from about 5 to about 50 μM or from about 10 to about 50 μM.

In some embodiments, the macromolecule is infused at a rate so as to establish and/or maintain an *in vivo* concentration of macromolecule in the range of from about 0.001mg/ml to about 2mg/ml, from about 0.01mg/ml to about 1mg/ml, or from about 0.05 to about 0.5mg/ml.

In some embodiments, in order to establish and/or maintain the *in vivo* concentration of macromolecule at a desired concentration, the macromolecule is infused at a desired rate. For example, if targeting a concentration of about 400 mg/L, the infusion rate may in some embodiments be in the range of from about 500 to about 3000mg/hr, from about 1000 to about 2000 mg/hr, or from about 1500 to about 1600 mg/hr (e.g. 1584 mg/hr) (e.g.400mg/L x 3.96 L/hr). For example, if targeting a concentration of about 200 mg/L, the infusion rate may in some embodiments be in the range of from about 250 to about 1500mg/hr, from about 500 to about 1000 mg/hr, or from about 750 to about 800 mg/hr (e.g. 792 mg/hr) (e.g.200mg/L x 3.96 L/hr).

In some embodiments, the effective amount is formulated at about 0.1% to about 10%w/w, or about 0.5% to about 10%,w/w or about 0.5% to 5%w/w, or about 0.5% to 3%w/w, or about 1% to 3% w/w of macromolecule. In some embodiments, the effective amount is formulated at about 0.5%w/w, at about 1%w/w, at about 2%w/w, at about 3%w/w, at about 4%w/w or about 5% w/w macromolecule. In some embodiments, the composition comprises about 0.5 mg/ml, or about 1 mg/ml, or about 2 mg/ml, or about 2.5 mg/mL, or about 5mg/ml, or about 10mg/ml, about 20mg/ml, about 30 mg/ml macromolecule.

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In some embodiments, the composition is administered in a volume of about 0.1 to about 50 ml, about 0.2 ml to about 1 ml, about 1 to about 25 ml, about 0.025 ml to 0.2 ml, or about 5 ml. In some embodiments, the composition is administered in a volume of about 0.025 ml, 0.05 ml, 0.1 ml or about 0.2 ml.

When used in a delivery system the amount of antiviral composition included in the delivery system according to the present disclosure may for example be from about 0.10 g to about 2 g, or from about 0.1 g to about 0.5 g, or from about 0.1 g to about 0.25 g.

In some embodiments, when the composition is for nasal delivery the dose may administered in two actuations (sprays), one in each nostril. In some embodiments, when the composition is for nasal delivery the dose may administered in a volume of about 5 μL to about 200μL, about 5 μL to about 150μL, about 5 μL to about 100 μL, 5 μL to about 80 μL, 5 μL to about 70 μL, 5 μL to about 50 μL, 5 μL to about 40 μL, 5 μL to about 30 μL, or about 5 μL to about 10μL per nostril. In a preferred embodiment, the dose is administered in a volume of about 100 μL per nostril. The macromolecule may be administered on a dosage regimen that provides the desired effect. For example, the dosage, macromolecule, or composition, may be administered from 1 to 8 times per day, from 1 to 6 times per day, from 1 to 5 times per day, from 1 to 4 times per day, from 1 to 3 times per day or once daily. In an embodiment, the dosage, macromolecule or composition may be administered from 1 to 4 times per day. In an embodiment, the macromolecule, or composition is administered to each nostril (e.g. 4 times a day includes 4 times a day in each nostril). In some embodiments, the dosage, composition or macromolecule is administered for about 1 to 2 weeks, about 1 month, about 3 months or about 6 months. In some embodiments, the dosage, composition or macromolecule is administered, once per day, 4 times per day, 6 times per day, or 8 times per day. In an embodiment, the dosage, macromolecule or composition may be administered up to 4 times per day. In an embodiment, the dosage, macromolecule or composition may be administered up to 8 times per day. In some embodiments, the dosage, composition or macromolecule is administered for up to 10 consecutive days. In some embodiments, the dosage, composition or macromolecule is administered for

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up to 20 consecutive days. In some embodiments, the dosage, composition or macromolecule is administered for up to 30 consecutive days.

Delivery devices

Also described herein is a device for delivering a nasal, oral or pulmonary composition comprising a macromolecule as described herein. The devices as described herein can deliver the macromolecule to the upper and/or lower respiratory tract. In an embodiment, the device can deliver the macromolecule to the nasal cavity. In an embodiment, the device can deliver one or more doses. In an embodiment, the device is reusable.

In some embodiments, of the device as described herein comprises a composition as described herein.

In an embodiment, the device is a nasal delivery device. In an embodiment, the device is an oral delivery device. In an embodiment, the nasal delivery device is selected from a spray, inhaler, nebulizer or nasal wash.

In one embodiment, the device is a nasal spray. In an embodiment, the nasal spray is a pump spray. Such pumps can comprise an actuating means. In an embodiment, the nasal spray as described herein is a displacement pump. In an embodiment, the he pump is actuated by pressing the actuating means towards the bottle, a piston moves downward in the metering chamber. A valve mechanism at the bottom of the metering chamber will prevent backflow into the dip tube. So the downward movement of the piston will create pressure within the metering chamber which forces the air (before priming) or the liquid outwards through the actuator and generates the spray. When the actuation pressure is removed, a spring will force the piston and actuator to return to its initial position. The metering chamber ensures the right dosing and an open swirling chamber in the tip of the actuator will aerosolize the metered dose. In these pumps no measures are taken to prevent microbial contamination when in use, thus the composition often will contain preservatives, in most cases benzalkonium chloride (BAC) or parabens. In some embodiments, the device uses silver as a preservative. In an embodiment, the device uses a silver wire in the tip of the actuator, a silver coated spring and ball. Such systems are able to keep

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microorganisms from contaminating the composition between long dosing intervals. Another approach is to use tip seal technology to prevent backflow into the device. In some embodiments, the total volume expelled by each actuation of the device is about 25 to about 200 µL per actuation. In some embodiments, the volume expelled by each actuation is about 50 to about 150 µL per actuation. In one embodiment, the volume expelled by each actuation is about 150 µL per actuation. In one embodiment, the volume expelled by each actuation is about 100 µl per actuation. In one embodiment, the volume expelled by each actuation is about 50 µl per actuation.

In some embodiments, each actuation produces an average particle size of about 10 to about 200 µm. In some embodiments, each actuation produces an average particle size of about 20 to about 180 µm. In some embodiments, each actuation produces an average particle size of about 40 to about 160 µm. In some embodiments, each actuation produces an average particle size of about 60 to about 110 µm.

In some embodiments, the particle size is measured at a velocity of actuation of about 60 mm/s to about 110 mm/s. In some embodiments, the particle size is measured at a velocity of actuation of about 60 mm/s to about 90 mm/s. In some embodiments, the particle size is measured at a velocity of actuation of about 60 mm/s to about 80 mm/s. In some embodiments, the particle size is measured at a velocity of actuation of about 60 mm/s. In some embodiments, the particle size is measured at a velocity of actuation of about 80 mm/s. In some embodiments, the particle size is measured at a distance of about 30 mm to about 80 mm from dispersion point to the vertical laser path. In some embodiments, the particle size is measured at a distance of about 40 mm to about 80 mm. In some embodiment, the particle size is measured at a distance of about 50 mm to about 70 mm. In some embodiment, the particle size is measured at a distance of about 55 mm to about 65 mm. In some embodiments, particle size is measured using actuation of 60mm/s and a distance of 40 to 70mm.

In some embodiments, each actuation produces a droplet size distribution Dv10 of at least 10µm (i.e. 10% of particles have a diameter smaller than 10µm), or at least 15µum (i.e. 10% of particles have a diameter smaller than 15µm) at a distance of 40 to 70nm and 60mm/s actuation velocity. In some embodiments, each actuation produces a droplet size distribution Dv50 (median value) of at least 50 µm or at least 70µm, at a

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distance of 40 to 70nm and 60mm/s actuation velocity. In some embodiments, each actuation produces less than 5% or less than 10% of particles of less than 10 μm.

In some embodiments, the distance is measured from the actuation means. In some embodiments, the distance is measured from the dispensing opening in the actuating means.

In an embodiment, the device is an oral delivery device. A person skilled in the art will appreciated that the oral delivery device may be a pulmonary oral delivery device, for example as described in Ibrahim et al (2015) or Chandel et al (2019). In an embodiment, the oral delivery device is selected from a spray, inhaler, nebulizer or oral wash. In an embodiment, the device can deliver one or more doses. In an embodiment, the device is reusable. In an embodiment, the spray is a multi-dose spray.

In an embodiment, the oral device is an oral spray. In an embodiment, the oral spray is a pump spray.

In an embodiment, the device is an inhaler. In an embodiment, the inhaler is a metered-dose inhaler. In an embodiment, the inhaler is a multi-dose inhaler. In an embodiment, the inhaler is a dry powder inhaler. Examples of inhalers can be found in Chandel et al (2019).

In some embodiments, the total volume expelled by each actuation of the inhaler is about 5 to about 150 μL per actuation. In some embodiments, the total volume expelled by each actuation of the inhaler is about 10 to about 110 μL per actuation. In one embodiment, the total volume expelled by each actuation of the inhaler is about 20 μL to about 100 μL per actuation. In one embodiment, the total volume expelled by each actuation of the inhaler is about 100 μL per actuation. In one embodiment, the total volume expelled by each actuation of the inhaler is about 40 μL to about 80 μL per actuation.

In an embodiment, each inhaler actuation produces an average particle size of about 0.01 to about 7 μm. In an embodiment, each nebuliser actuation produces an average particle size of about 0.01 to about 5 μm. In an embodiment, each nebuliser actuation produces an average particle size of about 0.5 to about 5 μm. In an embodiment, each nebuliser actuation produces an average particle size of about 1 to

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about 5 μm. In an embodiment, each nebuliser actuation produces an average particle size of about 2 to about 4 μm.

In an embodiment, the nebuliser is a jet nebuliser. In an embodiment the nebuliser is an ultrasonic nebuliser. In an embodiment, the nebuliser is a vibrating mesh nebuliser. In an embodiment, the nebuliser is a breath actuated nebuliser. In an embodiment the nebuliser is a breath enhanced nebuliser. In an embodiment, the nebuliser is selected from a: Spiriva Respimat®, the AERx® Pulmonary Drug Delivery System, AeroEclipse® II BAN (Monaghan Medical Corporation), CompAIR™ NE-C801 (OMRON Healthcare Europe BV), I-neb AAD System (Koninklijke Philips NV), Micro Air® NE-U22 (OMRON Healthcare Europe BV), PARI LC® Plus (PARI international), PARI eFlow® rapid (PARI international) and a AKITA® Inhalation System (Activaero)

In some embodiments, the total volume delivered by the nebuliser is about 5 to about 150 μL per actuation. In some embodiments, the total volume delivered is about 10 to about 110 μL per actuation. In one embodiment, the total volume delivered is about 20 μL to about 100 μL per actuation. In one embodiment, the total volume delivered is about 100 μL per actuation. In one embodiment, the total volume delivered is about 40 μL to about 80 μL per actuation.

In an embodiment, the nebuliser produces an average particle size of about 0.01 to about 7 μm. In an embodiment, the nebuliser produces an average particle size of about 0.01 to about 5 μm. In an embodiment, the nebuliser produces an average particle size of about 0.5 to about 5 μm. In an embodiment, the nebuliser produces an average particle size of about 1 to about 5 μm. In an embodiment, the nebuliser produces an average particle size of about 2 to about 4 μm.

*Nasal sprays*

In some embodiments, the macromolecule or composition as described herein is delivered to the nasal cavity and/or nasal mucosa via a nasal spray device. Nasal spray devices of the present invention comprise compositions of the present invention. Actuation of a nasal spray device as described herein comprising a composition as

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described herein delivers a moisturising protective barrier to the nasal mucous that helps keep the nasal mucous moist and acts as a physical barrier to respiratory viruses.

In an embodiment, compositions as described herein are packaged in a container–closure system comprising an integral spray pump unit that upon activation delivers an accurately metered amount of the composition as a spray. In an embodiment, dispersion as a spray is accomplished by forcing the composition through the nasal actuator and its orifice.

In this embodiment, the container holds about 1 mL to about 50 mL of composition. In this embodiment, the container holds about 4 mL to about 40 mL of composition. In this embodiment, the container holds about 8 mL to about 25 mL of composition. In this embodiment, the container holds about 10 mL to about 20 mL of composition. In this embodiment, the container holds about 10 mL to about 15 mL of composition. In this embodiment, the container holds about 10 mL of composition. In an embodiment, the device is a multi-dose nasal spray device.

In an embodiment, the nasal spray device comprises about 20 to about 120 sprays of the composition . In an embodiment, the nasal spray device comprises about 40 to about 100 sprays of the composition. In an embodiment, the nasal spray device comprises about 60 to about 80 sprays of the composition. In an embodiment, the spray comprises about 80 sprays of the composition. In a preferred embodiment, the metered amount of the composition is about 100 µL.

The nonsterile, pre-filled nasal spray device consists of SPL7013 formulated into a mucoadhesive formulation, containing a small amount of preservative, that adheres at least to the nasal turbinates, nasopharynx, and/or oropharynx. The mucoadhesive composition adheres in the nasal cavity where respiratory viruses that cause colds, flu, and more severe respiratory illness, first attach and start to multiply. As shown in the experiments described herein SPL7013 has antiviral activities against RSV and thus can act as a physical barrier to respiratory viruses such as RSV helping to reduce exposure to respiratory viral pathogens and reducing viral infection load. Reducing infectious viral load may help prevent acquisition or transmission of infection. Due to its physical size and negative charge, SPL7013 is not absorbed into

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the bloodstream following topical nasal application. The inactivated viruses are eliminated naturally through the nasal mucus.

In an embodiment, the nasal spray device comprises a composition comprising a formulation as described herein. In an embodiment, the formulation is Variant 1 as described herein. In an embodiment, the formulation is Variant 2 as described herein. In an embodiment, the formulation is Variant 3 as described herein. In an embodiment, the formulation is Variant 4 as described herein. In an embodiment, the formulation is Variant 5 as described herein.

In an embodiment, the nasal spray device as described herein, comprising a composition as described herein, delivers a nasal moisture barrier dressing upon actuation. As used herein, a "nasal moisture barrier dressing" refers to a substance applied to the nasal passages (nares) to provide a protective moisture barrier to the external environment and to hydrate and soothe the nasal mucosa. In an embodiment, the nasal moisture barrier dressing has a Global Medical Device Nomenclature code 47679.

In an embodiment, the nasal moisture barrier dressing as described herein comprises one or more of the following features: i) moisturises the nasal mucosa, ii) inactivates an RSV, iii) reduces the viral load of an RSV.

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Co-administration

Whilst in some embodiments of the present disclosure, the macromolecules or salts thereof may be the sole active ingredients used, in other embodiments the macromolecule is used are used in combination with one or more further active ingredients, e.g. a further active agent for preventing, treating or reducing the likelihood of infection with a virus. In one embodiment, the virus can infect individuals via the respiratory tract. In one embodiment, the virus can infect individuals via the respiratory tract is selected from: coronavirus, rhinovirus, respiratory syncytial virus, influenza virus, syncytial virus, parainfluenza, adenovirus, metapneumovirus and enterovirus. In one embodiment, the virus is a RSV.

In an embodiment, the active agent is selected from one or more of: an antiviral active agent, a vaccine, an immunomodulator, a bronchodilator, an antibacterial agent,

neuraminidase inhibitors, cap-dependent endonuclease inhibitors, adamantanes, anti-coagulants, drugs boosting platelet formation, angiotensin-converting enzyme inhibitors, vitamins, convalescent plasma therapy and/or an anti-inflammatory agent.

As used herein the term "antiviral active agent" refers to a compound that is directly or indirectly effective in specifically interfering with at least one viral action selected from one or more of: virus penetration of a eukaryotic cell, virus replication in a eukaryotic cell, virus assembly, virus release from infected eukaryotic cells, or that is effective in unspecifically inhibiting virus titre increase or in unspecifically reducing a virus titre level in a eukaryotic or mammalian host system. It also refers to an agent that prevents or reduces the likelihood of getting a viral infection.

In an embodiment, the antiviral agent is selected from an antiviral agent described in Gordon et al., 2020 or Ghareeb et al (2021). In an embodiment, the antiviral active agent is selected from one or more of: carrageenan, GM-CSF, IL-6R, CCR5, S protein of MERS, and drugs including, ribavirin, tilorone, favipiravir, Kaletra (lopinavir/ritonavir), Prezcobix (darunavir/cobicistat), nelfinavir, mycophenolic acid, Galidesivir, Actemra, OYA1, BPI-002, Ifenprodil, APN01, EIDD-2801, baricitinib, camostat mesylate, lycorine, Brilacidin, BX-25, amostat, umifenovir, lopinavir, ritonavir, pleconaril, and favipiravir, an interferon ( e.g. IFNβ), antimalarial chloroquine combined and the antibiotic azithromycin.

In an embodiment, the anti-inflammatory agent is selected from one or more of: indomethacin, tocilizumab, JAK inhibitors and ruxolitinib

In an embodiment, the active agent is selected from one or more of: acetaminophen, motavizumab, albuterol, epinephrine, ribavirin and palivizumab.

Examples of carrageenan are described for example in CA2696009. In one embodiment, the carrageenan is selected from an iota-carrageenan, kappa-carrageenan and a lambda-carrageenan. In one embodiment, the carrageenan is an iota-carrageenan.

In an embodiment, the active agent reduces the symptoms of one or more RSVs. In an embodiment, when the virus is an RSV the active agent is selected from one or more of: acetaminophen, motavizumab, albuterol, epinephrine, ribavirin and palivizumab.

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In one embodiment, the antibacterial agent is an antibiotic. In an embodiment, the antibiotic is a broad-spectrum antibiotic.

In one embodiment, the immunomodulator is an immunosuppressant, a cytokine inhibitor, an antibody, or an immunostimulant. The immunomodulator may suppress inflammation of airways.

The macromolecules or salts thereof may also be used in combination with nonsteroidal anti-inflammatory drug (NSAID). For example, the NSAID may be used to treat the symptoms of an RSV infection, whilst the macromolecule or salt thereof may be used to prevent transmission of the virus to another individual.

The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however, that the description following is illustrative only and should not be taken in any way as a restriction on the generality of the invention described above.

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**Examples**

**Example 8: Evaluation of antiviral properties of SPL7013 against respiratory syncytial virus (RSV)**

The concentrations of the Test Product were prepared using approximately 1:3 dilutions from the starting concentration determined following the cytotoxicity test.

The host cell culture was washed with PBS, and 1.0 mL aliquots of test product dilutions added to the cells. Cells were then incubated for 1 hour ± 15 minutes for equilibration. After the incubation, 1.0 mL aliquots of virus was added to the wells and incubated for 1 hour ± 15 minutes for virus adsorption. Following incubation, the mixture was removed and replaced with TM. The plates were then incubated in a $CO_2$ incubator. The plates were incubated until viral plaques in the virus control could be microscopically registered (approximately 5-10 days).

For the cytotoxicity control, the host cell culture was washed with PBS. The cells were then overlaid with 1.0 mL of the highest non-toxic test product concentration and incubated for 1 hour ± 15 minutes for equilibration. After the incubation, 1.0 µl aliquots of MM (mock infection) was added to the wells and incubated for 1 hour ± 15

minutes. Following incubation, the mixture was removed and replaced with TM. The plates were then incubated in a $CO_2$ incubator.

For the virus control, the host cell culture was washed with PBS, and 1.0 mL aliquots of MM (in place of test product) were added to the wells designated for virus control and incubated for 1 hour ± 15 minutes for equilibration. After the incubation was complete, 1.0 mL aliquots of virus were added to the wells and incubated for 1 hour ± 15 minutes for virus adsorption. Following incubation, virus was removed and replaced with TM. The plates were incubated in a $CO_2$ incubator.

Intact cell culture monolayers were used as the control of cell viability. The GM was replaced by TM in the cell culture control wells.

Following incubation, fixation and staining was performed by removing the TM, washing the plates with PBS and fixed using 4% formaldehyde solution for 4 to 6 hours. Fixed cells were stained using Crystal Violet stain. Unstained zones of cell lysis (viral plaques) were counted.

*Antiviral post-treatment test – determination of product cytotoxicity:* The highest non-cytotoxic concentration of the test product was determined. The host cell culture was washed with PBS. 1.0 mL aliquots of the test product were added to the cells and incubated in a $CO_2$ incubator for 24 hours ± 1 hour at 37 °C ± 2 °C. Toxicity was evaluated using CCK-8 assay and read with a VERSAmax™ Tunable Microplate Reader at 450nm. The concentrations used for antiviral test were determined in the cytotoxicity test. Results are presented as percent of cell viability where 100% cell viability is approximately equal to the mean of the cell control. The TC50 concentration of the test product were determined using GraphPad Prism 5.0 statistical software. The antiviral post-treatment test included the procedures outlined in Table 11.

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**Table 11. Antiviral post-treatment test parameters.**

| Parameter | Summary | Replicates |
|---|---|---|
| Test | Infection of cells with ≤ 100 PFU/mL virus →Inoculation of Product Dilutions → Incubation → Fixation → Staining | 2 |
| Cytotoxicity Control | Inoculation of a Product onto cells → Incubation → Fixation → Staining → Visual assessment | 2 |
| Virus Control | Infection of cells with a virus → Incubation → Fixation → Staining → Counting of Plaques | 2 |
| Cell Culture Control | Maintenance medium → Incubation → Fixation → Staining → Visual assessment | 2 |

The concentrations of the test product were prepared using approximately 1:3 dilutions from the starting concentration determined following the cytotoxicity test.

The host cell culture was washed with PBS, and 1.0 mL aliquots of virus added to the wells and incubated for 1 hour ± 15 minutes for virus adsorption. After incubation, virus inoculum was removed and replaced with aliquots of the test product concentrations in TM. The plates were then incubated in a $CO_2$ incubator. The plates were then incubated until viral plaques in the virus control can be microscopically registered (approximately 5-10 days).

For the cytotoxicity control, the host cell culture was washed with PBS. The cells were then overlaid with the highest non-toxic test product concentration in TM and incubated in a $CO_2$ incubator.

For the virus control, the host cell culture was washed with PBS. 1.0 mL aliquots of ≤ 100 PFU/mL virus will be added to the wells and incubated for 1 hour ± 15 minutes for virus adsorption. After incubation, virus inoculum was removed and replaced with aliquots of TM. The plates were incubated in a $CO_2$ incubator.

For the cell culture control, intact cell culture monolayers were used as the control of cell viability. The GM was replaced by TM in the cell culture control wells.

Following incubation, fixing and staining was performed by removing the TM, washing with PBS and fixed using 4% formaldehyde solution for 4 to 6 hours. Fixed cells were stained using Crystal Violet stain. Unstained zones of cell lysis (viral plaques) were counted.

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*Assessment of antiviral properties:* The antiviral properties EC50 and/or EC90 was determined using non-linear regression analysis, GraphPad Prism 5.0 software.

*Antiviral test acceptance criteria:* A valid test as described in the Example requires that: 1) The plaques in test and control samples are countable; 2) no significant cytotoxic effect is present in cytotoxicity control; 3) cell control wells are viable and attached to the bottom of the well; 4) that the medium is free of contamination in all wells of the plate.

Results:

Results are summarized in Table 12 and Figure 2.

**Table 12. Summary of results of antiviral screening of SPL7013.**

| Virus Designation | Product Application | EC50, mg/mL | | EC90, mg/mL | | TC50, mg/mL | | Selectivity Index TC50/EC50 |
|---|---|---|---|---|---|---|---|---|
| | | Best Fit Value | 95% CI | Best Fit Value | 95% CI | Best Fit Value | 95% CI | |
| Human Respiratory Syncytial Virus | Pre-Treatment | 0.045 | 0.038 to 0.053 | 0.180 | 0.125 to 0.258 | 35.64 | 34.02 to 37.34 | 792 |
| | Post Treatment | 0.107 | 0.064 to 0.181 | 1.159 | 0.368 to 3.649 | 30.90 | 28.69 to 33.28 | 289 |

EC = Effective Concentration; TC = Toxic Concentration; CI = Confidence Interval.

**Example 9: SPL7013 nasal spray**

An embodiment of the device as described herein is a nasal spray. An embodiment of the nasal spray is provided in this example and referred to as the "SPL7013 Nasal Spray". The SPL7013 Nasal Spray comprises an aqueous nasal composition containing SPL7013, referred to as the "SPL7013 Nasal Spray Composition". SPL7013 is intended to inactivate viruses, including RSV, and to reduce exposure to viral load. Reducing viral load can reduce acquisition or transmission of infection. The SPL7013 Nasal Spray, when comprising the SPL7013 Nasal Spray

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Composition, produces droplets sizes suitable for administration and delivery to the nasal cavity with less than 5% of droplets being 10 µM or less (particles of 10 µM are more suitable for delivery to the lungs).

Actuations from the SPL7013 Nasal Spray, comprising the SPL7013 Nasal Spray composition, produces a moisturising and protective mucoadhesive barrier for the nasal mucosa that can be used to inactivate and act as a barrier to respiratory viruses.

The SPL7013 Nasal Spray Composition comprises SPL7013 and a viscosity modifying mucoadhesive substance. The SPL7013 Nasal Spray Composition is as described in "Variant 4" listed in Table 14 or "Variant 5" shown below in Table 13. Variant 5 is the Variant 4 formulation additionally pH adjusted with hydrochloric acid. The formulation comprises a carbomer homopolymer type B to achieve an appropriate viscosity, aid in the ease of administration, and facilitate retention of the product in the nasal cavity.

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**Table 13: SPL7013 Nasal Spray Formulation (variant 5).**

| Component | % w/w | Quantity 1% w/w (kg/ 100 kg batch) |
|---|---|---|
| Purified water | q.s 100% | 98.51* |
| Astrodrimer sodium (SPL7013) | 1.0 | 1.0* |
| Propylene glycol | 1.0 | 1.0 |
| Glycerol | 1.16 | 1.0 |
| Methylparaben | 0.18 | 0.18 |
| Carbomer 974P (Carbopol 974P) | 0.05 | 0.05 |
| Propylparaben | 0.02 | 0.02 |
| Edetate disodium dehydrate | 0.005 | 0.005 |
| Sodium hydroxide^ | Adjust pH to 6 | N/A |
| Hyrochloric acid^ | Adjust pH to 6 | N/A |

* The final amounts of SPL7013 and water are determined by the water content of SPL7013 at the time of manufacture.^ At a concentration of 0.1 N, prepared using purified water (EP).

The SPL7013 Nasal Spray is supplied as a 10 mL multi-dose, metered nasal spray device that delivers ~100 µL of SPL7013 Nasal Spray Composition per actuation. Other embodiments of the SPL7013 Nasal Spray may comprise a slightly smaller or larger volume or smaller or larger metered dose. The SPL7013 Nasal Spray Composition can be self-administered for up to 30 consecutive days by the user as

required, and/or up to 4 times daily (in each nostril), as needed, for inactivation of viruses and reduced exposure to viral load.

In reference to the Global Medical Device Nomenclature (GMDN), the term applicable to SPL7013 Nasal Spray is "nasal moisture barrier dressing" with GMDN code 47679. Given the physical nature of the mechanism of viral inactivation by SPL7013, and the physical mode of action of the device, the product is considered a Class I medical device under the European Medical Device Directive 93/42/EEC.

SPL7013 Nasal Spray, when comprising the SPL7013 Nasal Spray Composition, upon actuation provides i) a moisturising and protective mucoadhesive formulation which when applied to the nasal mucosa acts as a barrier to respiratory viruses; ii) inactivates viruses and reducing exposure to viral load; iii) as a result of i) and/or ii) reduces viral load. A reduction in viral load may help prevent acquisition or transmission of infection.

The acceptance criteria for the SPL7013 Nasal Spray composition is summarised below. Osmolality and pH of a Nasal Spray Composition are aligned to the physiological situation of <500 mOsmol with a pH of 5.5 – 6.5. The acceptance criteria for SPL7013 Nasal Spray for osmolality and pH are 200-400 mOsmol and 5.5-6.5, respectively. The SPL7013 Nasal Spray typically has a density of ~1 g/mL, suitable for retention in the nasal cavity. The release and expiry acceptance limit for Assay of SPL7013 is 0.80 – 1.20 % w/w. The acceptance criteria for methylparaben and propylparaben are 0.14% – 0.23% and 0.015% – 0.025%, respectively. Any microbial content in SPL7013 Nasal Spray is determined by a Microbial Limits Test, as per Ph. Eur. 2.6.12 Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests and Ph. Eur. 2.6.13 Microbial Examination of Non-Sterile Products: test for Specified Micro-Organisms. Both the total aerobic count and total yeasts and moulds present in the test material are determined using standard pour plate methodology. The specification for the microbial content follows the established limits described in Ph. Eur. 5.1.4 Microbiological Quality of Pharmaceutical Preparations. The specified organisms are based on Ph. Eur 5.1.4, Microbiological Quality of Non-Sterile Pharmaceutical Preparations and Substances for Pharmaceutical Use. .

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SPL7013 Nasal Spray is packaged as a non-pressurised, compact container–closure system. The container–closure system includes a delivery system (pump with actuator) that administers 100 µL of a spray of droplets of SPL7013 Nasal Spray Composition. The delivery device consists of a pump screwed onto a polyethylene (HDPE) bottle and , the dip tube, housing, gasket and stem of the pump are made from polyethylene polymers. The ball is made from stainless-steel 1.430 and is corrosion resistant. The liner is made of polyoxymethylene.

**Example 10: Biological evaluation of the SPL7013 nasal spray**

A comprehensive biological evaluation was conducted for the example SPL2013 Nasal Spray described in Example 9.

The SPL7013 Nasal Spray is a surface device which comes into contact with mucosal membranes (nasal), with prolonged exposure time (>24 hr to 30 days). In accordance with ISO 10993, tests for *in vitro* cytotoxicity (ISO 10993-5), nasal irritation following repeated administrations in the rat (ISO 10993-10) and skin sensitisation in a guinea pig model (ISO 10993-10) were conducted on SPL7013 Nasal Spray packaged in container-closure system described in Example 9.

*In vitro cytotoxicity:* The results of the *in vitro* cytotoxicity study demonstrated that at 5,000 µg/mL, SPL7013 Nasal Spray is not cytotoxic. In a nasal irritation study, rats were administered 100 µL of 1% SPL7013 Nasal Spray in each nostril, four times a day for 14 consecutive days. The results of the study from the in-life phase and the histopathological examinations showed no findings associated with the product and indicate that SPL7013 Nasal Spray is not an irritant.

*Skin sensitisation:* The skin sensitisation study consisted of a Guinea Pig Maximization Test (GMPT) according to Magnusson and Kligman (1969). The test demonstrated that 1% SPL7013 Nasal Spray is not a sensitiser.

*Nasal tolerance and PK:* SPL7013 Nasal Spray containing 1% or 3% SPL7013 was also administered nasally 4 times a day (50 µL per nostril) for 7 days to rats to test local toxicity as well as potential for systemic absorption of SPL7013. The study showed that repeated nasal administration of SPL7013 Nasal Spray was well-tolerated and did not cause any clinical signs of local or systemic toxicity. In addition, plasma

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samples were collected from animals in this study on Study Day 1 before first administration of product and at 15 min, 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr and 6 hr after first administration, and on Study Day 7 before the last administration of product for the day and at 15 min, 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr and 6 hr after last administration for the day. Bioanalysis of pooled plasma samples by capillary electrophoresis showed that SPL7013 was not detected at or above the lower limit of quantitation (LLOQ, 0.5µg/mL) of the assay in any samples from animals administered 1% or 3% SPL7013 Nasal Spray 4 times daily for 7 days, with the exception of one sample from animals in the 1% group, which showed a result just above the LLOQ (0.635µg/mL) for a 3 hr sample (data not shown). The data indicate that SPL7013 is not absorbed systemically following application to the nasal mucosa in rats following 4 times daily administration for 7 days, and the result for one sample in the lower dose group is an aberration.

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**Example 11: SPL7013 formulation and testing**

SPL7013 (astodrimer sodium) formulations were prepared as described in Table 14.

**Table 14. SPL7013 example formulations.**

| Component (%w/w) | Variant 1 | Variant 2 | Variant 3 | Variant 4 | Anticipated activity |
|---|---|---|---|---|---|
| SPL7013 | 1.00 | 1.00 | 1.00 | 1.00 | Active component, physically inactivates the virus |
| Water | 95.50 | 90.00 | 89.00 | 95.52 | Solvent (will vary depending upon pH adjustment) |
| Carbopol 974P | - | - | - | 0.05 | Rheology modifier, viscosity modifier and bio-adhesive |

| | | | | | |
|---|---|---|---|---|---|
| Hydroxypropylmethyl-cellulose | 0.10 | | | | Rheology modifier, viscosity modifier and bio-adhesive |
| Microcrystalline cellulose /carboxy methyl cellulose | | 2.00 | 2.00 | | Rheology modifier, viscosity modifier and bio-adhesive |
| Glycerin/glycerol | 1.00 or 1.16 | 1.00 | 2.30 | 1.00 or 1.16 | Humectant/aids solubility of parabens/tonicity adjustment |
| Propylene glycol | 1.00 | 1.00 | | 1.00 | Humectant/ aids solubility of parabens |
| Methyl paraben | 0.18 | 0.18 | | 0.18 | Preservative |
| Propyl paraben | 0.02 | 0.02 | | 0.02 | Preservative |
| Benzalkonium chloride | | | 0.05 | | Preservative |
| EDTA | 0.005 | 0.005 | 0.005 | 0.005 | Antioxidant/Chelator/ preservative |
| Sodium hydroxide | 1.20 | 1.20 | 1.20 | 1.20 | pH modifier, alkalizing agent |
| Check/adjust pH to | 6.0 | 6.0 | 6.0 | 6.0 | |

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Viscosity and Osmolality were measured within a few hours after preparation. Results are provided below in Table 15.

**Table 15. SPL7013 example formulation characteristics.**

| | **Variant 1** | **Variant 2** | **Variant 3** | **Variant 4** |
|---|---|---|---|---|
| Glycerin (%w/w) | 1.16 | 1.00 | 2.30 | 1.16 |
| Osmolality (mOsmol) | 295 | 283 | 344 | 280 |
| Viscosity (cP) | 2.66 | 107.1 | 110.7 | 1.78 |

To assess the suitability of the formulations for nasal delivery, the formulations were screened using three nasal aerosol pumps and the particle size measured at 30mm and 60mm as shown in Table 16.

**Table 16. SPL7013 example formulations droplet size distribution (DSD) testing.**

| Formulation | Dispenser 1 (100ul) | | | | |
|---|---|---|---|---|---|
| | **Distance** | **Dv10** | **Dv50** | **Dv90** | **%vol <10µm** |
| Variant 1 | 30mm | 20.76 | 66.46 | 155.10 | 2.655 |
| Variant 2 | 30mm | 18.61 | 59.51 | 126.10 | 3.208 |
| Variant 3 | 30mm | 18.62 | 58.93 | 130.50 | 3.334 |
| Variant 4 | 30mm | 14.51 | 42.84 | 97.69 | 5.304 |
| Variant 1 | 60mm | 23.93 | 57.71 | 136.20 | 2.23 |
| Variant 2 | 60mm | 21.40 | 51.70 | 112.40 | 2.73 |
| Variant 3 | 60mm | 20.97 | 47.49 | 100.10 | 3.21 |
| Variant 4 | 60mm | 16.75 | 42.04 | 92.32 | 4.31 |
| **Formulation** | **Dispenser 2 (100ul)** | | | | |
| | **Distance** | **Dv10** | **Dv50** | **Dv90** | **%vol <10µm** |
| Variant 1 | 30mm | 11.96 | 30.57 | 76.34 | 7.28 |
| Variant 2 | 30mm | 10.25 | 27.81 | 69.81 | 9.55 |
| Variant 3 | 30mm | 11.79 | 31.59 | 81.75 | 7.27 |
| Variant 4 | 30mm | 10.36 | 28.22 | 72.13 | 9.41 |
| Variant 1 | 60mm | 14.13 | 33.47 | 66.63 | 6.04 |
| Variant 2 | 60mm | 13.79 | 31.45 | 62.85 | 5.86 |
| Variant 3 | 60mm | 14.70 | 33.00 | 69.31 | 5.15 |
| Variant 4 | 60mm | 13.61 | 30.50 | 59.36 | 6.21 |
| **Formulation** | **Dispenser 3 (100ul)** | | | | |
| | **Distance** | **Dv10** | **Dv50** | **Dv90** | **%vol <10µm** |
| Variant 1 | 30mm | 9.54 | 25.26 | 59.40 | 10.80 |

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| | | | | | |
|---|---|---|---|---|---|
| Variant 2 | 30mm | 9.02 | 22.98 | 48.57 | 11.75 |
| Variant 3 | 30mm | 9.51 | 24.62 | 55.86 | 10.85 |
| Variant 4 | 30mm | 9.06 | 21.88 | 45.63 | 11.87 |
| Variant 1 | 60mm | 12.32 | 30.71 | 62.09 | 7.31 |
| Variant 2 | 60mm | 15.10 | 30.62 | 53.51 | 5.31 |
| Variant 3 | 60mm | 12.93 | 29.60 | 54.04 | 6.75 |
| Variant 4 | 60mm | 12.46 | 28.90 | 52.53 | 7.49 |

These results demonstrate that the formulations provide suitable particle size for intranasal delivery in a variety of nasal pump delivery devices.

Further DSD studies were conducted on the Variant 4 formulation to further investigate particle size at suitable velocities for delivery and are shown below in table 17. Experiments were conducted with a Spraytec Open Spray with a 300 mm lens.

**Table 17. Variant 4 formulation droplet size distribution (DSD) testing.**

| | **Velocity of actuation: 60mm/s** | | | | **Velocity of actuation: 80mm/s** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Dv10** | **Dv50** | **Dv90** | **%V<10µm** | **Dv10** | **Dv50** | **Dv90** | **%V<10µm** |
| **Distance** | **30 mm** | | | | | | | |
| **Mean** | 19 | 58.9 | 120.6 | 3.82 | 14.51 | 42.84 | 97.69 | 5.304 |
| **%RSD** | 10.7 | 11.4 | 9.5 | | - | - | - | |
| **Distance** | **40 mm** | | | | | | | |
| **Mean** | 30.42 | 89.32 | 180.79 | 1.66 | - | - | - | - |
| **%RSD** | 15.4 | 13.7 | 10.7 | | - | - | - | |
| **Distance** | **60mm** | | | | | | | |
| **Mean** | - | - | - | - | 16.75 | 42.04 | 92.32 | 4.31 |
| **%RSD** | - | - | - | | - | - | - | |
| **Distance** | **70 mm** | | | | | | | |
| **Mean** | 32.55 | 78.96 | 166.46 | 1.64 | - | - | - | - |
| **%RSD** | 13.3 | 13.8 | 10.8 | | - | - | - | |

RSD = relative standard deviation.

**Example 12: SPL7013 hygroscopic assessment**

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A hygroscopic assessment was performed as described in European Pharmacopoeia 5.11. Results from the assay are interpreted as follows: deliquescent - sufficient water is absorbed to form a liquid; very hygroscopic - increase in mass is equal to or greater than 15%; hygroscopic - increase in mass is less than 15% and equal to or greater than 2%; slightly hygroscopic - increase in mass is less than 2% and equal to or greater than 0.2% and not hygroscopic - if increase in mass is less than 0.2%, then the compound is not hygroscopic.

Hence, SPL7013 was found to be very hygroscopic in nature with an increase in mass of greater than 15% (21.97%). The hygroscopicity results were confirmed by water content analysis with a Karl Fischer test.

**Example 14: Rat SPL7013 biocompatibility studies**

Biocompatibility studies of SPL7013 in formulation variant 4 were conducted in rats (data not shown).

The product was tested to evaluate its cytotoxic effect in Balb/c 3T3 cells. In conclusion, the solution of 5mg/ml SPL7013 is not cytotoxic.

The product was tested to evaluate its sensitising properties in ten Albino Guinea pigs after intradermal and topical administration followed by challenge after 14 days. In conclusion, no macroscopic cutaneous reactions attributable to allergy were recorded after the challenge phase and the product is not classified as a skin sensitiser in accordance with ISO 10993-10.

The product was administered to 3 female Sprague Dawley rats four times a day for 14 days by the intranasal route at a dose of 0,1ml in each nostril. No mortality was observed, no clinical signs related to administration of the test product were observed, no erythema or odema was registered on the treatment site and body weight remained normal. There was no evidence of inflammatory change or effect on the epithelia. In conclusion the test product was well tolerated and did not induce any evidence of irritation assessed in accordance with ISO 10993-10.

**Example 15: Clinical study**

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A clinical study was conducted in 40 patients receiving 1% SPL7013 in formulation variant 4 or placebo (formulation 4) administered 100µl in each nostril four times a day for 14 days by spray device. No serious adverse events were reported and the formulation was generally well tolerated with minimal irritation.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the above-described embodiments, without departing from the broad general scope of the present disclosure. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

This application claims priority from Australian Provisional Application No. 2020901194 entitled "Method of Prophylaxis of Coronavirus infection" filed on 15 April 2020, Australian Provisional Application No. 2020902993 entitled "Method of Prophylaxis of Coronavirus infection" filed on 21 August 2020, and Australian Provisional Application No. 2020904246 entitled "Method of prophylaxis of respiratory syncytial virus infection" filed on 17 November.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

The steps, features, integers, compositions and/or compounds disclosed herein or indicated in the specification of this application individually or collectively, and any and all combinations of two or more of said steps or features.

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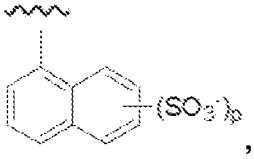
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**Claims**

1. A macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier for use in preventing or reducing the likelihood of Respiratory syncytial virus (RSV) infection in an individual,

wherein the macromolecule comprises a dendrimer of 3 to 5 generations with at least 15 sulfonic acid- or sulfonate-containing moieties attached to one or more surface groups of the dendrimer,

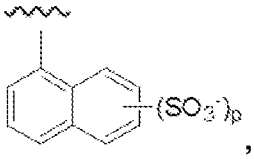
wherein the sulfonic acid- or sulfonate-containing moiety is  ,

wherein p is an integer of 2, and

wherein the macromolecule comprises a linker wherein the linker is a group -X1-(CH2)q-C(O)-, wherein X1 is the atom which is attached to the sulfonic acid- or sulfonate-containing moiety and is O; q is an integer of 1; and the carbon of the -C(O)- group is attached to the dendrimer.

2. A macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier for use in treating a Respiratory syncytial virus (RSV) infection in an individual,

wherein the macromolecule comprises a dendrimer of 3 to 5 generations with at least 15 sulfonic acid- or sulfonate-containing moieties attached to one or more surface groups of the dendrimer,

wherein the sulfonic acid- or sulfonate-containing moiety is  ,

wherein p is an integer of 2, and

wherein the macromolecule comprises a linker wherein the linker is a group -X1-(CH2)q-C(O)-, wherein X1 is the atom which is attached to the sulfonic acid- or sulfonate-containing moiety and is O; q is an integer of 1; and the carbon of the -C(O)- group is attached to the dendrimer.

3. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof

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and a pharmaceutically acceptable carrier, for use of claim 1 or claim 2, wherein the RSV is selected from: RSV subtype A (RSVA) and RSV subtype B (RSVB).

4. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of any one of claims 1 to 3, wherein the macromolecule or a pharmaceutically acceptable salt thereof, or composition is administered topically or administered to the respiratory tract.

5. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of claim 4, wherein the macromolecule or a pharmaceutically acceptable salt thereof, or composition is administered to one or more of: upper respiratory tract, lower respiratory tract, nasal mucosa, nasal cavity, oral cavity, sinuses, throat, pharynx, larynx, nasal turbinates, nasopharynx, oropharynx, trachea, primary bronchi and lungs.

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6. The composition, for use of any one of claims 1 to 5, wherein the composition comprises one or more of the following features:

(a) 0.5% to 5% by weight of the macromolecule or pharmaceutically acceptable salt thereof;

(b) 1% by weight of the macromolecule or pharmaceutically acceptable salt thereof;

(c) 0.1 to 5 mg of the macromolecule or pharmaceutically acceptable salt thereof per dose;

(d) 1 mg of the macromolecule or pharmaceutically acceptable salt thereof per dose.

7. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of any one of claims 1 to 6, wherein the macromolecule or a pharmaceutically acceptable salt thereof is administered in a nasal spray or an oral spray.

8. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of any one of claims 1 to 7, wherein the macromolecule or a pharmaceutically acceptable salt thereof is administered 1 to 8 times daily.

9. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of any one of claims 1 to 8, wherein the macromolecule or a pharmaceutically acceptable salt thereof is administered for 1 to 2 weeks, or 1 to 3 weeks, or for less than 30 days.

10. The composition, for use of any one of claims 1 to 9, wherein the composition comprises a rheology modifier selected from a polyacrylic acid, hydroxypropylmethyl-cellulose and microcrystalline cellulose /carboxy methyl cellulose.

11. The composition for use of claim 10, wherein the polyacrylic acid is a homopolymer of acrylic acid or a crosslinked polyacrylic acid, and wherein the crosslinked polyacrylic acid is crosslinked with an allyl ether of pentaerythritol, an allyl ether of sucrose, and/or an allyl ether of propylene.

12, The composition for use of any one of claims 1 to 11, wherein the rheology modifier is present in an amount of from 0.01% to 0.1% w/w of the composition.

13. The composition, for use of any one of claims 1 to 12, wherein the composition comprises:

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(a) a rheology modifier selected from one or more of: hydroxypropylmethyl-cellulose or microcrystalline cellulose /carboxy methyl cellulose;

(b) a preservative selected from one or more of: methyl paraben, propyl paraben, and benzalkonium chloride

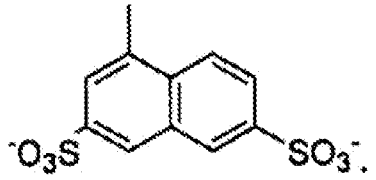
(c) an excipient selected from one or more of: glycerine, propylene glycol, ethylenediamine tetraacetic acid; and

(d) a pH modifier.

14. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of any one of claims 1 to 13, wherein the macromolecule or pharmaceutically acceptable salt thereof is a dendrimer comprising lysine building units of from 3 to 5 generations, and the sulfonic acid- or sulfonate-containing moieties are napthyldisulfonate moieties.

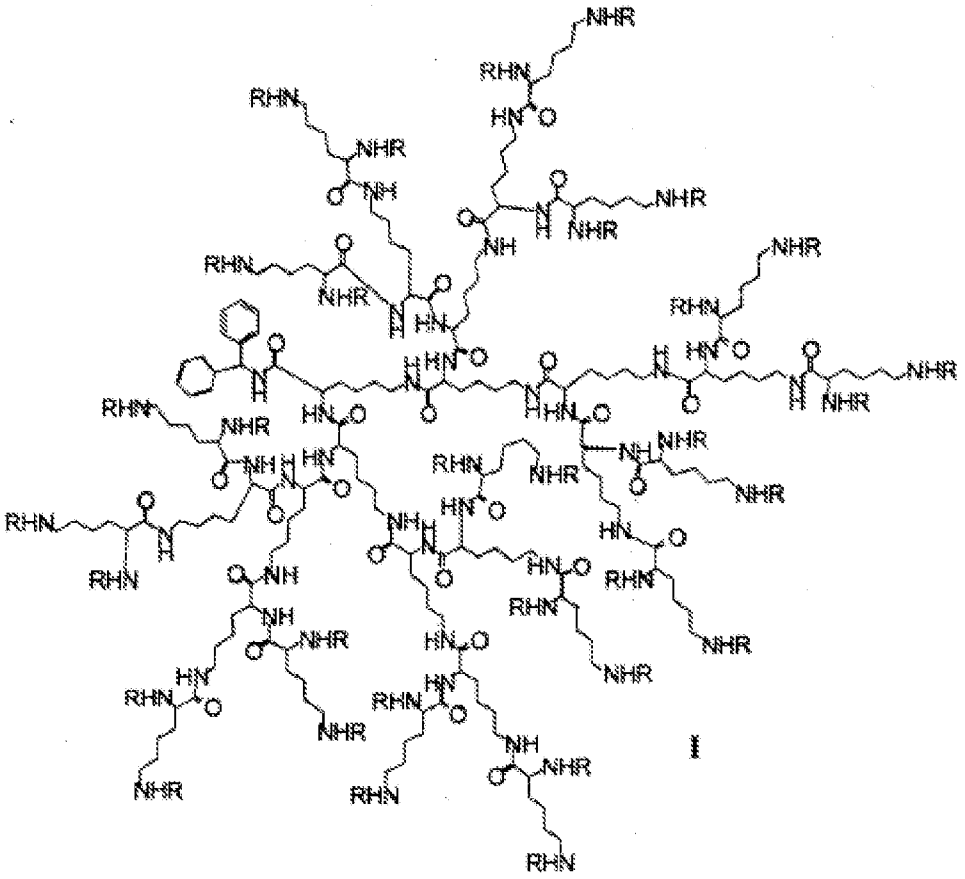
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15. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of claims 1 to 14, wherein the sulfonic acid-containing moiety is

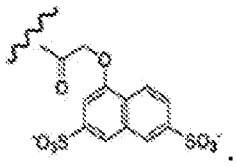



16. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of any one of claims 1 to 15, wherein the dendrimer is a polylysine dendrimer.

17. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of claim 16, wherein the dendrimer is



and wherein at least 50% of R is



18. The macromolecule or a pharmaceutically acceptable salt thereof, or a composition comprising the macromolecule or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, for use of any one of claims 1 to 17, wherein the pharmaceutically acceptable salt is a sodium salt.

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