2001, *69*, 177-90). Human NE is known to be mainly responsible for extracellular proteolysis and contributes to tissue damage by catalyzing the hydrolysis of a wide variety of matrix macromolecules, plasma proteins, inflammatory mediators, and cell surface receptors with important local and systemic consequences (C. A. Oven; E. J. Campbell; *J. Leukoc. Biol.* **1999**, *65*, 137-150). Thus, inhibitors of human NE are valuable novel drug candidates for infectious inflammatory diseases, including lung diseases like chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), cystic fibrosis (CF) and ischemic-reperfusion injury, (H. Ohbayashi, *Expert Opin. Investig. Drugs* **2002**, *11*, 965-980; B. Korkmaz, T. Moreau, F. Gauthier, *Biochimie* **2008**, *90*, 227). Inhibitors of human cathepsin G, elastase, or tryptase have been found such as β-hairpin peptidomimetics (WO 2006/087001; WO 2015/096872; WO 2015/096873). They can meet a significant need for new therapies effectively preventing or treating and/or mitigating these diseases or conditions.

Routes of administration can be classified whether the effect of the drug is local (topical administration) or systemic (enteral or parenteral administration). The delivery of pharmaceuticals to the bronchi and lungs (pulmonary drug delivery) has been used for the local treatment of diseases and conditions of the respiratory system. However, the feasibility of inhalation as an alternate route of administration for treatment of systemic diseases utilising the large surface of the lungs for absorption has been demonstrated as well (J. S. Patton, P. R. Byron, *Nat. Rev. Drug Discov*. **2007**, *6*, 67-74; M. Hohenegger, *Curr. Pharm. Des*. **2010**, *16*, 2484-2492).

In particular, drug substances can be delivered to the respiratory system as aerosolized dry powders or aerosolized liquids, the latter being either solutions or dispersions, such as drug substance suspensions (EP 2 567 691). Various devices have been developed to convert a solid or liquid composition into an aerosol to enable inhalation. For the conversion of aqueous-based drug substance solutions or suspensions into inhalable aerosols nebulizers are normally used. They are particularly useful for diseases that require high pulmonary doses, e.g. CF, and

patients , e.g. children, who are unable to coordinate or achieve flow rates necessary

for use of other inhalation devices (M. Knoch, M. Keller, *Expert Opin. Drug Del*. **2005**, *2*, 377-390; WO 2007/091266; WO 98/19694; WO 2007/090646; and WO 2008/025560).

Inhalation of drug substances may be favourable for the prophylaxis and/or treatment of respiratory tract infections and/or diseases associated with neutrophil elastase activity. There is evidence that airway infiltration by neutrophils will lead to an increase in neutrophil elastase within the extracellular compartment and thereby inducing deleterious effects. In a mouse model of neutropil allergen challenge it could be demonstrated that the inhibition of neutrophil elastase by sivelelstat attenuates airway hyperresponsiveness and inflammation (H. Koga, N. Miyahara et al., *Respir.Res.* **2013**, 14:8). In a different mouse model delivery of unglycosylated rhalpha1PI, a recombinant form of the elastase inhibitor alpha-1-proteinase inhibitor (alpha1PI), to the airway surface of CD-1 mice by nasal instillation was found to be highly protective against elastase-mediated injury, even significantly more protective than glycosylated blood-derived alpha1PI. These results suggest that aerosol delivery of rhalpha1PI could be an effective strategy for controlling elastase-dependent pathophysiology associated with cystic fibrosis lung disease. Recently, R. Siekmeier summarized the results of so far completed clinical studies aiming at lung deposition of inhaled alpha1PI of patients with hereditary alpha1PI-deficiency or cystic fibrosis (*Eur. J. Med. Res*. **2010**, *15* [Suppl. II], 164). For both therapeutic areas most of the studies indicate that the administration of alpha1PI by inhalation may serve as a potent therapy to neutralize the excess of inflammatory proteins and neutrophil elastase. Whereas the latter effects do not automatically lead to improvements on patient's lung function, a clear reduction of airway inflammation after alpha1PI treatment may precede pulmonary structural changes (M. Griese, P. Latzin et al., *Eur. Respir. J*. **2007**, *29*, 240).

Generally, the benefit of drug substance delivery via inhalation is that it can afford delivery of sufficient therapeutic dosages of the drug directly to the primary site of

action, e.g. in case of respiratory diseases, while minimizing the risks of systemic

toxicity. Additionally, suboptimal pharmacokinetics and/or pharmacodynamics associated with systemic drug exposure may be avoided. Furthermore, inhalation (at home) is a more convenient mode of administration than intravenous injection (medical ward).

Still, the effectiveness of a therapy based on inhaled drug substance delivery depends mainly on the drug which is selected, a pharmaceutical composition thereof suitable for inhalation and the device that is employed. Thus, there is a strong need for further pharmaceutical compositions, aerosols and therapeutic kits which are suitable for the prevention, management or treatment of diseases or conditions being mediated by or resulting from human neutrophil elastase activity improving the outcome of presently known therapies and/or overcoming the disadvantages of presently known therapies.

Summary of the invention

The invention provides a pharmaceutical aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase. The scope of the invention is defined by the appended claims. The dispersed liquid phase comprises aqueous droplets comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof. The droplets of the dispersed phase have a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm with a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7. Further provided by the invention is the pharmaceutical aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase comprises aqueous droplets comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject.

In another aspect, the invention provides liquid and solid pharmaceutical compositions from which the above aerosol can be prepared. The liquid composition comprises the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, in a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL, preferably, within a range from ~~about~~ 17 mg/mL to ~~about~~ 95 mg/mL, or ~~about~~ 35 mg/mL to ~~about~~ 95 mg/mL, respectively, and more preferably, within a range from ~~about~~ 70 mg/mL to ~~about~~ 95 mg/mL.

In still another aspect, the invention provides a kit comprising a nebulizer and a liquid or solid composition, wherein the nebulizer is adapted to aerosolize the liquid composition into an aerosol, as described above. Further provided by the invention is a kit comprising a nebulizer and a liquid or solid composition, wherein the nebulizer is adapted to aerosolize the liquid composition into an aerosol, as described above, for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject.

In still another aspect, the invention further discloses a method of preparing and delivering an aerosol for pulmonary administration. The method comprises the step of providing a liquid pharmaceutical composition comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, in a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL, preferably, within a range from ~~about~~ 17 mg/mL to ~~about~~ 95 mg/mL, or ~~about~~ 35 mg/mL to ~~about~~ 95 mg/mL, respectively, and more preferably, within a range from ~~about~~ 70 mg/mL to ~~about~~ 95 mg/mL, or providing a solid pharmaceutical composition for preparing the liquid composition, wherein the composition comprises the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, and wherein the solid composition is dissolvable or dispersible in an aqueous liquid solvent, and

wherein the liquid composition comprises a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL, preferably, within a range from ~~about~~ 17 mg/mL to ~~about~~ 95 mg/mL, or ~~about~~ 35 mg/mL to ~~about~~ 95 mg/mL, respectively, and more preferably, within a range from ~~about~~ 70 mg/mL to ~~about~~ 95 mg/mL, of the active compound, or any pharmaceutically acceptable salt thereof, and the step of providing a nebulizer capable of aerosolizing said liquid pharmaceutical composition at a mean delivery rate of at least ~~about~~ 0.8 mg of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, per minute, the nebulizer being further adapted to emit an aerosol comprising a dispersed liquid phase having a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm, and having a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7. In a subsequent step the nebulizer is operated to aerosolize the liquid pharmaceutical composition which finally can be inhaled by mammals, more preferably, by human subjects.

In still another aspect, the invention provides a pharmaceutical composition comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, and optionally one or more pharmaceutically acceptable diluents, excipients or carriers, for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject.

In still another aspect, the invention provides a kit comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, and a package insert wherein the package insert comprises instructions for treating a subject for diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity using the active compound.

cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof. The droplets of the dispersed phase have a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm with a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7.

The aerosol of the invention is for pulmonary delivery, which is preferable achieved via oral inhalation of the aerosol. As used herein in the description and the claims, pulmonary delivery means aerosol delivery to any part or feature of the lungs including the so-called deep lungs, the peripheral lungs, the alveoli, the bronchi and the bronchioli.

Conditions of the pulmonary target regions in which the prevention, management or treatment of mammals, more preferably, of human subjects, using the aerosol of the invention is potentially useful include diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity, e.g. in particular, pulmonary diseases, such as alpha-1 antitrypsin deficiency (AATD), cystic fibrosis (CF), non-cystic fibrisis bronchiactasis (NCFB), or chronic obstructive pulmonary disease (COPD), or infections of the lungs causing diseases or conditions of the lungs, being mediated by human neutrophil elastase activity.

As used herein in the description and the claims, an aerosol is a dispersion of a solid and/or liquid phase in a gas phase. The dispersed phase, also termed discontinuous phase, comprises multiple solid and/or liquid particles. Both basic physical types of aerosols, i.e. solid and liquid dispersions in a gas phase, may be used as pharmaceutical aerosols.

According to the present invention, the aerosol comprises a dispersed liquid phase and a continuous gas phase. Such aerosols are sometimes referred to as “liquid aerosols” or aerosolized liquids. It should be noted that the requirement of a dispersed liquid phase does not exclude the presence of a solid phase. In particular,

salts may be formed with inorganic anions, such as chloride, bromide, iodide, phosphate (mono- or dibasic), sulfate, nitrate, acetate, trifluoroacetate, propionate, butyrate, maleate, fumarate, methanesulfonate, ethanesulfonate, 2-hydroxy-ethylsulfonate, n-propylsulfonate, isopropylsulfonate, lactate, malate, and/or citrate.

The term pharmaceutically acceptable salt or pharmaceutical salt is used to refer to an ionisable drug or active compound that has been combined with a counter ion to form a neutral complex. Converting a drug or active compound into a salt through this process can, for example, increase its chemical stability, render the complex easier to administer and/or allow manipulation of the agent's pharmacokinetic profile.

In a preferred embodiment of the invention, the counter ion of the active compound is acetate.

The aerosol is further characterized in that the droplets of the dispersed liquid phase have a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm with a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7. The mass median diameter (MMD), as used herein in the description and the claims, is the mass median diameter of the dispersed liquid phase as measured by laser diffraction. Various appropriate analytical apparatuses to determine the MMD are known and commercially available, such as the Malvern MasterSizer X or Malvern SprayTec. The geometric distribution including the geometric standard deviation (GSD) of the aerosolized liquid particles or droplets may be determined simultaneously with the MMD. The GSD describes how spread out is a set of numbers the preferred average of which is the geometric mean.

In a preferred embodiment, the aerosol is for pulmonary delivery and the dispersed liquid phase of such an aerosol has a MMD in the range from ~~about~~ 2.0 µm to ~~about~~ 4.5 µm and a GSD in the range from ~~about~~ 1.2 to ~~about~~ 1.7. More preferably, the

aerosol of the invention has a MMD in the range from ~~about~~ 2.5 µm to ~~about~~ 3.5 µm and a GSD in the range from ~~about~~ 1.4 to ~~about~~ 1.6. Each of these sets of combinations is particularly useful to achieve a high local concentration of the active compound in the lungs, including the bronchi and bronchioli, relative to the amount of active compound which is aerosolized.

In another preferred embodiment, the aerosol is emitted from an aerosol generator at a rate of at least ~~about~~ 0.1 mL/min. In another embodiment, the (total) output rate being the rate at which the aerosol is emitted from the aerosol generator is at least ~~about~~ 0.150 mL/min or at least ~~about~~ 150 mg/min for those liquid aerosols the densities of which are – for practical purposes – close to 1 g/mL, i.e. within the range from ~~about~~ 0.95 g/mL to ~~about~~ 1.05 g/mL. In further embodiments, the output rate is within the range from ~~about~~ 200 mg/min to ~~about~~ 700 mg/min, or from ~~about~~ 250 mg/min to ~~about~~ 650 mg/min, respectively.

In another preferred embodiment, the aerosol is emitted from an aerosol generator at a mean delivery rate of at least ~~about~~ 0.8 mg of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, per minute. The (mean) delivery rate of a drug or active compound is one of two discrete metrics or parameters being defined and measured according to e.g. Ph. Eur. (Pharmacopeia Europaea) 2.9.44 and/or USP (United States Pharmacopeia) 1601 to determine the amount of drug or active compound a patient might be expected to receive during a treatment period. In further embodiments, the mean delivery rate of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, is within the range from ~~about~~ 3 mg to ~~about~~ 25 mg per minute or within the range from ~~about~~ 5 mg to ~~about~~ 18 mg per minute, respectively.

Appropriate aerosol generators, in particular nebulizers, which are suitable for generating the aerosol(s) described herein in the description and the claims are discussed in more detail herein-below.

In another aspect, the present invention is directed to a liquid pharmaceutical composition for preparing the aerosol as described above comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, in a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL.

As defined herein in the description and the claims, a liquid pharmaceutical composition is a liquid material which comprises at least one active compound and at least one pharmaceutically acceptable, pharmacologically substantially inert excipient. It should be noted that the term “liquid composition” does not necessarily mean that no solid material is present. For example, a liquid suspension representing a dispersion of solid particles in a continuous liquid phase is also embraced in the above term.

Preferably, the liquid composition from which the aerosol is prepared is an aqueous composition; consequently, water is the predominant liquid constituent of such composition. Solvents and co-solvents other than water should be avoided. In another embodiment, the composition comprises at least ~~about~~ 80 wt.-% of water. In yet another embodiment, at least ~~about~~ 90 wt.-% of the liquid constituents of the composition is water.

If the incorporation of a non-aqueous solvent, such as ethanol, glycerol, propylene glycol or polyethylene glycol, cannot be avoided, the excipient should be selected carefully and in consideration of its physiological acceptability and the therapeutic use of the composition. According to a preferred embodiment, the composition is substantially free of non-aqueous solvents.

The concentration of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, in the liquid composition is within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL. Preferably, the concentration of the above active compound, or any pharmaceutically acceptable salt thereof, is within the range from ~~about~~ 17 mg/mL to ~~about~~ 95 mg/mL, or ~~about~~ 35 mg/mL to ~~about~~ 95 mg/mL, respectively, or, more preferred, ~~about~~ 70 mg/mL to ~~about~~ 95 mg/mL. A high concentration of an active compound in a composition suitable to be aerosolized provides for patient convenience and compliance: The higher such concentration the smaller the total volume of liquid composition comprising the effective dose of the active compound to be inhaled and the shorter the total time being necessary for inhalation of such an effective dose.

The dynamic viscosity of the liquid composition has an influence on the efficiency of nebulization and on the particle size distribution of the aerosol formed by nebulization. The dynamic viscosity should preferably be adjusted to a range from ~~about~~ 0.8 mPas to ~~about~~ 1.7 mPas. In other embodiments, the dynamic viscosity is in the range from ~~about~~ 1.0 mPas to ~~about~~ 1.7 mPas, or in the range from ~~about~~ 1.2 mPas to ~~about~~ 1.6 mPas, respectively.

In order to obtain an aerosol which is highly suitable for pulmonary administration, the surface tension of the liquid composition of the invention should preferably be adjusted to a range from ~~about~~ 25 mN/m to ~~about~~ 80 mN/m, more preferably, to a range from ~~about~~ 30 mN/m to ~~about~~ 70 mN/m, or even more preferably, to a range from ~~about~~ 45 mN/m to ~~about~~ 55 mN/m.

In general, the quality of an aerosol and the efficiency of the nebulisation could be adversely affected in the lower parts of the above presented embodiments; however, the results of the studies described below indicate that there are no significant changes in the performances of the liquid compositions of the invention in the above respect.

It is well known in the art that addition of a surfactant to an aqueous liquid composition may result in a surface tension being reduced fairly markedly below that of water or physiological buffer solution. Therefore, a compromise has to be found in each case depending on the intended application.

In order to be well-tolerated an aerosol should – as far as possible – have a physiological tonicity or osmolality. Thus, it may be desirable to incorporate an osmotically active excipient to control the osmolality of the aerosol. Such an excipient, or excipients, if e.g. a combination of substances is used, should be selected to ideally reach an osmolality of the aerosol which does not deviate too much from that of physiological fluids, i.e. from ~~about~~ 150 mOsmol/kg. However, a compromise has again to be found between the physical-chemical and/or pharmaceutical needs on one hand and the physiological requirements on the other hand. In general, an osmolality up to ~~about~~ 800 mOsmol/kg may be acceptable. In particular, an osmolality in the range from ~~about~~ 200 mOsmol/kg to ~~about~~ 600 mOsmol/kg is preferred. In further embodiments, the osmolality is in the range from ~~about~~ 250 mOsmol/kg to ~~about~~ 500 mOsmol/kg or in the range from ~~about~~ 300 mOsmol/kg to ~~about~~ 450 mOsmol/kg, respectively.

One approach to improve the effectiveness and/or efficacy of the composition may be to enhance the local retention time of the composition after deposition of the aerosol in the target regions. For example, a prolonged residence time of the deposited composition in the lungs may lead to a higher continuous exposure of the active compound at the site of action. At the same time, it may reduce the required frequency of administration and therefore, enhance patient convenience and compliance.

In order to achieve a prolonged retention of the active compound in general, various formulation strategies may be pursued, e.g. conversion of the highly water soluble active compound into a less soluble solid form, such as a poorly soluble salt. As a

consequence, the compound is present in the aerosol in undissolved form, such as in form of a micro- or nanosuspension. Upon deposition of the aerosol droplets, the liquid phase of the composition combines with the physiological fluid, e.g. mucus, and allows the drug to dissolve.

A different formulation strategy is based on the fact that polymeric excipient(s), as described below, may have an effect on the release of the active compound from the formulation, and/or on the local residence time of the composition after deposition onto the target tissue. Therefore, such excipients affect the local bioavailability of the active compound at the site of action as well.

In one of the preferred embodiments, the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, is formulate with a polymeric excipient to effect slow release and prolonged local retention. Potentially suitable polymers include, in particular, pharmaceutically acceptable water-soluble or water-dispersible polymers, such as methylcellulose, hydroxyethylcellulose, alginate, galactomannan, dextran, agar, guar gum, tragacanth, and mixtures thereof.

If one or several polymeric excipients are present in the liquid composition of the invention, care should be taken of the influence on the dynamic viscosity of such a composition in order to ensure efficient aerosolization. Thus, the dynamic viscosity should not exceed ~~about~~ 1.7 mPas. In general, the exact grade of the polymer(s) and the presence of other excipients should be considered to determine the content of the polymer(s) in such liquid composition.

It is known that other excipients, namely complexing agents, such as cyclodextrins, di- or multivalent metal salts, such as calcium- magnesium- or aluminium salts, chelating agents, such as ethylenediaminetetraacetic acid including its salts, or amphiphilic

agents, such as phospholipids or lecithins, may in a similar manner prolong the release of the active compound as e.g. polymeric excipients.

The liquid composition of the invention may comprise further pharmaceutically acceptable excipients, e.g. osmotic agents, such as inorganic salts; excipients for adjusting and/or buffering the pH, such as organic or inorganic salts, acids and bases, bulking agents and lyophilisation aids, such as sucrose and lactose, sugar alcohols, like mannitol, sorbitol, and xylitol, stabilizers and antioxidants, such as vitamin E including its derivatives, lycopene including its derivatives and ascorbic acid, ionic and non-ionic surfactants, such as phospholipids and polysorbates, taste-modifying agents, disintegrants, colouring agents, sweeteners, and/or flavours.

~~In one of the preferred embodiments, o~~One or more osmotic agents, such as sodium chloride, are incorporated in the composition to adjust the osmolality to a value in a preferred range as outlined herein above. ~~In a more preferred embodiment, the osmotic agent is sodium chloride.~~

In order to provide a well tolerated aerosol, the preparation according to the invention should be adjusted to a euhydric pH. The term “euhydric” implies that there may be a difference between pharmaceutical and physiological requirements so that a compromise has to be found which, for example, ensures that, on one hand, the preparation is sufficiently stable during storage, but, on the other hand, is still well tolerated. Preferably, the pH value lies in the slightly acidic to neutral region, i.e. between ~~about~~ 4 and ~~about~~ 8. In general, deviations towards a weakly acidic milieu are tolerated better than an alkaline shift. Particularly preferred is a composition having a pH lying within the range from ~~about~~ 4.5 and ~~about~~ 7.5.

For adjusting the pH of the composition of the invention and/or buffering such composition, physiologically acceptable acids, bases, salts, and combination of these may be used. Suitable excipients for lowering the pH value and/or as acidic components of a buffer system are strong mineral acids, such as sulphuric acid and

term “dissolvable” means that the solid composition and the aqueous liquid solvent can be combined to form a solution or colloidal solution, whereas the term “dispersible” should be interpreted to include the formation of liquid dispersions, in particular, emulsions and microsuspensions. The term “aqueous” means that the major liquid constituent of the solvent is water. Solvents and co-solvents other than water should be avoided. In another embodiment, the aqueous liquid solvent comprises at least ~~about~~ 80 wt.-% of water. In yet another embodiment, at least ~~about~~ 90 wt.-% of the liquid constituents of the solvent is water. If the incorporation of a non-aqueous solvent, such as ethanol, glycerol, propylene glycol or polyethylene glycol, cannot be avoided, the excipient should be selected carefully and in consideration of its physiological acceptability and the therapeutic use of the composition. According to a preferred embodiment, the composition is substantially free of non-aqueous solvents. If the incorporation of a non-aqueous solvent, such as ethanol, glycerol, propylene glycol or polyethylene glycol, cannot be avoided, the same precautions have to be considered as described above. According to another preferred embodiment, the aqueous solvent to dissolve or disperse the solid composition is substantially free of non-aqueous solvents.

The amount of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, in the solid composition has to correspond to a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL following dissolution or dispersion in an aqueous liquid solvent. More preferably, the amount of the above active compound, or any pharmaceutically acceptable salt thereof, has to correspond to a concentration within the range from ~~about~~ 17 mg/mL to ~~about~~ 95 mg/mL, or ~~about~~ 35 mg/mL to ~~about~~ 95 mg/mL, respectively, or, even more preferred, ~~about~~ 70 mg/mL to ~~about~~ 95 mg/mL, following dissolution or dispersion in an aqueous liquid solvent.

In a further embodiment, the counter ion of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-) in the solid composition is acetate.

The solid composition of the invention for reconstitution may be part of a pharmaceutical kit. Such kit preferably comprises the solid composition in sterile form. As used herein in the description and the claims the terms “sterile” or “sterility” are defined according to the usual pharmaceutical meaning and thus to be understood as the absence of germs which are capable of reproduction. Sterility is determined with suitable tests which are defined in the relevant pharmacopoeias. According to current scientific standards, a sterility assurance level (SAL) of 10^{-6}, i.e. assurance of less than one chance in one million that viable micro-organisms are present in a sterilized article), is regarded as acceptable for sterile preparations. In practice, contamination rates may be higher, and contamination rates for aseptically manufactured preparations might amount to ~~about~~ 10^{-3}. For practical reasons, it remains difficult to demand sterility in an absolute sense. Therefore, the sterility of the composition of the invention should be understood herein in the description and the claims in such manner that said composition meets the requirements of the relevant pharmacopeia with respect to sterility.

The solid composition of the invention may be prepared by providing a liquid composition being similar to the liquid composition ready for aerosolization and subsequently drying it, e.g. by lyophilisation. Similar means that the liquid composition from which the solid composition is prepared by drying may not comprise all solid ingredients of the ready-to-go liquid composition, for example, in the case that the liquid carrier for reconstitution is designed to comprise one or more of the excipients. It is even not necessary, that the concentrations of the ingredients of these two liquid compositions are identical. The solid composition of the invention may even be prepared, for example, by providing the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, and, optionally, at least one excipient, in powder form and subsequently mixing such powder with a powder comprising the remaining excipients to finally form a powder mixture.

In another aspect, the invention provides a pharmaceutical kit for the preparation and delivery of a pharmaceutical aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase comprises aqueous droplets comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, has a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm, and has a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7. The kit is further characterized by comprising an aerosol nebulizer and an composition comprising a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL of the active compound, or any pharmaceutically acceptable salt thereof; or comprising a nebulizer and a solid pharmaceutical composition for preparing the liquid composition, wherein the composition comprises the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, and wherein the solid composition is dissolvable or dispersible in an aqueous liquid solvent, and wherein the liquid composition comprises a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL of the active compound, or any pharmaceutically acceptable salt thereof.

Nebulizers are devices capable of aerosolizing liquids. Preferably, the nebulizer of the kit of the invention is selected from jet nebulizers, ultrasonic nebulizers, piezoelectronic nebulizers, jet collision nebulizers, electrohydrodynamic nebulizers, capillary force nebulizers, perforated membrane nebulizers and perforated vibrating membrane nebulizers (M. Knoch, M. Keller, *Expert Opin. Drug Deliv.*, **2005**, *2*, 377). Particularly preferred are piezoelectric, electrohydrodynamic and/or perforated membrane-type nebulizers, e.g. nebulizers from the drug delivery platforms Mystic™ (Battelle Pharma [Battelle Memorial Institute], United States), eFlow™ (Pari GmbH, Germany), Aeroneb™, Aeroneb Pro™, Aero Dose™ (Aerogen Inc, United States). These types of nebulizers are particularly useful if the aerosol is to be delivered to the bronchi and/or lungs.

Preferably, the nebulizer should be selected or adapted to be capable of aerosolizing the liquid composition at a rate of at least ~~about~~ 0.1 mL/min. More preferably, the nebulizer is capable of an (total) output rate (the rate at which the aerosol is emitted from the aerosol generator) of at least ~~about~~ 0.150 mL/min or at least ~~about~~ 150 mg/min for those liquid compositions the densities of which are – for practical purposes – close to 1 g/mL, i.e. within the range from ~~about~~ 0.95 g/mL to ~~about~~ 1.05 g/mL. In further embodiments, the output rate of the nebulizer is within the range from ~~about~~ 200 mg/min to ~~about~~ 700 mg/min, or from ~~about~~ 250 mg/min to ~~about~~ 650 mg/min, respectively.

The nebulizer should also preferably be selected or adapted to be capable of aerosolizing and emitting the liquid composition at a mean delivery rate of at least ~~about~~ 0.8 mg of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, per minute. The (mean) delivery rate of a drug or active compound is a parameter to determine the amount of drug or active compound a patient might be expected to receive during a treatment period. In further embodiments, the nebulizer is selected or adapted to enable a mean delivery rate of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, at the range from ~~about~~ 3 mg per minute to ~~about~~ 25 mg per minute or at the range from ~~about~~ 5 mg per minute to ~~about~~ 18 mg per minute, respectively.

According to a further preference, the nebulizer should be selected or adapted to be capable of aerosolizing and emitting at least of ~~about~~ 70 wt.-% of the loaded dose of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, whereas said fraction of the loaded dose is comprised of droplets having a mass median diameter of not more than ~~about~~ 5 µm. A fraction of a dispersed phase having a droplet size of not more than ~~about~~ 5 µm is often referred to as the respirable fraction, as droplets of said size – in contrast to larger droplets – have a high chance of being deposited in the lungs,

instead of the trachea and the pharynx. More preferably, at least of ~~about~~ 80 wt.-% of the dose filled into the nebulizer is aerosolized to droplets of a size of not more than ~~about~~ 5 µm and emitted from the device. Such a device may be best selected by using an, optionally customized, electronic nebulizer based on the vibrating perforated membrane design, such as a nebulizer from the eFlow™ drug delivery platform (Pari GmbH, Germany). According to even more preferred embodiments, a least of ~~about~~ 85 wt.-% and ~~about~~ 90 wt.-%, respectively, of the loaded dose is aerosolized to droplets of a size of not more than ~~about~~ 5 µm and emitted.

In another aspect the invention provides a method of preparing and delivering an aerosol for pulmonary administration, said method comprising the steps of providing a liquid pharmaceutical composition comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, in a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL, or providing a solid pharmaceutical composition for preparing the liquid composition, wherein the composition comprises the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, and wherein the solid composition is dissolvable or dispersible in an aqueous liquid solvent, and wherein the liquid composition comprises a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL of the active compound, or any pharmaceutically acceptable salt thereof, and providing a nebulizer capable of aerosolizing said liquid pharmaceutical composition at a mean delivery rate of at least ~~about~~ 0.8 mg of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, per minute, the nebulizer being further adapted to emit an aerosol comprising a dispersed liquid phase having a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm, and having a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7, and operating the nebulizer to aerosolize the liquid pharmaceutical composition.

In a preferred embodiment the diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity are pulmonary diseases, wherein the pulmonary disease is non-cystic fibrosis bronchiactasis (NCFB) or cystic fibrosis (CF).

In a more preferred embodiment the diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity are pulmonary diseases, wherein the pulmonary disease is cystic fibrosis (CF).

In one embodiment the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, is administered to the subject as pharmaceutical aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase

(a) comprises aqueous droplets comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; wherein

OctG is (*S*)-2-aminodecanoic acid;

^{D}Pro is D-proline;

(b) has a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm; and

(c) has a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7.

Preferably the aerosol being emitted from an aerosol generator at a rate of at least ~~about~~ 0.1 mL dispersed liquid phase per minute.

Equally preferably the aerosol being emitted from an aerosol generator at a mean delivery rate of at least ~~about~~ 0.8 mg of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; per minute.

The aerosol is preferably emitted from an aerosol generator at a rate and at a mean delivery rate as described in the preferred embodiments above.

In one embodiment the pharmaceutical composition for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject, is a liquid pharmaceutical composition for preparing an aerosol as described herein, wherein the liquid pharmaceutical composition comprises the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, in a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL, preferably, within a range from ~~about~~ 17 mg/mL to ~~about~~ 95 mg/mL, or ~~about~~ 35 mg/mL to ~~about~~ 95 mg/mL, respectively, and more preferably, within a range from ~~about~~ 70 mg/mL to ~~about~~ 95 mg/mL.

In another aspect the invention provides a pharmaceutical aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase

(a) comprises aqueous droplets comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; wherein

OctG is (*S*)-2-aminodecanoic acid;

^{D}Pro is D-proline;

(b) has a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm; and

(c) has a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7, for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject.

of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or a pharmaceutically acceptable salt thereof, may be provided in a single dose or multiple doses to achieve the desired treatment endpoint.

The frequency of dosing will depend on the pharmacokinetic parameters of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, administered, the route of administration, and the particular disease treated. The dose and frequency of dosing may also depend on pharmacokinetic and pharmacodynamic, as well as toxicity and therapeutic efficiency data. For example, pharmacokinetic and pharmacodynamic information ~~about~~ the active compound or a pharmaceutically acceptable salt thereof, can be collected through preclinical in vitro and in vivo studies, later confirmed in humans during the course of clinical trials. Thus, for the active compound or a pharmaceutically acceptable salt thereof, used in the methods provided herein, a therapeutically effective dose can be estimated initially from biochemical and/or cell-based assays. Then, dosage can be formulated in animal models to achieve a desirable circulating concentration range. As human studies are conducted further information will emerge regarding the appropriate dosage levels and duration of treatment for various diseases and conditions.

Toxicity and therapeutic efficacy of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g. , for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the "therapeutic index", which typically is expressed as the ratio LD_{50}/ED_{50}. Compounds that exhibit large therapeutic indices, i.e. , the toxic dose is substantially higher than the effective dose, are preferred. The data obtained from such cell culture assays and additional animal studies can be used in formulating a range of dosage for human use. The

doses of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity.

An exemplary treatment regime entails administration once daily, twice daily, three times daily, every day, every second day, every third day, every fourth day, every fifth day, every sixth day, twice per week, once per week. The active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, is usually administered on multiple occasions. Intervals between single dosages can be, for example, less than a day, a day, two days, three days, four days, five days, six days or a week. The combination of the invention may be given as a continous uninterrupted treatment. The combination of the invention may also be given in a regime in which the subject receives cycles of treatment (administration cycles) interrupted by a drug holiday or period of non-treatment.

In one embodiment the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, of the pharmaceutical composition or the pharmaceutical aerosol for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject is administered to the subject at a dose between ~~about~~ 0.1 and ~~about~~ 10000 mg/day.

In one embodiment the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, of the pharmaceutical composition or the pharmaceutical aerosol for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject is is administered to the subject at a dose between ~~about~~ 0.001 and ~~about~~ 100 mg/kg.

In one embodiment the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, of the

pharmaceutical composition or the pharmaceutical aerosol for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject is administered to the subject at a dose between ~~about~~ 5 and ~~about~~ 1000 mg/day.

In one embodiment the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, of the pharmaceutical composition or the pharmaceutical aerosol for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject is administered to the subject at a dose between ~~about~~ 20 and ~~about~~ 960 mg/day.

In one embodiment the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, of the pharmaceutical composition or the pharmaceutical aerosol for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject is administered to the subject at a dose between ~~about~~ 80 and ~~about~~ 320 mg/day.

In one embodiment the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, of the pharmaceutical composition or the pharmaceutical aerosol for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject is administered to the subject at a dose of ~~about~~ 20, ~~about~~ 60, ~~about~~ 120, ~~about~~ 240, ~~about~~ 480 or ~~about~~ 960 mg/day.

In one embodiment the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, of the pharmaceutical composition or the pharmaceutical aerosol for use in a method for

the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject is administered to the subject at a dose of ~~about~~ 80, ~~about~~ 160, or ~~about~~ 320 mg/day.

In another aspect the invention provides a kit for the preparation and delivery of a pharmaceutical aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase

(a) comprises aqueous droplets comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; wherein

OctG is (*S*)-2-aminodecanoic acid;

^{D}Pro is D-proline;

(b) has a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm; and

(c) has a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7;

and wherein the kit comprises a nebulizer and a liquid composition comprising a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL of the active compound; or any pharmaceutically acceptable salt thereof;

or comprises a nebulizer and a solid pharmaceutical composition for preparing the liquid composition, wherein the composition comprises the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; and wherein the solid composition is dissolvable or dispersible in an aqueous liquid solvent, and wherein the liquid composition comprises a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL of the active compound; or any pharmaceutically acceptable salt thereof, for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject.

In one embodiment the nebulizer of the kit for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject is adapted to be capable of aerosolizing the liquid composition at a rate of at least ~~about~~ 0.8 mg of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; per minute.

In one embodiment at least ~~about~~ 70 wt.-% of the loaded dose of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro- Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, comprised by the kit is comprised of droplets having a mass median diameter of not more than ~~about~~ 5 µm.

In one embodiment the counter ion of the active compound comprised by the kit is as described for the active compound above and is preferably acetate.

In another aspect the invention provides a kit comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof; wherein
OctG is (*S*)-2-aminodecanoic acid;
^{D}Pro is D-proline;
and a package insert wherein the package insert comprises instructions for treating a subject for diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity using the active compound.

In one embodiment the kit comprises the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, as aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase
(a) comprises aqueous droplets comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any

pharmaceutically acceptable salt thereof;

(b) has a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm; and

(c) has a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7.

In one embodiment at least ~~about~~ 70 wt.-% of the loaded dose of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-), or any pharmaceutically acceptable salt thereof, comprised by the kit is comprised of droplets having a mass median diameter of not more than ~~about~~ 5 µm.

In one embodiment the counter ion of the active compound comprised by the kit is as described for the active compound above and is preferably acetate.

The following Examples illustrate the present invention but are not to be construed as limiting its scope in any way.

CLAIMS

1. A pharmaceutical composition comprising

the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);

or any pharmaceutically acceptable salt thereof; wherein

OctG is (*S*)-2-aminodecanoic acid;

^{D}Pro is D-proline;

sodium chloride;

and optionally one or more pharmaceutically acceptable diluents, excipients or carriers;

for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject~~,~~.

~~2. A pharmaceutical composition for use according to claim 1,~~ wherein the diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity are pulmonary diseases ~~such as~~ alpha-1 antitrypsin deficiency (AATD), cystic fibrosis (CF), non-cystic fibrosis bronchiactasis (NCFB), or chronic obstructive pulmonary disease (COPD), or infections of the lungs causing diseases or conditions of the lungs, being mediated by human neutrophil elastase activity.

~~3~~2. A pharmaceutical composition for use according to claim ~~2~~ 1, wherein the pulmonary disease is non-cystic fibrosis bronchiactasis (NCFB) or cystic fibrosis (CF).

~~4~~3. A pharmaceutical composition for use according to claim ~~2~~ 1, wherein the pulmonary disease is cystic fibrosis (CF).

~~5~~4. A pharmaceutical composition for use according to any one of claims 1-~~4~~3, wherein the counter ion of the active compound is acetate.

~~6~~5. A pharmaceutical composition for use according to any one of claims 1-~~5~~4, wherein the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);

or any pharmaceutically acceptable salt thereof; is administered to the subject as pharmaceutical aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase

(a) comprises aqueous droplets comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);

or any pharmaceutically acceptable salt thereof;

(b) has a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm; and

(c) has a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7.

~~7~~6. A pharmaceutical composition for use according to claim ~~6~~ 5, wherein the aerosol being emitted from an aerosol generator at a rate of at least ~~about~~ 0.1 mL dispersed liquid phase per minute.

~~8~~7. A pharmaceutical composition for use according to claim ~~6~~ 5, wherein the aerosol being emitted from an aerosol generator at a mean delivery rate of at least ~~about~~ 0.8 mg of the active compound

cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);

or any pharmaceutically acceptable salt thereof; per minute.

~~9~~8. A pharmaceutical composition for use according to any one of claims 1 to ~~8~~ 7, wherein the pharmaceutical composition is a liquid pharmaceutical composition for preparing an aerosol comprising the active compound

cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);

or any pharmaceutically acceptable salt thereof; in a concentration within a range from ~~about~~ 4 mg/mL to ~~about~~ 100 mg/mL.

~~10~~9. A pharmaceutical composition for use according to any one of claims 1 to ~~9~~ 8, wherein the active compound

cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);

or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose between ~~about~~ 0.1 and ~~about~~ 10000 mg/day.

~~11~~10. A pharmaceutical composition for use according to any one of claims 1 to ~~9~~ 8, wherein the active compound
cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);
or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose between ~~about~~ 0.001 and ~~about~~ 100 mg/kg.

~~12~~11. A pharmaceutical composition for use according to any one of claims 1 to ~~9~~ 8, wherein the active compound
cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);
or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose between ~~about~~ 5 and ~~about~~ 1000 mg/day.

~~13~~12. A pharmaceutical composition for use according to any one of claims 1 to ~~9~~ 8, wherein the active compound
cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);
or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose of ~~about~~ 20, ~~about~~ 60, ~~about~~ 120, ~~about~~ 240, ~~about~~ 480 or ~~about~~ 960 mg/day.

~~14~~13. A pharmaceutical composition for use according to any one of claims 1 to ~~9~~ 8, wherein the active compound
cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);
or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose between ~~about~~ 80 and ~~about~~ 320 mg/day.

~~15~~14. A pharmaceutical composition for use according to any one of claims 1 to ~~9~~ 8, wherein the active compound
cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);

or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose of ~~about~~ 80, ~~about~~ 160, or ~~about~~ 320 mg/day.

~~16~~15. A pharmaceutical composition for use according to any one of claims 1 to ~~15~~ 14, wherein the active compound
cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);
or any pharmaceutically acceptable salt thereof is administered to the subject by oral inhalation.

~~17~~16. A pharmaceutical aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase
(a) comprises aqueous droplets comprising the active compound
cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);
or any pharmaceutically acceptable salt thereof; wherein
OctG is (*S*)-2-aminodecanoic acid;
^{D}Pro is D-proline;
(b) has a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm; and
(c) has a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7, as measured as described in the description;
for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject~~,~~.

~~18. An aerosol for use according to claim 17,~~ wherein the diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity are pulmonary diseases ~~such as~~ selected from alpha-1 antitrypsin deficiency (AATD), cystic fibrosis (CF), non-cystic fibrosis bronchiactasis (NCFB), or chronic obstructive pulmonary disease (COPD), or infections of the lungs causing diseases or conditions of the lungs, being mediated by human neutrophil elastase activity.

~~19~~17. An aerosol for use according to claim ~~18~~ 16, wherein the pulmonary disease is non-cystic fibrosis bronchiactasis (NCFB) or cystic fibrosis (CF).

~~20~~18. An aerosol for use according to claim ~~18~~ 16, wherein the pulmonary disease is cystic fibrosis (CF).

~~21~~19. An aerosol for use according to any one of claims ~~17~~ 16 to ~~20~~ 18, wherein the counter ion of the active compound is acetate.

~~22~~20. An aerosol for use according to any one of claims ~~17~~ 16 to ~~21~~ 19, wherein the aerosol being emitted from an aerosol generator at a rate of at least ~~about~~ 0.1 mL dispersed liquid phase per minute.

~~23~~21. An aerosol for use according to any one of claims ~~17~~ 16to ~~21~~ 19, wherein the aerosol being emitted from an aerosol generator at a mean delivery rate of at least ~~about~~ 0.8 mg of the active compound
cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);
or any pharmaceutically acceptable salt thereof; per minute.

~~24~~22. An aerosol for use according to any one of claims ~~17~~ 16 to ~~23~~ 21, wherein the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);
or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose between ~~about~~ 0.1 and ~~about~~ 10000 mg/day.

~~25~~23. An aerosol for use according to any one of claims ~~17~~ 16 to ~~23~~ 21, wherein the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);
or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose between ~~about~~ 0.001 and ~~about~~ 100 mg/kg.

~~26~~24. An aerosol for use according to any one of claims ~~17~~ 16 to ~~23~~ 21, wherein the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose between ~~about~~ 5 and ~~about~~ 1000 mg/day.

~~27~~25. An aerosol for use according to any one of claims ~~17~~ 16 to ~~23~~ 21, wherein the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose of ~~about~~ 20, ~~about~~ 60, ~~about~~ 120, ~~about~~ 240, ~~about~~ 480 or ~~about~~ 960 mg/day.

~~28~~26. An aerosol for use according to any one of claims ~~17~~ 16 to ~~23~~ 21, wherein the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose between ~~about~~ 80 and ~~about~~ 320 mg/day.

~~29~~27. An aerosol for use according to any one of claims ~~17~~ 16 to ~~23~~ 21, wherein the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; is administered to the subject at a dose of ~~about~~ 80, ~~about~~ 160, or ~~about~~ 320 mg/day.

~~30~~28. An aerosol for use according to any one of claims ~~17~~ 16 to ~~29~~ 27, wherein the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; is administered to the subject by oral inhalation.

~~31. A kit for the preparation and delivery of a pharmaceutical aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase~~

~~(a) comprises aqueous droplets comprising the active compound~~

~~cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);~~
~~or any pharmaceutically acceptable salt thereof; wherein~~
~~OctG is (*S*)-2-aminodecanoic acid;~~
~~^{D}Pro is D-proline;~~
~~(b) has a mass median diameter from about 1.5 µm to about 5 µm; and~~
~~(c) has a droplet size distribution having a geometrical standard deviation from about 1.2 to about 1.7;~~
~~and wherein the kit comprises a nebulizer and a liquid composition comprising a concentration within a range from about 4 mg/mL to about 100 mg/mL of the active compound; or any pharmaceutically acceptable salt thereof;~~
~~or comprises a nebulizer and a solid pharmaceutical composition for preparing the liquid composition, wherein the composition comprises the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; and wherein the solid composition is dissolvable or dispersible in an aqueous liquid solvent, and wherein the liquid composition comprises a concentration within a range from about 4 mg/mL to about 100 mg/mL of the active compound; or any pharmaceutically acceptable salt thereof; for use in a method for the prevention, management or treatment of diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity in a subject.~~

~~32. A kit according to claim 31, wherein the nebulizer is selected from the group consisting of jet nebulizers, ultrasonic nebulizers, piezoelectronic nebulizers, jet collision nebulizers, electrohydrodynamic nebulizers, capillary force nebulizers, perforated membrane nebulizers and perforated vibrating membrane nebulizers.~~

~~33. A kit according to claims 31 or 32, wherein the nebulizer is adapted to be capable of aerosolizing the liquid composition at a rate of at least about 0.8 mg of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; per minute.~~

~~34~~29. A kit comprising

a pharmaceutical composition comprising

the active compound

cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-);

or any pharmaceutically acceptable salt thereof; wherein

OctG is (*S*)-2-aminodecanoic acid;

^{D}Pro is D-proline; and

sodium chloride;

and a package insert wherein the package insert comprises instructions for treating a subject for diseases or conditions of the lungs being mediated by or resulting from human neutrophil elastase activity using the active compound.

~~35~~30. A kit according to claim ~~34~~ 29, wherein the kit comprises the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; as aerosol for pulmonary administration comprising a dispersed liquid phase and a continuous gas phase, wherein the dispersed liquid phase

(a) comprises aqueous droplets comprising the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof;

(b) has a mass median diameter from ~~about~~ 1.5 µm to ~~about~~ 5 µm; and

(c) has a droplet size distribution having a geometrical standard deviation from ~~about~~ 1.2 to ~~about~~ 1.7.

~~36~~31. A kit according to any one of claims ~~31~~ 29 to ~~35~~ 30, wherein at least ~~about~~ 70 wt.-% of the loaded dose of the active compound cyclo(-OctG-Glu-Thr-Ala-Ser-Ile-Pro-Pro-Gln-Lys-Tyr-^{D}Pro-Pro-); or any pharmaceutically acceptable salt thereof; is comprised of droplets having a mass median diameter of not more than ~~about~~ 5 µm.

~~37~~32. A kit according to any one of claims ~~31~~ 29 to ~~36~~ 31, wherein the counter ion of the active compound is acetate.