TREATMENT AND PREVENTION OF RESPIRATORY DISEASES

TECHNICAL FIELD

This invention relates to the treatment or prevention of respiratory diseases by administrating compositions comprising human normal immunoglobulin (IgG) by inhalation.

BACKGROUND

Respiratory diseases include any disease or disorder that affects the airways or the lungs. These diseases can be chronic, such as non-cystic fibrosis bronchiectasis (NCFB), chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF), or result from a short-term inflammation of the lungs, *e.g*. caused by an infection, like pneumonia.

Infections are known to be one of the main drivers of exacerbations and subsequent disease progression in many respiratory diseases. A respiratory tract infection can be any infectious disease of the upper or lower respiratory tract. Upper respiratory tract infections include the common cold, laryngitis, pharyngitis/tonsillitis, acute rhinitis, acute rhinosinusitis and acute otitis media. Lower respiratory tract infections include acute bronchitis, bronchiolitis, pneumonia and tracheitis. Patients with chronic lung diseases, such as NCFB, COPD, and CF, are likely to suffer from recurrent respiratory tract infections, which can trigger an acute exacerbation. Cumulatively the damage from consecutive exacerbations leads to the loss of pulmonary function, exercise capacity, quality of life, and often results in reduced life expectancy.

Antibiotics are commonly prescribed to treat respiratory tract infections. However there is evidence from randomised placebo-controlled trials that antibiotics have limited efficacy in treating a large proportion of respiratory tract infections [1]. In addition, the prevalence of antimicrobial resistance is increasing globally. There is therefore an unmet need for an effective therapy for respiratory diseases that are associated with respiratory tract infections.

The present invention provides a new treatment for respiratory diseases, which involves administering human normal immunoglobulin (IgG) by inhalation. The present invention is based on the surprising realisation that inhalation of nebulized IgG aerosol is safe and well tolerated,

and at particular doses can effectively reduce bacterial load in the respiratory tract. The ability to treat infections in the respiratory tract is useful for treating or preventing a range of respiratory diseases, in particular NCFB, COPD, CF and pneumonia.

DISCLOSURE OF THE INVENTION

The inhalation of a nebulized drug results in the rapid delivery of the drug directly into the respiratory tract. However, this route of administration is only useful if it can consistently deliver a drug intact and at the desired dose to the respiratory tract. It was unknown in the art whether IgG's function would be retained after nebulization. Furthermore, while the safety profile of IgG was known for intravenous and subcutaneous administration, it was unknown whether administering nebulized IgG aerosol would be safe.

The inventors have shown for the first time that IgG can be effectively delivered to the respiratory tract by nebulizing the IgG to form an aerosol and administering the aerosol by inhalation. In addition, IgG's function, based on the Fc and Fab portions, remains intact after nebulization. The inhalation administration route is particularly useful because it offers a localized delivery of IgG to the affected region and restricts the biopharmaceutical distribution of IgG to the lungs. The inventors have demonstrated the safety of nebulized IgG aerosol administered by inhalation in both primate models and human patients. The examples demonstrate that 0.3-6 mg/kg of IgG administered in a single inhalation session in healthy human volunteers and over repeated daily inhalation sessions in NCFB subjects has a favourable safety profile. The present application therefore demonstrates a new and advantageous administration route for IgG.

The inventors have also shown for the first time that nebulized IgG aerosol inhaled administered by inhalation at a dose of 1-6 mg/kg can effectively reduce bacterial load in the sputum. Sputum (also referred to as phlegm) refers to the mucus made in the respiratory system (*i.e.* the lungs and airways). Therefore, the inventors have identified for the first time that nebulized IgG aerosol administered by inhalation at particular doses can effectively treat respiratory tract infections, which are the main driver of disease progression across many respiratory diseases. The application therefore provides a new and effective treatment for various respiratory diseases, including NCFB, COPD, CF and pneumonia. Patients with these diseases lack the ability to mount an effective antimicrobial, anti-viral and anti-fungal defences; have been infected or colonized with difficult to treat bacterial strains (e.g. antibiotic resistant strains) or the diseased

tissue/disease state hinders the ability of the patient's immune system/exogenous therapy to effectively clear the pathogen.

The inventors have also identified that the nebulized IgG aerosol is useful for treating or preventing respiratory tract infections, for example in patients with primary and secondary immunodeficiencies. These patients have an increased risk of catching respiratory tract infections due to their compromised immune systems.

The invention relates to administering IgG by inhalation, which involves nebulizing a composition comprising IgG to form an aerosol and then administering the aerosol to the patient by inhalation (preferably by mouth inhalation).

In one aspect, the invention provides a composition comprising human normal immunoglobulin (IgG) for use in a method of treating or preventing a respiratory disease in a subject, wherein the composition is nebulized to form an aerosol and the aerosol is administered by inhalation, and wherein the IgG is administered at a dose of 1-15 mg/kg.

The invention also provides a method of treating or preventing a respiratory disease in a subject comprising nebulizing a therapeutically or prophylactically effective amount of a composition comprising human normal immunoglobulin (IgG) to form an aerosol and administering the aerosol by inhalation to the subject, wherein the IgG is administered at a dose of 1-15 mg/kg.

The invention further provides a use of a composition comprising human normal immunoglobulin (IgG) in the manufacture of a medicament for treating or preventing a respiratory disease in a subject, wherein the composition is to be nebulized to form an aerosol and the aerosol is to be administered by inhalation to the subject and wherein the IgG is administered at a dose of 1-15 mg/kg.

The invention further provides a composition comprising human normal immunoglobulin (IgG) for treating or preventing a respiratory disease, wherein the composition is to be nebulized to form an aerosol and the aerosol is to be administered by inhalation to the subject, wherein the IgG is administered at a dose of 1-15 mg/kg.

The IgG is typically delivered at a dose of 4-8 mg/kg, such as 6 mg/kg. In general, the composition is repeatedly administered, for example the composition is administered once a day. The IgG can be administered at a dose of 1-15 mg/kg/day, typically 6 mg/kg/day or 12 mg/kg/day.

A range of respiratory diseases can be treated or prevented with the compositions, including NCFB, COPD, CF or pneumonia. As demonstrated in the examples, IgG can effectively treat NCFB. Therefore, in preferred embodiments, the respiratory disease is NCFB.

The composition can also be used to treat or prevent a bacterial pulmonary infection. In particular, the composition may be useful for treating or preventing respiratory diseases that are associated with bacterial pulmonary infections, such NCFB, COPD, CF or pneumonia. In addition, the composition can be used to treat or prevent a bacterial pulmonary infection in the subject with an immunodeficiency. This immunodeficiency can be a primary or secondary immunodeficiency.

The composition can reduce bacterial load in the sputum of the subject, for example bacterial load can be reduced by at least 0.5-3 $\log_{10}$ CFU/ml. Preferably, bacterial load is reduced by at least 1.0 $\log_{10}$ CFU/ml. The composition may be useful for reducing specific bacteria in the sputum, for example the composition can reduce the level of one or more of *Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis, Streptococcus pneumoniae*, *Enterobacterales* family or *Staphylococcus aureus* in the sputum. The inventors have found that the composition is particularly effective at reducing the level of *Pseudomonas aeruginosa* in the sputum.

The subject can test positive for one or more of *Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis, Streptococcus pneumoniae*, *Enterobacterales* family or *Staphylococcus aureus,* in particular *Pseudomonas aeruginosa.*

In some embodiments, the composition can increase the Quality of Life Questionnaire – Bronchiectasis (QoLB) score of the subject. The minimal clinically important difference (MCID) in the QoLB score can be defined as being 8 points or more within any domain including QoL-B Respiratory symptoms, or in the total QoL-B score. Therefore, preferably the composition can increase the QoLB score by at least 8 points, in particular by at least 10 points.

The human normal immunoglobulin (IgG) is generally derived from human plasma. Typically, the composition further comprises a stabilizer, such as proline or serine. The amount of IgG in the

composition can vary, for example the IgG can be at a concentration of 2-15%. Preferably, the IgG is at a concentration of 7%. The IgG in the composition normally has a high purity, for example the IgG has a purity of at least 95%, or more preferably a purity of at least 98%.

The examples demonstrate that the compositions can be effectively administered using a nebulizer. Preferably, the nebulizer incorporates a vibrating membrane.

Definitions

The practice of the present invention will employ, unless otherwise indicated, conventional methods of chemistry, biochemistry, molecular biology, immunology and pharmacology, within the skill of the art. Such techniques are explained fully in the literature.

The terms “administration” or “administering” or “administered” are used interchangeably herein. Unless specifically stated otherwise the term administration refers to the inhalation of nebulized composition.

The terms “treatment”, “therapy” and “treating” are used interchangeably herein and refer to therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder. The terms “treatment”, “therapy” and “treating” may include prophylaxis, unless indicated otherwise. The terms “treatment”, “therapy” and “treating” also include on-demand treatment. By a “therapeutically effective amount” it is meant that the administration of that amount of human normal immunoglobulin to a subject, either in a single dose or as part of a series, is effective for treatment. By a “prophylactically effective amount” it is meant that the administration of an amount of human normal immunoglobulin to a subject, either in a single dose or as part of a series, is effective for prevention. A disorder is treated or prevented if administration of human normal immunoglobulin as described herein to a subject (*e.g.*, a human with a respiratory disease, such as NCFB, COPD, CF or pneumonia, or a human with a pulmonary infection) results in a therapeutic or prophylactic effect, which can mean that there is a change in one or more of the following factors, at least temporarily following treatment:

(a) a reduction in bacterial load in the sputum, including but not limited to P*seudomonas aeruginosa*, which can be measured by determining the colony forming units as a measure of sputum bacterial density as described in the examples;

(b) an improvement in the Quality of Life Questionnaire – Bronchiectasis (*i.e.* an increase in the score), which is described in [36] and the examples;

(c) an improvement in an LCI score (*i.e.* a reduction in the LCI score), which can be measured by the multiple breath nitrogen gas washout technique described in [35] and the examples;

(d) a reduction in viral load in the nasal a nasal swab or the sputum, which can be measured by PCR.

Any reference to a composition comprising human normal immunoglobulin (IgG) for use in a method of treatment, also covers a method of treatment comprising administering the composition comprising IgG to a subject, as well as the use of the composition comprising IgG in a method of treatment, and the use of the composition comprising IgG in the manufacture of a medicament for treating a disease.

The term "subject" refers to any animal (*e.g.*, a mammal), including, but not limited to, humans, non-human primates, canines, felines, rabbits, rodents, and the like, which is to be the recipient of a particular treatment. The subject is preferably a human. Typically, the terms "subject" and "patient" are used interchangeably herein in reference to a human subject. The subject can be male or female. The subject can be a child (*i.e.* patients who are 18 years old or younger) or an adult (*i.e.* patients who is 18 years old or older). The subject can also be elderly, for example patients who are over the age 50 or over the age of 70.

The term "pharmaceutically acceptable" refers to a substance approved or approvable by a regulatory agency of the Federal government or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, including humans.

The terms "pharmaceutically acceptable excipient, carrier, or adjuvant" or "acceptable pharmaceutical carrier" refer to an excipient, carrier, or adjuvant that can be administered to a patient, together with at least one agent of the present disclosure, and which does not destroy the pharmacological activity thereof and is non-toxic when administered in doses sufficient to deliver a therapeutic effect. In general, those of skill in the art and the U.S. FDA consider a pharmaceutically acceptable excipient, carrier, or adjuvant to be an inactive ingredient of any formulation.

The term "substantially pure" refers to a preparation comprising at least 90% by weight of IgG, particularly at least 95% by weight, or at least 96%, 97%, 98%, or 99% by weight, *e.g.*, 95-99%

or more by weight of IgG. Purity may be measured by methods appropriate for the compound of interest (*e.g.*, chromatographic methods, polyacrylamide gel electrophoresis, HPLC analysis, and the like).

The term "comprising" encompasses "including" as well as "consisting", "consisting of" and/or "consisting essentially of", *e.g.*, a composition "comprising" X may consist exclusively of X or may include something additional, *e.g.*, X + Y. It is also understood that wherever embodiments are described herein with the language "consisting essentially of" otherwise analogous embodiments described in terms of "consisting of" are also provided.

The term "about" in relation to a numerical value x is optional and means, for example, x±10%.

The word "substantially" does not exclude "completely", *e.g.*, a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

The term "and/or", *e.g.*, "X and/or Y" shall be understood to mean either "X and Y" or "X or Y" and shall be taken to provide explicit support for both meanings or for either meaning.

As used herein, the verb "to comprise" and its conjugations is used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. In addition, the verb "to consist" may be replaced, if necessary, by "to consist essentially of" meaning that a product as defined herein may comprise additional component(s) than the ones specifically identified, said additional component(s) not altering the unique characteristic of the invention.

Unless specifically stated, a process or method comprising numerous steps may comprise additional steps at the beginning or end of the method, or may comprise additional intervening steps. Also, steps may be combined, omitted or performed in an alternative order, if appropriate.

As used in the present disclosure and claims, the singular forms "a", "an" and "the" include plural forms unless the context clearly dictates otherwise.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

Various embodiments of the invention are described herein. It will be appreciated that the features specified in each embodiment may be combined with other specified features, to provide further embodiments. In particular, embodiments highlighted herein as being suitable, typical or preferred may be combined with each other (except when they are mutually exclusive).

Respiratory diseases

Infections are a common driver for respiratory diseases. For example, a high pathogenic load of viruses and/or bacteria in the respiratory tract is a common trigger for exacerbations in NCFB, COPD, and CF patients. Furthermore, bacterial infections in these patients can become resistant to antibiotics, produce mucus or proteinases for defence, form collective biofilms and colonize the lung. This presents difficulties in ensuring effective treatment. The disease state itself can change the characteristics of the airways and tissue to such an extent that it effectively enhances a pathogen's ability to evade detection by the immune system, prevents or limits access of exogenous therapy and results in the pathogen's ability to successfully inhabit or colonize the lung. In addition, bacterial infections in the respiratory tract are also a cause of pneumonia.

The clinical trial in the examples demonstrates for the first time the bactericidal efficacy of nebulized IgG aerosol administered by inhalation at 1-6 mg/kg in NCFB patients. The inventors have realised that because there is commonality between the pathogens in respiratory diseases, the same dose of IgG (*i.e.* 1-6 mg/kg) is likely to useful for treating respiratory diseases that are triggered or associated with bacterial infections, such as COPD, CF and pneumonia. Therefore, the compositions can treat or prevent NCFB, COPD, CF or pneumonia, in particular NCFB.

These patient populations lack the ability to mount an effective antimicrobial, anti-viral or anti-fungal defence; have been infected or colonized with difficult to treat bacterial strains (*e.g.* antibiotic resistant) or the diseased tissue or disease state hinders the ability of the patient's immune system or exogenous therapy to effectively clear the pathogen.

Pulmonary infections

In view of the data in the examples, which demonstrate the bactericidal efficacy of IgG administered by inhalation at certain doses, the inventors have realized that IgG may be useful for treating or preventing pulmonary infections. For example, the compositions can treat or

prevent pulmonary infections in patients that have been diagnosed with NCFB, COPD, an immunodeficiency, CF or pneumonia.

In one aspect, the invention provides a composition comprising human normal immunoglobulin (IgG) for use in a method of treating or preventing a pulmonary infection in a subject, wherein the composition is nebulized to form an aerosol and the aerosol is administered by inhalation, and wherein the IgG is administered at a dose of 1-15 mg/kg/day. In some embodiments, the patient has NCFB, COPD, an immunodeficiency (e.g. a primary or a secondary immunodeficiency), CF or pneumonia, in particular NCFB. Preferably, the infection is a pulmonary bacterial infection.

The compositions are also expected to be useful to treat or prevent viral infections, for example, a viral lung infection that is associated with a respiratory disease. For example, the composition can treat or prevent a viral lung infection in a patient who has NCFB, COPD, an immunodeficiency (e.g. a primary or a secondary immunodeficiency), CF or pneumonia.

Bacterial load

The examples demonstrate that at all doses tested IgG administered by inhalation led to a reduction in bacterial load. The mean colony forming unity (CFU) reduction was 1.66 log_{10} units for the 1 mg/kg cohort and 1.86 log_{10} CFU/ml for the 6 mg/kg cohort. For the 6 mg/kg cohort at Day 8 their levels of *Pseudomonas aeruginosa* dropped by a mean of 0.9 log_{10} CFU/ml with a further drop from Baseline levels of 2.48 log_{10} CFU/ml at Day 15. The compositions are therefore useful for reducing bacterial load in the lungs. The term units is used herein as a synonym for CFU/mL.

In some embodiments, the composition reduces bacterial load by at least 1, 1.5, 2, 2.5, 3, 3.5 or 4 log_{10} CFU/ml. In particular, the composition can reduce bacterial load by at least 1 or 1.5 log_{10} CFU/ml after 15 days of treatment. In particular, the composition can reduce bacterial load by at least 0.9 log_{10} units after 8 days of treatment and/or the composition can reduce bacterial load by at least 2.0 log_{10} CFU/ml after 15 days of treatment.

The patients in the clinical trial tested positive for one or more of the following bacteria (*i.e.* bacteria were present in a sputum culture from the patient): *Haemophilus influenza*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, members of *Enterobacterales* family or *Staphylococcus aureus.* Possible members of the *Enterobacterales*

family include *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae*. The compositions may therefore be useful at reducing the level of one or more of the following bacteria: *Haemophilus influenza*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, members of *Enterobacterales* family or *Staphylococcus aureus* in the sputum of a subject. In particular, the composition are useful at reducing the levels of *Haemophilus influenza* and *Pseudomonas aeruginosa.* The patients to be treated preferably test positive for one or more of the following bacteria (*i.e.* bacteria are present in a sputum culture from the patient): *Haemophilus influenza*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, members of *Enterobacterales* family or *Staphylococcus aureus.* In particular, the patients to be treated test positive for *Haemophilus influenza* and *Pseudomonas aeruginosa*.

As demonstrated in the examples, treatment with nebulized IgG aerosol at a dose of 1-6 mg/kg resulted in a reduction in the levels of *Pseudomonas aeruginosa* in the sputum. This is advantageous because *P. aeruginosa* is known to be resilient to antibiotic therapy and appears to be the most potent bacterial stimulus of neutrophil recruitment and release of neutrophil elastase in the bronchiectasis airways [2]. About 30% of NCFB patients are colonized with *P. aeruginosa*, which is suspected to be the pathogen responsible for recurrent exacerbations in those patients. *P. aeruginosa* is also known to be one of the most harmful bacteria found in subjects with COPD and during exacerbations of COPD [3]. In 2017, multidrug-resistant *P. aeruginosa* caused an estimated 32,600 infections among hospitalized patients and 2,700 estimated deaths in the United States [4]. *P. aeruginosa* is also commonly found in CF patients where it has been identified as a particularly difficult bacteria to eradicate and has been linked to the loss of pulmonary function and disease progression [5]. Resistant strains of *P. aeruginosa* are on the rise and associated with hospital acquired infections including pneumonia in critically ill and immunocompromised patients [6]. PID patients are also at particular risk of contracting *P. aeruginosa* infections which often develop into chronic colonization because they are antibody deficient by definition and normal human immunoglobulin delivered IV may not be sufficient to protect the lungs [7].

The inventors have identified a new and effective treatment for reducing *P. aeruginosa* in the lung. In other words, the inventors have identified a new and effective treatment for a lung infection. This is highly advantageous because antimicrobial therapies do not always result in effective treatment of *P. aeruginosa* infections in all patients. The compositions are therefore particularly useful at treating or preventing respiratory diseases that are associated with *P. aeruginosa*, such as NCFB, COPD, CF and pneumonia. In addition, the compositions are particularly useful at

treating or preventing a *P. aeruginosa* pulmonary infection, for example in patients that have an immunodeficiency.

In preferred embodiments, the composition reduces the level of *P. aeruginosa*, for example in the sputum. In further preferred embodiments, the compositions treats or prevents a respiratory disease that is associated with *P. aeruginosa*.

Lung Clearance Index

The Lung Clearance Index (LCI) is a measure of the effort required to evacuate a known quantity of gas derived from the multiple breath inert gas washout technique [35]. Improvements are noted as lower scores. The examples demonstrate that patients treated with IgG had improvements in their LCI (i.e. they had lower LCI scores) as demonstrated in the Change from Baseline assessments. In 3 subjects who underwent LCI testing in the 6 mg/kg cohort, the mean (SD) LCI measurement of 9.317 (1.2968) decreased to 8.553 (2.1710) at Day 14 representing a total improvement of -0.763 (1.1769).

Therefore, in some embodiments the composition reduces the LCI score of the subject. The composition may reduce the LCI score by more than 0.5, by more than 1, by more than 2 or by more than 3. After the composition is administered this can result in an LCI score that is lower than 9, such as 7.5.

The examples demonstrate that IgG administered at a dose of 6 mg/kg can reduce the LCI score. Therefore, a reduction in the LCI score that is greater than 0.5 may be observed when the IgG is administered at a dose of 6 mg/kg.

Spirometry

Spirometry is a common type of pulmonary function test. This test measures how much air a patient can breathe in and out of your lungs, as well as how easily and fast the patient can the blow the air out of their lungs. Forced expiratory volume (FEV) measures how much air a person can exhale during a forced breath. The amount of air exhaled may be measured during the first (FEV_1) of the forced breath. The forced vital capacity (FVC) is the total amount of air that can be forcible exhaled after taking deepest breath possible. Average FVC values in healthy subjects aged 20-60 range from 4.75 to 5.5 L in males and from 3.75 to 3.25 L in females. Healthy subjects

have a FEV1/FVC ratio of greater than 0.70 and FEV_1 and FVC values above 80% of the predicted value. As demonstrated in the examples, spirometry can be performed using reference values from the 2012 Global Lung Initiative.

As set out above, the inventors have realised that IgG administered by inhalation may be useful for treating or preventing pulmonary infections. The compositions may be useful for stabilising pulmonary function by reducing inflammation in the respiratory tract that is caused by the infection. Therefore, in some embodiments, the composition stabilizes pulmonary function.

Quality of Life-Bronchiectasis questionnaire

The Quality of Life–Bronchiectasis questionnaire is a self-administered, patient reported outcome measure assessing symptoms, functioning, and health related quality of life for patients, which contains 37 items on 8 domains: Respiratory Symptoms; Physical, Role, Emotional, and Social Functioning; Vitality; Health Perceptions; and Treatment Burden. Improvements are noted as higher scores [36]. As demonstrated in the examples, patients treated with nebulized IgG aerosol compositions consistently recorded improvements in their Respiratory Symptoms score on the Quality of Life–Bronchiectasis questionnaire. Therefore, in some embodiments, the composition increases the Quality of Life Questionnaire – Bronchiectasis (QoLB) score of the subject. This improvement can be in a single domain (for example the Respiratory Symptoms score) or in two or more domains. In preferred embodiments, the composition increases the Respiratory Symptoms score, any other domain score, or the total QoLB score. In some embodiments, the composition increases the QoLB score by at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points, at least 10 points, at least 11 points, at least 12 points, at least 12 points, at least 13 points, at least 14 points or at least 15 points. Generally, the minimal clinically important difference (MCID) in a QoLB score is 8 points. Therefore, in preferred embodiments, the composition increases the QoLB score by at least 8 points, at least 10 points or at least 12 points.

Non-cystic fibrosis bronchiectasis (NCFB)

Bronchiectasis refers to a heterogeneous group of respiratory diseases that are characterized by permanent abnormal dilation of the bronchi that leads to chronic productive cough, recurrent infections, and dyspnoea. Bronchiectasis can be classified into two broad categories: cystic fibrosis and non-cystic fibrosis (NCFB). There are many subtypes of NCFB, which include

congenital defects affecting the ciliary function in the respiratory epithelium, inherited disorders of immunity, destructive infections, inhalation of toxins, and foreign body aspiration [8]. NCFB may be diagnosed with other concomitant pulmonary disorders, such as COPD, severe asthma or an immunodeficiency (e.g. a primary immunodeficiency).

Non-cystic fibrosis bronchiectasis (NCFB) is a chronic, progressive respiratory disorder which is characterized by irreversible, abnormal dilation of bronchi, a persistent cough, excessive sputum production and recurrent pulmonary infections. These pathological changes in the bronchial walls may be due to chronic inflammation resulting from recurrent or chronic infections in the lung, but the exact cause is unknown. NCFB symptoms include intermittent episodes of pulmonary infections with excessive mucus production, persistent daily expectoration of viscous, a chronic cough, dyspnoea, chronic fatigue, and haemoptysis [9].

NCFB has a high unmet medical need due to the increasing prevalence and limited symptomatic treatment available. In NCFB the main burden and pathomechanism that drives exacerbations, chronic inflammation and lung damage is infections [10], [11] and [12]. Every moderate or severe exacerbation accelerates disease progression with the risk of a further decline in lung function, exercise capacity, QoL and a cumulative potential reduction in expected lifespan. One of the main triggers for exacerbations is a high bacterial load in the lower respiratory tract or viral infections in the upper respiratory tract.

NCFB has recently become much more prevalent in the general population. Studies report a prevalence ranging from 486 to 1106 per 100,000 persons with an incidence that appears to be rising, particularly in women and older individuals [13] and [14]. NCFB patients often require long hospital stays and frequent outpatient care.

The standard management of NCFB aims to reduce symptoms and the risk of future complications, while improving the patient's quality of life, and preventing further decline in pulmonary function. The main recommended treatments include antibiotics, mucolytic agents (which aid in the clearance of mucus), bronchodilators, airway clearance techniques, pulmonary rehabilitation and surgery [15]. However, the clinical outcomes of these therapeutic interventions remain largely symptomatic (*i.e.* the therapy eases the symptoms without addressing the basic cause of the disease) and do not provide adequate control or protection against active pulmonary infections that result in the need for further therapy. Thus, there remains an unmet medical need for more effective treatments for NCFB.

The present invention advantageously provides a new safe and effective treatment for NCFB that involves administering nebulized human normal immunoglobulin (IgG) aerosol by inhalation. The examples demonstrate that this effective treatment can involve improving a patient's Quality of Life Questionnaire – Bronchiectasis (QoLB) score and reducing their Lung Clearance Index (LCI). Previous treatments for NCFB failed to establish these improvements in patient scores.

The examples demonstrate that administrating nebulized IgG aerosol by inhalation can reduce bacterial load in the sputum of NCFB patients, and reduce *Pseudomonas aeruginosa* levels in particular. A main clinical feature of NCFB is acute, chronic infections that damage the airways, and *Pseudomonas aeruginosa* is thought to be a responsible for recurrent exacerbations in around a third of NCFB patients. Therefore, administering IgG by inhalation can more effectively treat a central feature of NCFB. Without wishing to be bound by any particular theory, this reduction in bacterial load is thought to be useful to decrease the annual number of exacerbations experienced by NCFB patients, because infections are a major trigger for exacerbations. Therefore, in some embodiments, the compositions can reduce the annual number of exacerbations experienced by NCFB patients.

Therefore, the compositions are particularly useful for treating or preventing non-cystic fibrosis bronchiectasis (NCFB). The invention therefore provides a composition comprising human normal immunoglobulin (IgG) for use in a method of treating or NCFB in a subject, wherein the composition is nebulized to form an aerosol and the aerosol is administered by inhalation, and wherein the IgG is administered at a dose of 1-15 mg/kg. The invention also provides a method of treating NCFB in a subject comprising administering a therapeutically effective amount of a composition comprising IgG to form an aerosol and administering the aerosol by inhalation to the subject, wherein the IgG is administered at a dose of 1-15 mg/kg. The invention further provides a use of a composition comprising IgG in the manufacture of a medicament for treating NCFB in a subject, wherein the composition is to be nebulized to form an aerosol and the aerosol is to be administered by inhalation to the subject and wherein the IgG is administered at a dose of 1-15 mg/kg. The invention further provides a composition comprising IgG for treating NCFB in a subject, wherein the composition is to be nebulized to form an aerosol and the aerosol is to be administered by inhalation to the subject and wherein the IgG is administered at a dose of 1-15 mg/kg.

NFCB can occur in both adults and children. Therefore, the subject may be an adult (e.g. 18 years old or older) or a child (e.g. 18 years old or younger).

The incidence of bronchiectasis was found to be higher for women (34 per 100,000) than men (23 per 100,000), and increased substantially with age, from 2 per 100,000 persons for those between the ages of 18 to 34 years to 154 per 100,000 persons for those over the age of ≥ 75 years. At all ages, the incidence of bronchiectasis was approximately 1.1-fold to 1.5-fold higher among women compared to men [16]. Therefore, the compositions are particularly suitable for older patients, for example patients who 50 years or older, 60 years or older, 70 years or older or 80 years or older. Furthermore, the compositions are particularly suitable for female patients, for example female patients who are over the age 50 or over the age of 70.

In a hospital setting, there is a higher mortality mainly in older males (> 65 years of age) with histories of smoking, low lung function and mechanical ventilation [17]. The compositions are therefore useful for treating older male patients, for example men who are over the age of 65 years old.

The pathological dilation of the airways that occurs in NCFB can be clinically identified by radiographic demonstration of airway enlargement (*e.g.* by a CT scan) [218]. As shown in the examples, a patient can be diagnosed as suffering from NCFB if their CT scan showed bronchial wall dilatation with or without bronchial wall thickening. NCFB is preferably diagnosed using a CT scan.

A patient can also be identified as having NCFB based on their forced expiratory volume. In the examples, a patient was diagnosed as having NCFB if they had a forced expiratory volume in 1 second (FEV_1) ≥ 40% of the predicted value regarding age, height, gender, and ethnicity, and FEV_1 ≥ 1L (pre-bronchodilator values). Therefore, in some embodiments, the patient has a forced expiratory volume in 1 second (FEV_1) ≥ 40% and/or a FEV_1 ≥ 1L of the predicted value for their regarding age, height, gender, and ethnicity.

Exacerbations are considered to be key events in the progression of NCFB and can be triggered by infections caused by bacteria and/or viruses. During exacerbations, patients can suffer from increased hyperinflation, trapped gas, reduced expiratory flow, and increased dyspnoea. An exacerbation of NCFB may be defined as the acute worsening of one or more symptoms of NCFB beyond normal day-to-day variations, for example the requirement of antibiotics in the presence

of one or more symptoms such as increasing cough, increasing sputum volume, or worsening sputum purulence [19]. Alternatively, an exacerbation of NCFB can be defined using the criteria in Hill *et al*. [20], which define a patient with an exacerbation of bronchiectasis to have a deterioration in three or more of the following key symptoms for at least 48h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis; and a clinician determines that a change in bronchiectasis treatment is required.

The compositions can decrease the number of exacerbations experienced by a patient. In some embodiments, the composition can prevent the deterioration of one or more of the following key symptoms for at least 48 h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis; and a clinician determines that a change in bronchiectasis treatment is required. In addition, if the composition is prophylactically (*e.g*. if the composition is administered long term) then the composition can prevent exacerbations from occurring.

In preferred embodiments, the NCFB patients to be treated may have experienced 2 or more exacerbations in the previous year.

In other embodiments, the compositions may be useful for treating viral infections or neutralising viral infections in NCFB patients.

The examples demonstrate that at all doses tested IgG treatment in NCFB patients led to a reduction in bacterial load with a mean CFU reduction of 1.66 log_{10} CFU/ml for the 1 mg/kg cohort and 1.86 log_{10} CFU/ml for the 6 mg/kg cohort. For the 6 mg/kg cohort at Day 8 their CFU dropped by a mean of 0.9 log_{10} CFU/ml with a further drop from Baseline levels of 2.48 log_{10} CFU/ml at Day 15. A moderate sustained response was noted through Day 21, at 1 week after treatment cessation 0.93 log_{10} CFU/ml.

In some embodiments, the composition reduces bacterial load by at least 1, 1.5, 2, 2.5, 3, 3.5 or 4 log_{10} CFU/ml. In particular, the composition can reduce bacterial load by at least 1 or 1.5 log_{10} CFU/ml after 15 days of treatment. In particular, the composition can reduce bacterial load by at least 0.9 log_{10} CFU/ml after 8 days of treatment and/or the composition can reduce bacterial load by at least 2.0 log_{10} CFU/ml after 15 days of treatment.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is defined by the global initiative for chronic obstructive lung disease (GOLD) as a type of progressive lung disease characterized by persistent respiratory symptoms (dyspnoea, cough, sputum production and/or exacerbations) due to abnormalities of the airways and/or the alveoli that cause persistent, and often progressive, airflow obstruction [21]. The main symptoms of COPD include shortness of breath and a cough, which may or may not produce mucus. COPD progressively worsens, with everyday activities such as walking or dressing becoming difficult. The two most common types of COPD are emphysema and chronic bronchitis. Emphysema is defined as enlarged airspaces (alveoli) whose walls have broken down resulting in permanent damage to the lung tissue. Chronic bronchitis is defined as a productive cough (also known as a wet cough) that is present for at least three months each year for two years. Patients suffering from COPD typically have a post-bronchodilator FEV1 (forced expiratory volume at 1s) / FVC (forced vital capacity) ratio of less than 0.7. FEV1 and FVC can be measured by spirometry, using standard methods in the art [22].

The severity of COPD can be graded based on the severity of airflow limitation in a subject, as explained in [23]. The COPD can be mild, moderate, severe, or very severe. Briefly, in a subject with an FEV1/FVC ratio <0.7, the grading of severity of airflow limitation is based on the measured post-bronchodilator FEV1, and how this measured value compares to a predicted value for a healthy subject. A subject with mild COPD has an FEV1 at least 80% of predicted. A subject with moderate COPD has an FEV1 from 50% to 80% of predicted. A subject with severe COPD has an FEV1 from 30% to 50% of predicted. A subject with very severe COPD has an FEV1 less than 30% of predicted.

Factors that imply a potential role for bacteria in COPD include: (a) their presence in approximately 50% of lower airway samples in exacerbations; (b) approximately 50% of COPD patients have bacteria colonized in their airways; (c) chronic bronchitis, pulmonary infections and sputum bacterial counts are associated with lung function decline; (e) bacteria are associated with increased inflammatory markers in exacerbations; (f) chronic airway colonization is related to the frequency and severity of exacerbations and to levels of airway inflammatory markers and (g) bacteria activate lung T cells in COPD to produce a pro-inflammatory response [24]. A systematic review and meta-analysis identified that approximately 50% of exacerbations of COPD are associated with the isolation of bacteria from the lower respiratory tract; and *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Acinetobacter baumannii,*

Pseudomonas aeruginosa, and Staphylococcus aureus were found to be the most prevalent bacteria [25].

The examples demonstrate that nebulized IgG aerosol administered by inhalation at 1-6 mg/kg can effectively reduce bacterial load in the sputum. The inventors realised that nebulized IgG aerosol at particular doses may therefore be useful for treating COPD, because bacterial infections can be associated with exacerbations of COPD. Therefore, the compositions are particularly useful for treating COPD. For example, the composition is useful for treating COPD when the IgG is administered at a dose of 1-15 mg/kg.

Pneumonia

Pneumonia is usually caused by a bacterial or viral infection in the lungs. Symptoms typically include some combination of productive or dry cough, chest pain, fever, and difficulty breathing. The disease may be classified by where it was acquired, such as community- or hospital-acquired or healthcare-associated pneumonia. Chest X-rays, blood tests, and culture of the sputum can be used to diagnose pneumonia.

The examples demonstrate that nebulized IgG aerosol administered by inhalation at 1-6 mg/kg can effectively reduce bacterial load in the sputum. The inventors have realised that IgG may be useful for reducing the severity of infections and treating the underlying infection. The inventors have also realised that IgG may help to reduce the risk of pulmonary infections if administered prophylactically. Nebulized IgG at particular doses may therefore be useful for treating or preventing pneumonia. Therefore, the compositions are useful treating or preventing pneumonia, in particular when administered at a dose of 1-15 mg/kg.

Immunodeficiency

The examples demonstrate the bactericidal efficacy of IgG administered by inhalation at certain doses. The inventors therefore identified that nebulized IgG aerosol administered by inhalation may be useful for treating pulmonary infections in patients with primary and secondary immunodeficiencies. In addition, IgG may also help to reduce the risk of pulmonary infections in patients with primary and secondary immunodeficiencies if administered prophylactically. Nebulized IgG at particular doses may therefore be useful for treating and preventing a pulmonary

infection in a patient with an immunodeficiency, in particular when administered at a dose of 1-15 mg/kg.

Primary immunodeficiency (PID) or inborn errors of immunity (IEI) encompasses more than 400 genetic forms of immunodeficiency which do not arise as a complication of another disease and result in either a complete missing component of the immune system or one which is so affected that immune response is either incomplete or lacking. PID patients are at risk of recurrent pulmonary infections, including colonization with difficult to treat bacteria. As is the case with other pulmonary diseases the loss of pulmonary function, exercise capacity, quality of life, along with a generally reduced expected lifespan, are due to the exacerbation sequalae. The unmet medical need in PID patients is particularly high and unaddressed as no to little protective immune response can be expected in this population. The compositions are useful treating or preventing a pulmonary infection in patients with a primary immunodeficiency, in particular when the IgG is administered at a dose of 1-15 mg/kg. NCFB patients can also suffer from a primary immunodeficiency therefore, in a preferred embodiment the patient to be treated has NCFB and a primary immunodeficiency.

Secondary immunodeficiencies are caused when the immune system is significantly compromised by external factor(s). They are more common than primary immunodeficiencies. Examples include but are not limited to cancer treatments such as radiation and chemotherapy; chronic immunosuppressive therapies required for stem cell and solid organ transplants; immunosuppressive infections such as HIV and COVID; severe burns and malnutrition. All of the above external events can lead to potential serious and life-threatening pulmonary infections. The treatment of choice is to remove the inciting external factor(s) triggering the secondary immunodeficiency. However, this may not be possible in many cases. In this situation nebulized IgG aerosol administered by inhalation has the potential to reduce the risk of pulmonary infections if administered prophylactically and may reduce the severity of acute infections.

The compositions are useful treating or preventing a pulmonary infection in patients with a secondary immunodeficiency, in particular when the IgG is administered at a dose of 1-15 mg/kg. The secondary immunodeficiency can be caused by cancer treatments (e.g. radiation and/or chemotherapy), chronic immunosuppressive therapies, immunosuppressive infections (e.g. HIV and COVID) severe burns and malnutrition.

Cystic Fibrosis

Cystic fibrosis is a genetic disorder affected at least 100,000 persons worldwide whereby mutations in both copies of the cystic fibrosis transmembrane conductance regulator (CFTR) protein resulting in dysfunction across several organs including dangerously excessive mucus production and accumulation in the lung leading to breathing difficulties/deficiencies and increased capacity for pathogenic colonization including *Pseudomonas aeruginosa* [26] and [27]. Signs and symptoms typically emerge during infancy and early childhood. Treatments include antimicrobial therapy, mucolytics symptomatic control and CFTR modulators. There is a distinct lack of therapeutic options to treat or prevent pulmonary infections in this sensitive population.

The examples demonstrate that IgG administered by inhalation at 1-6 mg/kg can effectively reduce bacterial load in the sputum. The inventors realised that nebulized IgG at particular doses may therefore be useful for treating cystic fibrosis and treating or preventing pulmonary infections in patients with cystic fibrosis. The compositions are useful treating or preventing a pulmonary infection in patients with cystic fibrosis, in particular when the IgG is administered at a dose of 1-15 mg/kg.

Doses

The IgG can be administered at a dose of 1-15 mg/kg, *e.g.* 1-12 mg/kg or 1-10 mg/kg. The examples demonstrate that IgG administered by inhalation at a dose of 0.3-10 mg/kg is safe. The IgG can also therefore be administered at a dose of 0.3-10 mg/kg. Preferably the IgG is administered at a dose of 4-8 mg/kg, such as 6 mg/kg.

The composition is normally repetitively administered, for example the composition can be administered once a day, once every two days or once every three days. As demonstrated in the examples, IgG administered once a day was able to reduce bacterial load. Therefore, preferably, the IgG is administered at a dose 1-15 mg/kg/day *e.g.* 1-12 mg/kg/day, 1-10 mg/kg/day, 4-8 mg/kg/day or 6 mg/kg/day. The IgG can also be administered at a dose of 0.3-10 mg/kg/day. The IgG can be administered in a single daily inhalation session. For example, the IgG can be administered at a dose of 1-15 mg/kg in a single inhalation session, preferably 4-8 mg/kg in a single inhalation session. The inhalation sessions preferably occur every day. In other words, the IgG is administered in a single inhalation session at a dose of 1-15 mg/kg/day.

As demonstrated in the examples, IgG administered at a dose of 1-10 mg/kg per session has a favourable safety profile. Therefore, in preferred embodiments, IgG is administered at a dose of 1-10mg/kg per inhalation session, for example, 4-8 mg/kg per inhalation session, in particular 6 mg/kg per inhalation session.

The dose that can be delivered in one inhalation session is limited. It is therefore sometimes useful to administer the IgG more than once a day *i.e.* in repetitive daily inhalation sessions. In a preferred embodiment, the IgG is administered at a dose of 1-15 mg/kg/day in at least two inhalation sessions, preferably 4-8 mg/kg in at least two inhalation sessions. In particular, the IgG can be administered at a dose of 6 mg/kg per inhalation session and two inhalation sessions occur per day.

More than two inhalation sessions can occur in one day, for example the IgG can be delivered in three, four or five inhalation sessions in one day. The dose given in each inhalation session can be different, for example a 10 mg/kg/day dose can be administered in one inhalation session of 4 mg//kg and two further inhalation sessions of 3 mg/kg.

As described herein, the relevant dose of IgG refers to the dose in a single inhalation session or the total dose administered across multiple sessions on the same day. For example, a dose of 10 mg/kg or 10 mg/kg/day refers to a single inhalation session of 10 mg/kg or two inhalation sessions of 5 mg/kg on the same day. In a preferred embodiment, the IgG is administered in two inhalation sessions at a dose of 6 mg/kg, which results in an overall dose of 12 mg/kg/day. Alternatively, the IgG can be administered in a single daily inhalation session of 6 mg/kg, which results in an overall dose of 6 mg/kg/day.

The treatment period can be vary depending on the respiratory disease to be treated. For example, the composition can be administered for at least 1 week, at least 2 weeks or at least 3 weeks.

The composition can be administered for a longer period of time, in particular to treat or prevent NCFB, COPD or CF, or to treat or prevent a pulmonary infection in a patient with an immunodeficiency. For example, the composition is administered for at least one month, at least two months, at least three months, at least six months or at least a year. NCFB, COPD, an immunodeficiency and CF are chronic diseases therefore it can be advantageous to administer

the composition for multiple years or indefinitely. In other words it may be useful to continuously administered the composition.

If the patient suffers from pneumonia, then a shorter treatment period is preferred in order treat the underlying infection. Therefore, the composition can be administered to a patient suffering from pneumonia for up to 25 days, for example 10, 15, 20 or 25 days. For example, the composition can be delivered over a period of 5 to 25 days, preferably 10 to 15 days, such as 14 days. The composition is preferably delivered every day (*i.e.* daily) for 10 to 15 days, such as daily administration for 14 days.

The inventors have surprisingly identified that there is no pharmacokinetic advantage of weight-based dosing of IgG compared to flat dosing (also known as 'fixed dosing'). Weight base dosing alters the dose administered to a patient based on their body weight, whereas in flat dosing the same dose is administered to a patient regardless of their body weight. Flat dosing can provide several advantages, including ease of dose preparation, reduced chance of dosing errors, and minimized drug wastage. It is therefore advantageous to administer IgG at a flat dose, rather than by weight base dosing.

Without wishing to be bound by any particular theory, the inventors have realized that weight based dosing is likely to be effective because the size of a patient's lungs is independent from body weight (*i.e.* most patients have lungs that are the same size). The effect of IgG is expected to be local in the lung only and not systemic, therefore flat dosing is believed to have the same effect as weight based dosing.

Therefore, in alternative embodiment, the IgG is administered at flat (or fixed) dose that is independent of the weight of the subject. As demonstrated by Table 6 in the examples, the mean weight of the patients was around 80 kg. The examples therefore demonstrate that IgG administered at a dose of 24 mg, 80 mg, or 480 mg may be useful for treating respiratory diseases. Therefore, in some embodiments, the IgG is administered at a dose of 20 mg to 1200 mg, preferably the IgG is administered at a dose of 20 mg to 500 mg.

In one aspect, the invention provides a composition comprising human normal immunoglobulin (IgG) for use in a method of treating a respiratory disease in a subject, wherein the composition is nebulized to form an aerosol and the aerosol is administered by inhalation, and wherein the

IgG is administered at a dose of 20 mg to 1200 mg, preferably the IgG is is administered at a dose of 20 mg to 500 mg.

Human normal immunoglobulin

Immunoglobulin G is the most common antibody in the human body and can be produced during exposure to an antigen. Human normal immunoglobulin (referred to herein as IgG) contains mainly immunoglobulin G that is present in the normal population. It is preferred that the human normal immunoglobulin has a high purity of IgG, for example at least 95% IgG, or more preferably at least 98% IgG. Therefore, in some embodiments, the compositions comprise human normal immunoglobulin a purity of at least 95% IgG or at least 96% IgG, or more preferably at least 98% IgG or at least 99% IgG.

Human normal immunoglobulin is usually prepared from pooled human plasma from no fewer than 1000 donations. This results in a composition that is polyclonal that comprises multiple types of IgG for example the human normal immunoglobulin can comprise IgG1, IgG2, IgG3 and IgG4. This is advantageous because it results in the composition having a distribution of immunoglobulin G subclasses that is closely proportional to that in native human plasma. For example, the human normal immunoglobulin can comprise IgG1, IgG2, IgG3 and IgG4. The distribution of the different subclasses of IgG can vary, for example the distribution can be approximately 69% IgG1, 26% IgG2, 3% IgG3 and 2% IgG4.

CSL787 used in the examples is prepared from pooled human plasma using Good Manufacturing Practice (GMP) methodologies, which removes albumin and alpha- and beta-globulins, the majority of plasma lipids and non-IgG plasma proteins. Complementary approaches are used to prevent a potential contamination of the final medicinal product, namely: Selecting and testing the source material for the absence of detectable viral markers, testing the plasma pool used in fractionation for the absence of viral contaminations and virus inactivation and removal by manufacturing steps validated to inactivate and / or remove viruses.

The composition can contain trace amounts of IgA, typically less than 50 µg/mL.

Various different compositions of human normal immunoglobulin are commercially available, including Privigen™, Bivigam™, Clairyg™, Flebogam™ 5%, Flebogamma™ DIF 5%, Gammagard™ Liquid 10%, Gammaplex™, Gamunex™ 10%, IG Vena™ N, Intratect™, Kiovig™,

Nanogam™, Octagam™, Octagam™ 10%, Polyglobin™ N10%, Sandoglobulin™ NF liquid, Vigam™ and IQYMUNE™. In preferred embodiments, the composition is Privigen™ or has the same composition of IgG as Privigen™.

In preferred embodiments, the composition does not contain any carbohydrate stabilizers (*e.g.* sucrose or maltose) and no preservatives.

The concentration of human normal immunoglobulin within the composition can vary. However, it is preferable to administer higher concentrations of human normal immunoglobulin because this is advantageous for administration by inhalation. Utilizing higher doses minimizes the volume of the composition that needs administered as much as possible, which helps to keep the nebulization time as short as possible. This is particularly useful for maintaining subject compliance.

Therefore, the composition can have a high concentration of human normal immunoglobulin, for example the IgG in the composition can be at a concentration of 2-15% or 5-10%. The examples demonstrate that IgG at a concentration of 7% can safely and effectively treat NCFB. Therefore, it is preferred concentration of IgG in the composition is 7% or 10%. A 7% stock solution IgG can be administered to a subject or a 10% stock solution of human normal immunoglobulin G can be diluted to 7% using water and then administered to subjects by inhalation of an aerosol produced using a nebulizer. Preferably, the composition is a 7% stock solution of IgG.

Alternatively, the IgG can have a concentration of between about 20 and about 200 mg/ml. The concentration of the IgG may range between 20 and 190 mg/ml, 20 and 180 mg/ml, 20 and 170 mg/ml, 20 and 160 mg/ml, 20 and 150 mg/ml, 30 and 200 mg/ml, 30 and 190 mg/ml, 30 and 180 mg/ml, 30 and 170 mg/ml, 30 and 160 mg/ml, 30 and 150 mg/ml, 40 and 200 mg/ml, 40 and 190 mg/ml, 40 and 180 mg/ml, 40 and 170 mg/ml, 40 and 160 mg/ml, 40 and 150 mg/ml. Suitable IgG concentrations include between 20 and 140 mg/ml, 20 and 130 mg/ml, 20 and 120 mg/ml, 30 and 140 mg/ml, 30 and 130 mg/ml, 30 and 120 mg/ml, 40 and 140 mg/ml, 40 and 130 mg/ml, 40 and 120 mg/ml, 50 and 140 mg/ml, 50 and 130 mg/ml or 50 and 120 mg/ml; in particular, the concentration of IgG is about 50 mg/ml, about 60 mg/ml, about 70 mg/ml, about 80 mg/ml, about 90 mg/ml, about 100 mg/ml, about 110 mg/ml, or about 120 mg/ml. A preferred concentration of IgG is about 50 mg/ml to about 100 mg/ml, for example 60 mg/ml, 65 mg/ml, 70 mg/ml, 75 mg/ml, 80 mg/ml, 85 mg/ml, 90 mg/ml, 95 mg/ml or 100 mg/ml.

The human normal immunoglobulin can be formulated for nebulization as a pharmaceutical composition. The pharmaceutical composition may be formulated with a pharmaceutically acceptable carrier. The pharmaceutical composition is pharmaceutically acceptable and typically includes a suitable carrier. A thorough discussion of pharmaceutically acceptable carriers is available in reference [28]. The composition is preferably sterile, pyrogen- and/or preservative-free. The pharmaceutical composition is for administration to a subject, such as an animal, typically a human subject.

Liquid aqueous compositions predominantly consist of water but can sometimes contain small amounts of one or more liquids which are at least partly miscible with water. This type of composition is particularly suitable for inhalation as they can be nebulized to form an aerosol which can be administered to the respiratory tract of the subject. Therefore, the compositions are generally in liquid aqueous form. It will be understood by the person skilled in the art, that the features and preferences with respect to the liquid composition, as disclosed herein, may also be applied to the dispersed liquid phase of the aerosol generated therefrom and vice versa.

An aerosol can also be generated from a dry composition using a dry powder inhaler. The dry powder can be produced by lyophilization, particle replication in non-wetting templates, supercritical fluid drying, spray-drying, spray freeze-drying and similar techniques [29]. Therefore, in alternative embodiments the composition is a dry powder. Various forms of dry powder inhalers are available, such as capsule and multi-dose dry powder inhalers, single dosage forms such as a rotary inhaler, multi-dose such as Accuhaler and disc inhalers. Dry powder inhalers can be advantageous as they provide an inhalation system that is easy to use, fast and suitable for more frequent use.

Stabilizers

Typically, the composition contains one or more stabilizers. A commonly encountered issue when preparing liquid IgG compositions is that the immunoglobulins tend to aggregate and form precipitates if not sufficiently stabilized with appropriate additives. Therefore, it is useful to include a stabilizer in the composition, for example an amino acid, such as proline, serine glycine, isoleucine and histidine, or a saccharide, or a sugar alcohol, or a protein, such as albumin, or nicotinamide or a combination thereof. In preferred embodiments, the composition comprises proline or serine (e.g. L-proline or L-serine) as a stabilizer. As demonstrated in the examples, compositions comprising IgG and either proline or serine have good safety profiles.

As the IgG concentration in the composition is increased this results in a non-linear increase of viscosity. To avoid nebulization issues caused by this increase in viscosity, it has been found that proline is particularly suitable as a stabilizer, since a relatively low viscosity of the composition of the invention can be achieved even if the concentration of IgG is high, as disclosed in WO2011/095543. Proline provides the desired stability of IgG in a composition, and reduces the viscosity of the composition, thus allowing the nebulization of a small liquid volume with a high IgG concentration. Compositions that comprise proline are therefore particularly useful in methods for generating an aerosol with a mesh nebulizer, which results in fast and efficacious treatment by inhalation.

Generally, the concentration of proline or serine in the composition of can range from about 10 to about 1000 mmol/L, for example from about 100 to about 500 mmol/L, in particular 240-280 mmol/L or 250-270 mmol/L.

L-proline is particularly suitable for use in the compositions because it is normally present in the human body and has a very favourable toxicity profile. The safety of L-proline has been investigated in repeated-dose toxicity studies, reproduction toxicity studies, mutagenicity studies and safety pharmacology studies, and no adverse effects were noted. Therefore, in one preferred embodiment, the composition comprises L-proline. Preferably, the L-proline in the composition is at a concentration of 210-290 mmol/L, for example 250 mmol/L.

The viscosity of compositions that comprises IgG and proline, or IgG and serine, can range between 1 mPa-s and 17 mPa-s (at a temperature of 20.0°C +/- 0.1 °C). In a specific embodiment, the viscosity of a composition comprising 100 mg/mL IgG and 250 mmol/L of L-proline is about 3 mPa-s at a temperature of 20.0°C +/- 0.1 °C. In a specific embodiment, the viscosity of a composition comprising 100 mg/mL IgG and 250 mmol/L of L-serine is about 3 mPa-s at a temperature of 20.0°C +/- 0.1 °C.

The compositions that comprise IgG and proline, or IgG and serine, can have an osmolality of 260-330 mOsmol/kg, preferably 280 – 310 mOsmol/kg.

Typically, if the composition comprises IgG and proline, or IgG and serine, it has a pH of 4.2 to 5.4, preferably 4.6 to 5.0, most preferably about 4.8, which further contributes to the high stability of the preparation.

The inventors have demonstrated for the first time that compositions comprising IgG and serine have a good safety profile. As demonstrated in the examples, administration of L-serine or a composition comprising L-serine and IgG by inhalation using a nebulizer is well tolerated in monkeys. Therefore, in a preferred embodiment, the composition comprises L-serine. Preferably, the L-serine in the composition is at a concentration of 250-310 mmol/L, for example 270 mmol/L.

Combination therapy with antibiotics

As set out above, a main trigger for exacerbations in NCFB and COPD patients is a high bacterial load in the lungs or the respiratory tract. Bacterial infections are also the cause of pneumonia. It may therefore be useful to administer the compositions in combination with an antibiotic because the antibiotic can help to prevent or treat a bacterial respiratory tract infection. Therefore, in some embodiments, the composition can be administered in combination with an antibiotic. The composition can be administered prior to, concurrently or subsequent to the administration of the antibiotic. Antibiotics are usually administered by orally and parenterally, therefore the antibiotics would not be present in the composition that administered by inhalation.

The composition may be administered with an antibiotic during the acute phase of the bacterial infection, i.e. the composition is administered during the first two days, in particular during the first three days, during the first four days, or during the first five days of infection, in addition to standard antibiotic therapy.

As shown in the examples, NCFB patients who have not been treated with antibiotics within the last month can be effectively treated with compositions comprising IgG. Therefore, in some embodiments, the patient has not been treated with an antibiotic, or has not been treated with an antibiotic for at least a week, at least two weeks, at least month or at least two months.

Add-on maintenance therapy

The composition is particularly useful as an add-on maintenance treatment. An add-on therapy means that the composition is used in addition to another drug to treat the respiratory disease. Add-on maintenance therapy can occur prior to, concurrently or subsequent to the administration of one or more other drugs. An add-on therapy can be given to bolster or enhance the effectiveness of a previous therapy, especially when the primary treatment proved not to be fully

effective. Alternatively, the composition is administered after a patient has responded to the primary treatment.

Examples of primary treatments include antibiotics, corticosteroids, bronchodilators and mucolytics. The corticosteroids can be administered orally or by inhalation.

Inhalation

The invention involves nebulizing compositions comprising human normal immunoglobulin to form an aerosol and then administering the aerosol by inhalation. Compositions can be administered by inhalation to the respiratory tract of the subject using a nebulizer. Inhalation can be defined as administration within the respiratory tract by inhaling orally or nasally [30]. The nebulized aerosol can be inhaled by the nose or the mouth, known as mouth inhalation or nose inhalation. Preferably, the compositions are administered by mouth inhalation. It is also possible to inhale the aerosol by the nose and the mouth.

A nebulizer is a device which is capable of aerosolizing a material into a dispersed phase. An aerosol is a system comprising a continuous gas phase and, dispersed therein, a discontinuous or dispersed phase of solid or liquid particles. Typically, aerosols are generated from liquid compositions, but a nebulizer can also aerosolize solid particles.

Nebulizers are designed to deliver medications over an extended period of time over multiple breaths. They generate a continuous or breath actuated mist of aerosolized medication, allowing a patient to breathe normally and receive medications over a period of time, for example 5 – 20 minutes. The period of time that it takes for the medication to be delivered is defined herein as an inhalation session. Normally an inhalation session is the time it takes for all of the medication in the reservoir of the nebulizer to be administered.

A patient can undergo multiple sessions in a day, for example 2 or 3 sessions per day. The nebulizer can be connected to a mouthpiece or a mask, *i.e.* the aerosol is inhaled using a mouthpiece or a mask connected to the nebulizer. It is also possible to use the nebulizer without connecting the device to a mouthpiece or a mask.

There are three main types of nebulizer: a jet nebulizer where compressed air turns the medicine into a mist (tiny particles of medicine that float in the air); a mesh nebulizer where medicine is

passed through a mesh (membrane) to create a fine mist and an ultrasonic nebulizer where high frequency vibrations turn medicine into a mist. Mesh nebulizers are commonly used to deliver pharmaceutical drugs, because they have increased portability, are more convenient, have increased energy efficiency and are easier to use compared to jet nebulizers [31]. Therefore, the nebulizer is preferably a mesh nebulizer, for example a passive or an active mesh nebulizer.

Nebulizer can have different modes, for example intermittent, continuous, and breath activated. Further details of suitable nebulizers, in particular mesh nebulizers, are described below. As demonstrated in the examples, the nebulizer is preferably used in continuous mode. The nebulizer can be used according to the manufacturer's instructions.

The examples demonstrate for the first time that nebulized IgG aerosol administered by mouth inhalation at a dose of 1-10 mg/kg has a good safety profile. Drug delivery directly into the respiratory tract offers a localized delivery of IgG to the affected region and the restriction of biopharmaceutical distribution to the lungs and the respiratory tract. In chronic lung diseases (such as NCFB, COPD and CF) where a main clinical feature is chronic infections within the damaged airways, inhalation of IgG for intra-airway administration has the potential to treat a central feature of these diseases more effectively. Direct delivery of IgG to the respiratory tract may also be useful for treating pulmonary infections, such as pneumonia or pulmonary tract infections in patients with an immunodeficiency. Therefore, inhalation IgG at a dose of 1-15 mg/kg is particularly useful for treating respiratory diseases, such as NCFB, COPD CF, pneumonia and pulmonary tract infections in patients with an immunodeficiency.

Aerosol particle size

The respiratory tract is divided into two main parts: the upper respiratory tract, consisting of the nose, nasal cavity, the pharynx and the portion of the larynx above the vocal folds (cords); and the lower respiratory tract, consisting of the portion of the larynx below the vocal folds, trachea, bronchi, bronchioles and the lungs. The so-called tracheobronchial tree is a complex system that begins at the edge of the larynx and divides into two main bronchi and continues into the lungs. The tracheobronchial tree is partitioned into around 23 generations (divisions) of dichotomous branching, *i.e.* at each generation each airway is being divided into two smaller daughter airways. It extends from the trachea (generation 0) to the last order of terminal bronchioles (generation 23).

According to preferred embodiments of the present invention, the aerosol is target to the conducting airways of the subject, in particular generations one to sixteen of the respiratory tract of the subject, such as generations one to thirteen of the respiratory tract of the subject.

Aerosols are usually generated from liquid compositions and essentially consists of liquid droplets. Two values can be determined experimentally and may be useful to describe the particle size or droplet size of the generated aerosol: the mass median diameter (MMD) and the mass median aerodynamic diameter (MMAD). The difference between the two values is that the MMAD is normalized to the density of water (equivalent aerodynamic). The MMAD may be measured by an impactor, for example the Anderson Cascade Impactor (ACI) or the Next Generation Impactor (NGI). Alternatively, laser diffraction methods may be used, for example the Malvern MasterSizer X™, to measure the MMD.

Another parameter describing the dispersed phase of the aerosol is the particle size distribution of the aerosolized liquid particles or droplets. The geometric standard deviation (GSD) is an often used measure for the broadness of the particle or droplet size distribution of generated aerosol particles or droplets.

The selection of the precise MMAD and MMD should take the target region or tissue for deposition of the aerosol into account. For example, the optimal droplet diameter will differ depending on whether oral, nasal or tracheal inhalation is intended, and whether upper and/or lower respiratory tract delivery (e.g. to the oropharynx, throat, trachea, bronchi, alveoli, lungs, nose, and/or paranasal sinuses) is focused upon. Additionally, the age dependent anatomic geometry (e.g. the nose, mouth or respiratory airway geometry) as well as the respiratory disease and condition of the subjects and their breathing pattern belong to the important factors determining the optimal particle size (e.g. MMD and GSD) for drug delivery to the lower or upper respiratory tract.

It is known that the size of aerosol particles greatly influences the depth of inhalation and deposition into the airways. In general, inhaled particles with an MMAD of less than 0.8 µm are not deposited, but directly exhaled. Particles with an MMAD of 0.8–2 µm are deposited into the alveoli, and particles with an MMAD of 2–5 µm deposit within the lower airways [32].

The examples demonstrate that aerosols with a particle size of MMAD of 2-4 µm are well tolerated in monkeys. Therefore, the size of the aerosol particle produced by the nebulizer is preferably

between 2–5 µm, preferably 3-5 µm. The aerosol preferably also has a size distribution GSD of less than 2.2, for example less than 2.0, 1.8 or 1.6. Preferably, the GSD is ≤ 2.1.

Such particle size and particle size distribution parameters are particularly useful to achieve a high local drug concentration in the respiratory tract of humans, including the bronchi and bronchioli, relative to the amount of drug which is aerosolized. In this context it must be considered that deep lung deposition requires smaller MMD's than deposition in the central airways of adults and children and for infants and babies even smaller droplet sizes (MMD's) in the range from about 1 .0 to about 3.3 µm are more preferred and the range below 2.0 µm is even more preferred. Thus, in aerosol therapy it is common to evaluate the fraction of droplets smaller than 5 µm (representing the fraction that is respirable by an adult) and smaller than 3.3 µm (representing the fraction that is respirable by a child or is deposited in the deeper lungs of an adult). Also, the fraction of droplets smaller than 2 µm is often evaluated as it represents the fraction of the aerosol that could optimally reach terminal bronchioles and alveoli of adults and children and can penetrate the lungs of infants and babies.

In the invention, the fraction of droplets having a particle size smaller than 5 µm is preferably greater than 65%, more preferably greater than 70% and even more preferably greater than 80%. The fraction of droplets having a particle size smaller than 3.3 µm is preferably greater than 25%, more preferably greater than 30%, even more preferably greater than 35% and still more preferably greater than 40%. The fraction of droplets having a particle size smaller than 2 µm is preferably greater than 4%, more preferably greater than 6% and even more preferably greater than 8%.

Mesh nebulizer

The nebulizer used in the invention may be a mesh nebulizer, such as a vibrating mesh nebulizer. Vibrating mesh nebulizers have been described in detail [31]. The examples demonstrate that a vibrating mesh nebulizer can effectively nebulize IgG. Therefore, preferably, the mesh nebulizer is a vibrating membrane nebulizer.

Vibrating mesh nebulizers comprise a reservoir in which the liquid for the nebulization is filled. When operating the nebulizer, the liquid is fed to a mesh that is made to oscillate, i.e. vibrate (e.g. by means of a piezoelectric element). The liquid present at one side of the vibrating mesh is hereby transported through openings in the vibrating mesh (also referred to as "pores" or "holes")

and takes the form of an aerosol on the other side of the vibrating mesh, (e.g. Deepro Vibrating Mesh Nebulizer and AdheResp Vibrating Mesh Nebulizer from HCmed Innovations Co., Ltd., Taiwan, eFlow rapid and eRapid from PARI, HL100 from Health and Life as well as AeronebGo and AeronebSolo from Aerogen). Such nebulizers may be referred to as "active membrane nebulizers". As demonstrated in the examples, it is preferable that the vibrating mesh nebulizer is used in continuous mode, such as a Deepro Vibrating Mesh Nebulizer or AdheResp Vibrating Mesh Nebulizer used in continuous mode.

In other useful mesh nebulizers, the composition can be nebulized by vibrating the liquid rather than the membrane. Such an oscillating fluid mesh nebulizer comprises a reservoir in which the liquid to be nebulized is filled. When operating the nebulizer, the liquid is fed to a membrane via a liquid feed system that is made to oscillate (i.e. vibrate, e.g. by means of a piezoelectric element). This liquid feed system could be the vibrating back wall of the reservoir (e.g. AerovectRx™ Technology, Pfeifer Technology) or a vibrating liquid transporting slider (e.g. I-Neb™ device from Respironics, or U22™ device from Omron). These nebulizers may be referred to as "passive mesh nebulizers".

Different membrane types are available for the nebulization of liquids with a mesh nebulizer. These membranes are characterized by different pore sizes which generate aerosols with different droplet sizes (MMD's and GSD's). Depending on the characteristics of the composition and the desired aerosol characteristics, different membrane types (i.e. different modified mesh nebulizers or aerosol generators) can be used. In the invention, it is preferred to use membrane types which generate an aerosol with an MMD in the range of 2.0 µm to 5.0 µm, for example in the range of 3.0 µm to 4.9 µm or preferably in the range of 3.4 µm to 4.5 µm. In another embodiment of the invention, it is preferred to use membrane types built in aerosol generator devices which generate an aerosol, e.g. isotonic saline (NaCl 0.9%), with an MMD in the range of 2.8 µm to 5.5 µm, for example in the range of 3.3 µm to 5.0 µm, or preferably in the range 3.3 µm to 4.4 µm In another embodiment of the invention, it is preferred to use membrane types built in aerosol generator devices which generate an aerosol, e.g. isotonic saline, with an MMD in the range of 2.8 µm to 5.5 µm, for example in the range of 2.9 µm to 5.0 µm, or preferably in the range of 3.8 µm to 5.0 µm.

If the treatment is intended for targeting the lower respiratory tract such as the bronchi or the deep lungs, it is particularly preferred that a piezoelectric perforated mesh-type nebulizer is selected for generating the aerosol. Examples of suitable nebulizers include the passive mesh nebulizer,

such as I-Neb™, U22™, U 1™ , Micro Air™, the ultrasonic nebulizer, for example Multisonic™, and/or active mesh nebulizer, such as HL100™, Respimate™, eFlow™ Technology nebulizers, AeroNeb™, AeroNeb Pro™, AeronebGo™, and AeroDose™ device families as well as the prototype Pfeifer, Chrysalis (Philip Morris) or AerovectRx™ devices. A particularly preferred nebulizer for targeting the drug to the lower respiratory tract is a vibrating perforated membrane nebulizer or so called active mesh nebulizer, such as for example the eFlow™ nebulizer (electronic vibrating membrane nebulizer available from PARI, Germany). Alternatively, a passive mesh nebulizer may be used, for example U22™ or U1™ from Omron or a nebulizer based on the Telemaq.fr technique or the Ing. Erich Pfeiffer GmbH technique.

A preferred mesh nebulizer for targeting the upper respiratory tract is a nebulizer which generates the aerosol via a perforated vibrating membrane principle, such as a membrane nebulizer using the eFlow™ technology, but which is also capable of emitting a pulsating air flow so that the generated aerosol cloud pulsates (i.e. undergoes fluctuations in pressure) at the desired location or during transporting the aerosol cloud to the desired location (e.g. sinonasal or paranasal sinuses). Aerosols delivered by such a modified electronic nebulizer can reach sinonasal or paranasal cavities much better than when the aerosol is delivered in a continuous (non-pulsating) mode. The pulsating pressure waves achieve a more intensive ventilation of the sinuses so that a concomitantly applied aerosol is better distributed and deposited in these cavities.

More particularly, a preferred nebulizer for targeting the upper respiratory tract of a subject is a nebulizer adapted for generating an aerosol at an effective flow rate of less than about 5 liters/min and for simultaneously operating means for effecting a pressure pulsation of the aerosol at a frequency in the range from about 10 to about 90 Hz, wherein the effective flow rate is the flow rate of the aerosol as it enters the respiratory system of the subject. Examples of such electronic nebulization devices are disclosed in WO2009/027095.

In a preferred embodiment of the invention, the nebulizer for targeting the upper respiratory tract is a nebulizer which uses a transportation flow that can be interrupted when the aerosol cloud reaches the desired location and then starts the pulsation of the aerosol cloud, e.g. in an alternating mode. The details are described in WO2010/097119 and WO2011/134940.

Whether adapted for pulmonary or sinonasal delivery, the nebulizer should preferably be selected or adapted to be capable of aerosolizing a unit dose at a preferred output rate. A unit dose is defined herein as a volume of the liquid aqueous composition comprising the effective amount of

active compound, i.e. IgG, designated to be administered during a single administration. Preferably, the nebulizer can deliver such a unit dose at a rate of at least 0.1 mL/min or, assuming that the relative density of the composition will normally be around 1, at a rate of at least 100 mg/min. More preferably, the nebulizer is capable of generating an output rate of at least 0.4 mL/min or 400 mg/min, respectively. In further embodiments, the liquid output rates of the nebulizer or the aerosol generator are at least 0.50 mL/min, preferably at least 0.55 mL/min, more preferably at least 0.60 mL/min, even more preferably at least 0.65 mL/min, and most preferably at least 0.7 mL/min, such devices called aerosol generator with a high output or high output rate. Preferably, the liquid output rate ranges between about 0.35 and about 1 .0 mL/min or between about 350 and about 1000 mg/min; preferably the liquid output rate ranges between about 0.5 and about 0.90 mL/min or between about 500 and about 800 mg/min. Liquid output rate means the amount of liquid composition nebulized per time unit. The liquid may comprise an active compound, IgG, and/or a surrogate such as sodium chloride 0.9%.

The output rate of the nebulizer should typically be selected to achieve a short nebulization time of the liquid composition. Obviously, the nebulization time will depend on the volume of the composition which is to be aerosolized and on the output rate. Preferably, the nebulizer should be selected or adapted to be capable of aerosolizing a volume of the liquid composition comprising an effective dose of IgG, within not more than 20 minutes. More preferably, the nebulization time for a unit dose is not more than 15 minutes. In a further embodiment, the nebulizer is selected or adapted to enable a nebulization time per unit dose of not more than 10 minutes, and more preferably not more than 6 minutes and even more preferably not more than 3 minutes. Presently most preferred is a nebulization time in the range from 0.5 to 5 minutes.

The volume of the composition that is nebulized according to the invention is preferably low in order to allow short nebulization times. The volume, also referred to as the volume of a dose, or a dose unit volume, or a unit dose volume, should be understood as the volume which is intended for being used for one single administration or nebulizer therapy session. Specifically, the volume may be in the range from 0.3 ml. to 6.0 ml, preferably 0.5 ml. to 4.0 ml, or more preferably 1.0 ml. to about 3.0 ml, or even more preferably about 2.0 ml. In case a residual volume is desired or helpful, this residual volume should be less than 1.0 ml, more preferably less than 0.5 ml, and most preferably less than 0.3 ml. The effectively nebulized volume is then preferably in the range from 0.2 to 3.0 ml. or 0.5 to 2.5 ml, or more preferably in the range from 0.75 to 2.5 ml. or 1 .0 to 2.5 ml.

Preferably, the nebulizer is adapted to generate an aerosol where a major fraction of the loaded dose of liquid composition is delivered as aerosol, i.e. to have a high output. More specifically, the nebulizer is adapted to generate an aerosol which contains at least 50% of the dose of the IgG, in the composition, or, in other words, which emits at least 50% of the liquid composition filled in the reservoir. Especially in comparison with monoclonal antibodies, of which the doses do not need to be as high due to their specificity, it is important to select a nebulizer which can generate such high output of IgG. It was found that a mesh nebulizer as used in the method of the invention is capable of generating an aerosol of IgG, composition with a particularly high output.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Treatment regimen for single ascending dose (SAD) cohort. Healthy volunteers were treated with IgG at a dose of 0.3, 1, 3 or 10 mg/kg or placebo.

Figure 2: Treatment regimen for multiple ascending dose (MAD) cohort. NCFB patients were treated with IgG at a dose of 0.3, 1, or 6 mg/kg or placebo.

Figure 3: Summary of cohorts and dosages testing in clinical trial. Single ascending dose (SAD) cohort (A1, A2, A3 and A4) consisted of 10 subjects, who received either CSL787 or placebo in a 8:2 randomization ratio. Multiple ascending dose (MAD) cohort (B1, B2 and B3) consisted of 8 subjects, who received either CSL787 or placebo in a 6:2 randomization ratio. Enrolment into these cohorts was sequential and subsequent cohorts were enrolled after a safety review of the previous cohort. PBO = placebo.

Figure 4: Forced expiratory volume in 1 second (FEV_1) values in NCFB patients after IgG treatment at a dose of 0.3, 1, or 6 mg/kg or after placebo treatment. (A) FEV_1 values from baseline to Day 21 (end of study); (B) Mean change from baseline FEV_1 values.

Figure 5: Percentage of the forced expiratory volume in the first 1 second of expiration value (FEV_1 %) in NCFB patients after IgG treatment at a dose of 0.3, 1, or 6 mg/kg or after placebo treatment. (A) FEV_1 % from baseline to Day 21 (end of study); (B) Mean change from baseline FEV_1 %.

Figure 6: Forced expiratory flow (FEF) 75% in NCFB patients after IgG treatment at a dose of 0.3, 1, or 6 mg/kg or after placebo treatment. (A) FEF 75% from baseline to Day 21 (end of study); (B) Mean change from baseline FEF 75%.

Figure 7: Lung Clearance Index in NCFB patients after IgG treatment at a dose of 0.3, 1, or 6 mg/kg or after placebo treatment. (A) LCI from baseline to Day 21 (end of study); (B) Mean change from baseline LCI.

Figure 8: Changes in bacterial load in the sputum of NCFB patients after treatment with IgG at a dose of 0.3, 1, or 6 mg/kg or after placebo treatment. (A) Median bacterial density in log_{10} Colony Forming Units (CFU)/ml at baseline, Day 8, Day 15 and Day 21 (end of study); (B) Mean change from baseline in bacterial density in log_{10} CFU/ml at Day 8, Day 15 and Day 21.

Figure 9: Changes in *Pseudomonas aeruginosa* levels in the sputum of NCFB patients after treatment with IgG. (A) Bacterial density of *Pseudomonas aeruginosa* in log_{10} CFU/ml at baseline, Day 8, Day 15 and Day 21 (end of study) after treatment with IgG at a dose of 0.3, 1, or 6 mg/kg or after placebo treatment; (B) Mean change from baseline in bacterial density of *Pseudomonas aeruginosa* in log_{10} CFU /ml at Day 8, Day 15 and Day 21 at 6mg/kg of IgG or placebo treatment.

Figure 10: Subject-reported assessments in NCFB patients after treatment with IgG at a dose of 0.3, 1, or 6 mg/kg or after placebo treatment. (A) Quality of Life Questionnaire – Bronchiectasis (QoLB) scores at baseline, Day 8, Day 15 and Day 21 (end of study) after treatment with IgG at a dose of 0.3, 1, or 6 mg/kg or after placebo treatment; (B) Mean change from baseline in QoL respiratory symptom scores I at Day 8, Day 15 and Day 21 at 6mg/kg of IgG or placebo treatment.

Figure 11: Viral detection from nasal swabs in NCFB patients after treatment with 0.3, 1, or 6 mg/kg IgG or after placebo treatment at baseline, Day 8, Day 15 and Day 21.

EXAMPLES

The following examples are provided to illustrate various embodiments of the present invention. The examples are illustrative and are not intended to limit the invention in any way.

Example 1 – Toxicity studies of nebulized IgG

A study was conducted with cynomolgus monkeys to determine the potential toxicity of nebulized human normal immunoglobulin (IgG) aerosol when administered by inhalation. One of the objectives of this study was to determine whether nebulized IgG aerosol could be safely delivered to the lungs by inhalation. The local and systemic bioavailability of IgG was also analysed.

Study design

A 7% formulation of plasma-derived human normal immunoglobulin G (IgG) was administered to cynomolgus monkeys by inhalation. This formulation contained approximately 270 mmol/L of L-serine as a stabilizer and trace amounts of sodium. The formulation had a pH of 4.6 – 5.0 and an osmolality of 280 – 310 mOsmol/kg.

Three doses of IgG were tested – (1) a low dose (5 mg/kg/day); (2) an intermediate dose (13 mg/kg/day) and a high dose (24 mg/kg/day). Two controls were used – an air control and a L-serine vehicle control. A summary of the study design is provided in the table below:

Table 1 – Study design

Treatment Group	Phase	Number of Animals	
		Males	**Females**
Air Control	26 Week Main Study	3	3
Vehicle Control	4 Week Main Study	3	3
	26 Week Main Study	3	3
	13 Week Recovery	3	3
Low Dose	26 Week Main Study	3	3
Intermediate Dose	26 Week Main Study	3	3
High Dose	4 Week Main Study	3	3
	26 Week Main Study	3	3
	13 Week Recovery	3	3

The following parameters and end points were evaluated: mortality, clinical observations, body weights, respiratory measurements, electrocardiology, neurological examinations, clinical pathology parameters (haematology, coagulation, clinical chemistry, and blood and BAL urea nitrogen), biomarkers complement analysis (plasma and BAL), bioanalysis, anti-drug antibody analysis, bronchoalveolar lavage cell counts, organ weights and macroscopic and microscopic examinations.

Results

Nebulized IgG aerosol administered by inhalation had no effect on body weight, clinical signs, electrocardiography, respiratory measurements, haematology, coagulation, clinical chemistry, plasma biomarker (complement C3a and sC5b-9), BAL biomarker (complement C3a), BAL cell

counts, macroscopic pathology or organ weights in cynomolgus monkeys at any of the doses tested.

One BAL biomarker (sC5b-9) was elevated (mild to moderate) at all doses of IgG formulation (males and females). This finding was considered to be non-adverse. There were no BAL biomarker (sC5b-9) findings which were considered to be related to the daily administration of L-Serine.

Immunogenicity analysis revealed a positive immune response in all the animals that received IgG. No toxicological importance was attached to this finding as cynomolgus monkeys often develop an immune response to human derived proteins. Bioanalysis of plasma samples did not differentiate between monkey and human IgG, but IgG levels did not deviate measurably from endogenous baseline values. This suggests that any therapeutic effects of inhaled IgG will be localised in the lungs rather than systemic.

Bioanalysis of BAL samples at necropsy showed marginal or slight elevation in adjusted BAL IgG values at 12.6 and 24.0 mg IgG/kg/day, without evidence of bioaccumulation.

Following histopathological evaluation of the lungs, non-adverse perivascular/peribronchiolar mononuclear cell infiltration, peribronchiolar macrophage aggregates and increased cellularity of bronchial-associated lymphoid tissue (BALT) were generally observed in both sexes after 4 weeks at 22.7 mg IgG/kg/day and 26 weeks of dosing at all dose levels. There was recovery from these following a 13-week recovery period.

In addition, diffusely distributed alveolar macrophages were observed histopathologically at all timepoints in single males and females exposed to the vehicle L-Serine and therefore was considered a possible effect of vehicle administration. All instances of this finding were of a minimal grade so were considered non-adverse. An additional influence of IgG formulation was considered equivocal, as this finding was present at a higher incidence at 22.7 mg IgG/kg/day at the 4-week time point only.

The estimated delivered doses of IgG and L-Serine are summarized in Tables 2 and 3. No IgG or L-serine was measured in any in the air control sample.

Table 2 - Estimated Delivered Doses of IgG – Group Mean Values

Dose Group/ Treatment	Estimated Delivered Doses of IgG (mg/kg/day)					Difference from Target (± %)
	Target	Males	Females	Combined	%RSD	
26 Week Main and Recovery Study						
Low Dose	5	4.79	4.78	4.78	29.0	-4.3
Intermediate Dose	15	12.3	12.8	12.6	13.5	-16.2
High Dose	30	23.5	24.4	24.0	17.0	-20.1
4 Week Main Study						
High Dose	30	22.1	23.4	22.7	14.6	-24.2

Table 3 - Estimated Delivered Doses of L-serine – Group Mean Values

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Dose Group/ Treatment	Estimated Delivered Doses of L-Serine (mg/kg/day)			
	Males	Females	Combined	%RSD
26 Week Main and Recovery Study				
Vehicle Control	12.6	12.7	12.6	21.4
High Dose	10.0	10.4	10.2	17.8
4 Week Main Study				
Vehicle Control	9.57	10.0	9.80	21.4
High Dose	9.35	9.94	9.64	16.4

The estimated particle distribution size of the aerosols is summarized in the Table below.

Table 4 - Aerodynamic Particle Size Distribution

Dose Group/ Treatment	**MMAD (µm) and GSD**	
	Gravimetric	**Analytical**
Vehicle Control	1.67 (2.271) – 3.47 (2.873)	1.55 (2.516) – 3.67 (2.005)
Low Dose	1.54 (2.214) – 2.82 (1.690)	1.82 (1.354) – 3.13 (1.312)
Intermediate Dose	1.76 (3.442) – 3.08 (1.627)	1.71 (2.415) – 2.99 (1.300)
High Dose	1.89 (2.800) – 4.34 (4.460)	2.17 (1.809) – 3.26 (1.317)

In general, the aerosol particle size distribution was within target ranges (MMAD 2-4 µm). Excursions outside this range were considered not to impact respirability in this model of the delivered aerosols. For each group, delivered aerosols with L-serine and/or IgG were considered to be respirable to monkeys.

Summary

Test item-related findings in the lungs were typical of those reported previously with inhaled biologics [33].

Inhalation administration of the 7% formulation of human plasma-derived polyvalent immunoglobulin G (IgG), stabilized with serine as described above, once daily for 26 weeks was well tolerated in monkeys at up to 24.0 mg IgG/kg/day. Based on the target organ (lung) results, the no-observed-adverse effect level (NOAEL) was considered to be 24.0 mg IgG/kg/day.

In addition, inhalation administration of the vehicle L-Serine once daily for 26 weeks was well tolerated in monkeys at up to 12.6 mg L-Serine/kg/day. Based on the target organ (lung) results, the no-observed-adverse-effect level (NOAEL) was considered to be 12.6 mg L Serine/kg/day.

These data therefore demonstrate that nebulized IgG has a positive safety profile in cynomolgus monkeys. In addition, these data demonstrate that L-serine have a favourable safety profile alone and in combination with IgG. Therefore, this example demonstrates that L-serine can be useful as a stabilizer in IgG compositions that are nebulized to form an aerosol that are then administered by inhalation.

Example 2 – Phase 1 clinical trial to investigate the safety, tolerability and efficacy of nebulized IgG

A Phase 1, multicenter, randomized, double-blind, placebo-controlled, single and multiple ascending dose study was performed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of nebulized IgG aerosol in healthy subjects and patients with non-cystic fibrosis bronchiectasis (NCFB).

IgG (referred to as CSL787 in this study) or placebo were administered at doses of up to 10 mg/kg in the single ascending dose part of the study (SAD; Part A) and up to 6 mg/kg in the multiple ascending dose part of the study (MAD; Part B). As demonstrated by Figures 1-3.

Mild NCFB patients with active pulmonary bacterial infections during screening were recruited into the MAD study to assess the therapeutic efficacy of IgG.

Materials

CSL787: A 10% stock solution of plasma-derived human normal immunoglobulin G (IgG) was diluted to 7% using water, nebulized to form an aerosol and then administered to subjects by mouth inhalation. CSL787 contains approximately 250 mmol/L of L-proline as a stabilizer and trace amounts of sodium.

Placebo: Sterile 0.9% sodium chloride solution was also administered by mouth inhalation.

The solutions were aerosolized for nebulization using a Deepro Vibrating Mesh Nebulizer, HCmed Innovations Co., Ltd., Taiwan (continuous mode).

Patient selection

The study enrolled both healthy subjects (n=40) and subjects with mild-severe NCFB (n=24). Subjects were ≥ 18 years old and both male and female.

Healthy subjects who were free of medical conditions were enrolled in the SAD portion of the study.

The inclusion criteria for the MAD patients in this study included:

1. Diagnosis of NCFB made by a respiratory physician, confirmed per CT showing bronchial wall dilatation with or without bronchial wall thickening, with a FEV1 ≥ 40% of the predicted value regarding age, height, gender and ethnicity, and FEV1 ≥ 1L (pre- bronchodilator values), at the screening visit.
2. No antibiotic use within 1 month before the screening visit.
3. Presence of one or more of the following bacteria (*Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis, Streptococcus pneumoniae*, members of *Enterobacterales* family or *Staphylococcus aureus*) in the sputum culture at the Screening Visit.
4. Had been fully vaccinated against COVID-19 (as per country recommendations) at least 7 days prior to Day 1.

Dosage regimens tested

In Part A, the SAD portion of the study, 40 healthy subjects were randomized 8:2 (CSL787: placebo). As shown in Figure 1, Part A consists of a 21 day Screening Period, a treatment period with a single nebulized dose of CSL787 or placebo on Day 1, and a 7-day safety follow- up period after CSL787 or placebo administration (on Day 8). CSL787 was administered once during the treatment period at a dose of 0.3, 1, 3, or 10 mg/kg.

In Part B, the MAD portion of the study, 24 subjects with mild-severe NCFB were enrolled in 0.3, 1, or 6 mg/kg dose level cohorts. As shown in Figure 2, Part B consisted of a 28 day screening period, a treatment period with daily nebulized doses of CSL787 or placebo for 14 days, and a safety follow-up period ending 7 days after last CSL787 or placebo administration (Day 21; Figure 2). Each cohort consisted of 8 subjects, who received either CSL787 or placebo in a 6:2 ratio. Enrolment into these cohorts was (Figure 3) sequential and subsequent cohorts were enrolled after a safety review of the previous cohort.

Safety Evaluation

The primary objective of this study was to investigate the safety of nebulized IgG aerosol in NCFB patients and healthy volunteers based on reported treatment-emergent adverse events (TEAEs), serious adverse event (SAEs), vital signs, physical examination, safety biomarkers, and clinically

significant abnormalities in laboratory assessments reported as AEs during the Treatment Period and Follow-up Period. The period of observation extended from the time the subject gives informed consent until the end of study and were coded using the MedDRA dictionary, Version 26.0. TEAEs were defined as AEs reported at or after the start of treatment with CSL787 or placebo.

Pharmacokinetic and Pharmacodynamic Assessments

Subjects had sputum at various time points during the study for pharmacokinetic and pharmacodynamic analysis. Induced sputum was collected according to a standardized method, which includes spirometry assessments for safety [34].

In Part A of the study, sputum samples were collected at screening, as well as 20 minutes, 6 h, 24 h, 48 h, and 72 h after treatment and at the end of study (EOS) visit, Day 8, (168 h). In Part B of the study, samples of sputum were collected at screening, as well as 20 minutes, 6 h and 24 h after the first treatment on Days 1 and before dose on Day 8 and at 20 minutes, 6 h, 24 h, 48 h and 72 h after treatment on Day 14, and at the EOS (Day 21).

Efficacy Assessments

The efficacy of CSL787 to treat NCFB was assessed using the following:

- Lung function: Spirometry and LCI
- Viruses (polymerase chain reaction) in nasal swab and sputum
- Bacterial load (qualitative / quantitative bacteriology) in sputum
- Patient reported assessments

Spirometry

Spirometry, including reversibility testing at screening for subjects in Part B (MAD), was performed using reference values from the 2012 Global Lung Initiative. The following parameters were assessed: FEV1 (forced expiratory volume in 1 second), FEV1 % predicted, forced vital capacity (FVC), FVC% predicted, peak expiratory flow (PEF), FEV1 / FVC, forced expiratory flow (FEF) 75, change in FEV post bronchodilator, and change in FVC post bronchodilator.

Lung Clearance Index

The Lung Clearance Index (LCI) is a measure of the effort required to evacuate a known quantity of gas derived from the multiple breath nitrogen washout (MBNW) technique [35]. As the subject inhales pure oxygen, the percentage of nitrogen in each breath is measured and steadily declines as the endogenous nitrogen supply wanes. In this context LCI represents a measure of the lung volume turnover from the start of the procedure required to reduce the nitrogen concentrations to beneath 2.5% of the volume exhaled. LCI is calculated by dividing the cumulative expired volume (CEV) measured during the procedure by the functional residual capacity (FRC) determined at the start of the procedure. Normal LCI values range from 5.9 to 7.5 whereas patients with NCFB or CF typically have higher LCI values.

The LCI was calculated in NCFB patients by determining the cumulative expired volume and then dividing by the functional residual capacity.

Sputum Assessments

Nasopharyngeal swabs were collected at screening, Day 8 (before dose), Day 15 and Day 21 from NCFB patients. The sample was tested for respiratory viruses by polymerase chain reaction.

(a) Bacterial Load
Sputum samples were collected for bacterial load assessment. Assessments in Part B at Screening and on Days 8 and 15 and at the EOS Visit on Day 21 included qualitative and quantitative bacteriology including determination of colony forming units as a measure of sputum bacterial density.

(b) Viral Assessment
Sputum samples were collected at screening, Day 8 (before dose), Day 15 and Day 21 from NCFB patients. The sample will be tested for respiratory viruses by polymerase chain reaction.

Subject-Reported Assessments

The Quality of Life Questionnaire – Bronchiectasis (QoLB) is a self-administered, patient-reported outcome measure assessing symptoms, functioning and health-related quality of life for NCFB patients, which contains 37 items on 8 scales (respiratory symptoms, physical, role, emotional

and social functioning, vitality, health perceptions and treatment burden) [36]. Improvements are noted as higher scores. QOL-B assessments were performed before start of treatment (Day -1), after 1 week of treatment (Day 8), after 2 weeks of treatment (Day 14), as well as at the EOS visit (Day 21).

Results

No subjects from Part A withdrew from the study or study treatment. In Part B, 24 subjects were treated, but only 22 subjects (91.7%) completed the study: 16 CSL787-treated subjects (88.9%) and 6 placebo-treated subjects (100%). The 2 CSL787-treated subjects that discontinued the study and study treatment were in the 0.3 mg/kg cohort and 1 mg/kg cohort. Both subjects discontinued the study and study treatment due to AEs.

The demographic characteristics for the subjects in Parts A and B of the clinical trial are provided in the Tables below:

Table 5 Demographic Characteristics for Part A: Single Ascending Nebulized Doses in Healthy Volunteers (Safety Analysis Set)

Demographic Characteristics	CSL787 0.3 mg/kg (N=8)	CSL787 1 mg/kg (N=8)	CSL787 3 mg/kg (N=8)	CSL787 10 mg/kg (N=8)	CSL787 Total (N=32)	Placebo Total (N=8)	SAD Total (N=40)
Age (years)							
n	8	8	8	8	32	8	40
Mean (SD)	34.0 (7.96)	35.5 (9.06)	37.4 (7.76)	32.1 (4.97)	34.8 (7.47)	36.4 (11.95)	35.1 (8.40)
Median (minimum, maximum)	34.5 (21, 44)	32.5 (25, 50)	37.0 (29, 50)	33.0 (23, 38)	33.5 (21, 50)	35.5 (19, 54)	34.5 (19, 54)
Gender, n (%)							
Female	4 (50.0)	4 (50.0)	3 (37.5)	4 (50.0)	15 (46.9)	1 (12.5)	16 (40.0)
Male	4 (50.0)	4 (50.0)	5 (62.5)	4 (50.0)	17 (53.1)	7 (87.5)	24 (60.0)
Weight (kg) at Baseline							
n	8	8	8	8	32	8	40
Mean (SD)	80.1 (18.05)	74.9 (17.02)	80.8 (11.67)	74.6 (13.72)	77.6 (14.86)	79.5 (16.20)	78.0 (14.94)
Median (minimum, maximum)	80.5 (49, 101)	69.0 (56, 101)	81.5 (64, 102)	75.0 (56, 95)	75.5 (49, 102)	78.5 (59, 105)	75.5 (49, 105)

N = number of subjects in the treatment group; n = number of subjects in the specified category; SAD = single ascending dose; SD = standard deviation.

In Part A, the race reported for the majority of subjects (97.5%) was white. A higher percentage of male subjects than female subjects participated in Part A (60.0% vs. 40.0%). The mean (SD) overall age of treated subjects was 35.1 (8.40) years with an age range of 19 to 54 years. The mean weight or BMI among subjects administered placebo and the doses of CSL787 (Table 5) were similar.

Table 6 Demographic Characteristics for Part B: Multiple Ascending Nebulized Doses in Subjects with Non-cystic Fibrosis Bronchiectasis (Safety Analysis Set)

Demographic Characteristics	CSL787				Placebo	MAD
	0.3 mg/kg (N=6)	1 mg/kg (N=6)	6 mg/kg (N=6)	Total (N=18)	Total (N=6)	Total (N=24)
Age (years)						
n	6	6	6	18	6	24
Mean (SD)	58.5 (10.46)	59.8 (15.25)	65.5 (8.36)	61.3 (11.44)	52.7 (7.53)	59.1 (11.12)
Median (minimum, maximum)	61.0 (38, 67)	61.5 (34, 77)	67.0 (50, 75)	63.5 (34, 77)	53.0 (43, 63)	61.0 (34, 77)
Gender, n (%)						
Female	3 (50.0)	1 (16.7)	3 (50.0)	7 (38.9)	2 (33.3)	9 (37.5)
Male	3 (50.0)	5 (83.3)	3 (50.0)	11 (61.1)	4 (66.7)	15 (62.5)
Weight (kg) at Baseline						
Mean (SD)	81.3 (18.99)	77.3 (20.85)	74.3 (14.64)	77.7 (17.48)	77.3 (10.84)	77.6 (15.86)
Median (minimum, maximum)	77.0 (61, 117)	80.5 (47, 102)	73.5 (56, 91)	74.5 (47, 117)	78.0 (65, 95)	76.0 (47, 117)

Tables 5 and 6 demonstrate that the average weight of the participants in this study was around 80 kg.

In Part B, the race reported for the majority of subjects (91.7%) was white. A higher percentage of male subjects participated in Part B compared with female subjects (62.5% vs. 37.5%). The mean (SD) overall age of treated subjects was 59.1 (11.12) years with an age range of 34 to 77 years. The mean weight or BMI among subjects administered placebo and the doses of CSL787 (Table 6) were similar.

Adverse events

The safety and tolerability of IgG (CSL787) was a primary endpoint for this clinical trial. IgG administered by mouth inhalation across multiple daily doses of up to 6 mg/kg for 14 days demonstrated a favorable safety profile in healthy volunteers and NCFB patients.

The percentage of subjects with any Treatment Emergent Adverse Effects (TEAE) regardless of causality/relatedness is comparable between the IgG (55.6%) versus placebo (50.0%). The most frequently reported TEAE was headache reported in 4 subjects in the study representing 16.7% across all treatment arms, including placebo. Fatigue was reported in 8.3% (1 subject in the 6 mg/kg IgG and 1 subject on placebo). All other TEAEs were reported individually representing 4.2%.

The majority of events reported were of mild severity: 8 subjects (33.3% of both IgG and placebo, respectively). Moderate severity was reported in 5 subjects (22.2% and 16.7%, respectively). No SUSARS or severe AEs were reported in the study and no safety signals or safety trends were identified.

For the 40 participating subjects in Part A, there were a total of 16 AEs, with 14 subjects experiencing AEs and 11 subjects experiencing TEAEs. The percentage of subjects with any AEs was higher for CSL787-treated subjects compared to placebo-treated subjects (40.6% vs. 12.5%). TEAEs were also reported for a higher percentage of CSL787-treated subjects versus placebo-treated subjects (31.3% vs. 12.5%).

For the 24 subjects participating in Part B, there were a total of 31 AEs, with 13 subjects experiencing AEs and 13 subjects experiencing TEAEs. The percentage of subjects with AEs was higher for the CSL787-treated subjects compared with the placebo-treated subjects (55.6% vs. 50.0%). TEAEs were also reported for a higher percentage of CSL787-treated subjects compared to placebo-treated subjects (55.6% vs. 50.0%).

This study demonstrates that IgG administered by mouth inhalation was safe and well tolerated when administered as a single dose at 0.3, 1.0, 3.0, and 10.0 mg/kg in healthy volunteers and multiple doses at 0.3, 1.0, and 6.0 mg/kg in subjects with NCFB.

Overall, these data demonstrate that a single dose of nebulized IgG aerosol administered by mouth inhalation at a dose of 0.3-10 mg/kg and consecutive administrations of nebulized IgG aerosol over 14 days at a dose of 0.3-6 mg/kg has a favourable safety profile.

Spirometry

The spirometry parameters of FEV1, FEV1% predicted, and FEF 75% were included in the overall evaluation of pulmonary function. These data are provided in Figures 4-6. All assessments were stable observing neither improvements nor marked deteriorations. The majority of change from baseline assessments did not exceed the MCID for either FEV_1 (100 mL) or FEV_1% (3%) nor was there a significant deviation from placebo values. Of note, subjects enrolled in the 6 mg/kg IgG cohort demonstrated significantly lower pulmonary function at baseline and over the course of the study due to a relaxation of the original inclusion criteria from FEV_1% ≥65% to FEV_1% ≥40% prior to recruiting this last cohort.

A conspicuous drop in all three pulmonary function tests was recorded at the two time points when pulmonary function was measured 6 hours post administration on Day 1 and Day 14. As this drop was also registered in the placebo group it is not considered linked to IgG activity but rather the after-effects of sputum induction with saline. Recovery of pulmonary function was demonstrated within 24 hours on Day 2 and Day 15 respectively and remained stable thereafter.

Lung Clearance Index

IgG treatment resulted in improvements in the LCI for all active doses – see Figure 7B. The mean data appear to show overall worse LCI performance for the 6 mg/kg cohort across all time points with a substantial response at Day 14. The lower LCI at baseline and over the course of the study is likely due to worse pulmonary function as reflected by the reduced FEV_1% inclusion criteria whereas the sparse data set and/or reduced psuedomonas counts might explain the dramatic improvement on Day 14.

Bacterial load in the sputum

All NCFB patients participating in the MAD (n=24) were required to test positive for *Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis, Streptococcus pneumoniae,* members of *Enterobacterales* family *or Staphylococcus aureus* in sputum samples acquired

during screening. Bacterial load was re-assessed at Day 8 whilst the subject was undergoing treatment, on Day 15 one day following the end of treatment, and on Day 21 one week following the end of treatment. In the change from baseline at Day 15 assessment all active doses reduced bacterial load count whereby the 1 mg/kg and 6 mg/kg cohorts achieved median Colony Forming Units (CFU) reductions of 1.5 and 1.86 $\log_{10}$ units respectively (Figure 8B). Both groups demonstrated trends towards a return to baseline values a week after cessation of therapy at Day 21. Subjects administered with placebo registered a median increase of 1.20 $\log_{10}$ units in CFU. In comparison, a meta-analysis of 16 clinical trials (n=2,597) with inhaled antibiotics demonstrated a mean CFU reduction of 2.32 $\log_{10}$ units compared against placebo [37].

Of specific interest were the reductions in *Pseudomonas aeruginosa* counts in sputum samples. *P. aeruginosa* is known to be resilient to antibiotic therapy and a persistent driver of recurrent exacerbations in NFCB patients. One subject in the single low dose (0.3 mg/kg) arm tested positive for *P. aeruginosa* at baseline and demonstrated no significant improvement during the study. The 1 mg/kg group did register a drop in *P. aeruginosa* count levels between Day 8 and Day 15 in a single subject (Figure 9A), however the absence of *P. aeruginosa* counts at screening complicates definitive assessment. The two subjects who tested positive for *P. aeruginosa* at screening and received 6 mg/kg demonstrated a median CFU reduction of 2.48 $\log_{10}$ units by Day 15 with a trend towards rebound one week following the end of treatment on Day 21 (Figure 9B). The low number of subjects both treated with placebo and testing positive for pseudomonas infections varies significantly between screening, Day 8 and Day 15 complicating any assessment of the complete treatment group. Meta-analyses of inhaled antibiotic trials failed to demonstrate an effect to eradicate *Pseudomonas* infections and registered consistent increases in antibiotic resistance with treatment ([37] and [38]).

Subject-Reported Assessments

Quality of life outcomes were measured using QoL-B score which consists of 8 domains, *i.e.*, Respiratory Symptoms, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions, and Treatment Burden, where improvements are noted as higher scores [36]. Notable improvements in the Respiratory Symptoms scale were recorded for subjects in the CSL787 and placebo cohorts. However, after 14 days of treatment, no notable changes were observed for the other QoL-B domains.

Subjects in the 0.3 mg/kg cohort showed a slight benefit for CSL787 over placebo on the Respiratory Symptoms scale, but no treatment effect on this scale was observed for subjects in the 1 mg/kg cohort.

Subjects in the placebo cohort also reported a mean (SD) improvement 8.64 (12.54) points from Baseline at Day 14; however, this was not sustained through Day 21, where the change from Baseline was only 4.94 (10.9) points.

Figure 10B demonstrates that consistent improvements in the quality of life were recorded with the 6 mg/kg cohort which demonstrated an increase of a mean (SD) 5.6 points (11.65) by Day 8 compared with Baseline and in excess of the 8-point MCID on Day 14 (13.6 points [14.94]). This benefit was maintained through Day 21 1 week following cessation of therapy where the cohort registered a mean (SD) gain of 12.2 points (14.11) as compared to baseline.

Meta-analyses of inhaled antibiotic clinical trials and the Phase IIb placebo-controlled trial in bronchiectatic patients with brensocatib, an oral dipeptidyl peptidase 1 (DPP1) inhibitor developed by Insmed Inc., failed to establish benefit/exceed the MCID in the same QoL instrument, or others, i.e., St. George's Respiratory Questionnaire (SGRQ) [39].

Viral Assessment

As shown in Figure 11, no significant difference in viral detection was observed in the different treatment groups. Although viral detection by PCR was incorporated into Part B of the study, the treatment duration of 14 days was too short to demonstrate therapeutic benefit on chance encounters with viruses.

Summary

In summary, these data demonstrate that nebulized IgG aerosol administered by mouth inhalation at dose of 0.3-10mg/kg has a favourable safety profile. This included a single administration of nebulized IgG aerosol at a dose of 0.3-10mg/kg and consecutive daily administration of nebulized IgG over 14 days at a dose of 0.3-6 mg/kg.

These experiments also demonstrated that administering inhalation of nebulized IgG aerosol by at a dose of 1-6mg/kg resulted in a reduction in the bacteria load in the sputum and *Pseudomonas*

aeruginosa levels in particular. This is useful for treating a variety of respiratory disease, such as NCFB, COPD and pneumonia, that are caused or exacerbated by bacterial infections.

The clinical trial also demonstrated that nebulized IgG aerosol administered by mouth inhalation can effectively treat NCFB. In every efficacy assessment, with the exception of viral detection, 6 mg/kg was either equally favoured or strongly favoured while remaining safe and well tolerated.

Embodiments

The invention provides the following numbered embodiments:

1. A composition comprising human normal immunoglobulin (IgG) for use in a method of treating or preventing a respiratory disease in a subject, wherein the composition is nebulized to form an aerosol and the aerosol is administered by inhalation, and wherein the IgG is administered at a dose of 1-15 mg/kg.
2. The composition for use according to embodiment 1, wherein the IgG is administered at a dose of 1-10 mg/kg or 4-8 mg/kg.
3. The composition for use according to embodiment 1 or embodiment 2, wherein the IgG is administered at a dose of 6 mg/kg.
4. The composition for use according to embodiment 1, wherein the IgG is administered at a dose of 12 mg/kg.
5. The composition for use according to any one of embodiments 1-4, wherein the composition is administered once a day.
6. A composition comprising human normal immunoglobulin (IgG) for use in a method of treating or preventing a respiratory disease in a subject, wherein the composition is nebulized to form an aerosol and the aerosol is administered by inhalation, and wherein the IgG is administered at a dose of 1-15 mg/kg/day.
7. The composition for use according to embodiment 6, wherein the IgG is administered at a dose of 1-10 mg/kg/day or 6-12 mg/kg/day.
8. The composition for use according to embodiment 6 or embodiment 7, wherein the IgG is administered at a dose of 6 mg/kg/day or 12 mg/kg/day.
9. The composition for use according to any one of embodiments 1-8, wherein the respiratory disease is associated with a bacterial pulmonary infection.
10. A composition comprising human normal immunoglobulin (IgG) for use in a method of treating or preventing a pulmonary infection in a subject, wherein the composition is

nebulized to form an aerosol and the aerosol is administered by inhalation, and wherein the IgG is administered at a dose of 1-15 mg/kg/day.

11. The composition for use according to embodiment 10, wherein the pulmonary infection is bacterial.

12. The composition for use according to any one of embodiments 1-11, wherein the composition reduces bacterial load in the sputum of the subject.

13. The composition for use according to embodiment 12, wherein bacterial load is reduced by at least 0.5-3 $\log_{10}$ CFU/ml.

14. The composition for use according to any one of embodiments 1-13, wherein the composition reduces the level of one or more of *Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis, Streptococcus pneumoniae*, members of the *Enterobacterales* family or *Staphylococcus aureus.*

15. The composition for use according to embodiment 14, wherein the composition reduces the level of *Pseudomonas aeruginosa.*

16. The composition for use according to embodiment 14 or embodiment 15, wherein the level of bacteria is reduced by at least 0.5-3 $\log_{10}$ CFU/ml.

17. The composition for use according to any one of embodiments 1-16, wherein the subject tests positive for one or more of *Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis, Streptococcus pneumoniae*, members of the *Enterobacterales* family or *Staphylococcus aureus*.

18. The composition for use according to embodiment 17, wherein the subject tests positive for *Pseudomonas aeruginosa*.

19. The composition for use according to any one of embodiments 1-18, wherein the composition stabilizes pulmonary function.

20. The composition for use according to any one of embodiments 1-9 and 11-19, wherein the respiratory disease is non-cystic fibrosis bronchiectasis (NCFB), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) or pneumonia.

21. The composition for use according to embodiment 20, wherein the respiratory disease is NCFB.

22. The composition for use according to embodiment 10, wherein the subject has an immunodeficiency.

23. The composition for use according to embodiment 22, wherein the immunodeficiency is a primary and secondary immunodeficiency.

24. The composition for use according to embodiment 10, wherein the subject has NCFB, COPD, CF or pneumonia.

25. The composition for use according to embodiment 24, wherein the subject has NCFB.
26. The composition for use according to any one of embodiments 1-25, wherein the composition increases the Quality of Life Questionnaire – Bronchiectasis (QoLB) score of the subject.
27. The composition for use according to embodiment 26, wherein the composition increases the QoLB score by at least 8 points, in particular by at least 10 points.
28. The composition for use according to any one of embodiments 1-27, wherein the IgG is human plasma-derived.
29. The composition for use according to any one of embodiments 1-28, wherein the composition further comprises a stabilizer.
30. The composition for use according to embodiment 29, wherein the stabilizer is proline or serine.
31. The composition for use according to any one of embodiments 1-30, wherein the IgG is at a concentration of 2-15%, in particular 7%.
32. The composition for use according to any one of embodiments 1-31, wherein the IgG has a purity of at least 95%, in particular at least 98%.
33. The composition for use according to any one of embodiments 1-32, wherein the composition is nebulized using a vibrating membrane nebulizer.
34. The composition for use according to any one of embodiments 1-33, wherein the composition is nebulized using a nebulizer in continuous mode.
35. The composition for use according to any one of embodiments 1-34, wherein the aerosol is administered by mouth inhalation.

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CLAIMS

1. A composition comprising human normal immunoglobulin (IgG) for use in a method of treating or preventing a respiratory disease in a subject, wherein the composition is nebulized to form an aerosol and the aerosol is administered by inhalation, and wherein the IgG is administered at a dose of 1-15 mg/kg.

2. The composition for use according to claim 1, wherein the composition is administered at a dose of 4-8 mg/kg, in particular 6 mg/kg.

3. The composition for use according to claim 1 or claim 2, wherein the composition is administered once a day.

4. The composition for use according to any one of claims 1-3, wherein the respiratory disease is associated with a bacterial pulmonary infection.

5. The composition for use according to any one of claims 1-4, wherein the respiratory disease is non-cystic fibrosis bronchiectasis (NCFB), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) or pneumonia, in particular is NCFB.

6. The composition for use according to any one of claims 1-4, wherein the respiratory disease is a bacterial pulmonary infection, optionally wherein the subject has an immunodeficiency.

7. The composition for use according to any one of claims 1-6, wherein the composition reduces bacterial load in the sputum of the subject, optionally by at least 0.5-3 $\log_{10}$ CFU/ml.

8. The composition for use according to any one of claims 1-7, wherein the composition reduces the level of one or more of *Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella catarrhalis, Streptococcus pneumoniae*, *Enterobacterales* family or *Staphylococcus aureus,* in particular *Pseudomonas aeruginosa.*

9. The composition for use according to any one of claims 1-8, wherein the subject tests positive for one or more of *Haemophilus influenzae, Pseudomonas aeruginosa, Moraxella*

catarrhalis, Streptococcus pneumoniae, *Enterobacterales* family or *Staphylococcus aureus,* in particular *Pseudomonas* aeruginosa.

10. The composition for use according to any one of claims 1-9, wherein the composition increases the Quality of Life Questionnaire – Bronchiectasis (QoLB) score of the subject, optionally by at least 8 points, in particular by at least 10 points.

11. The composition for use according to any one of claims 1-10, wherein the IgG is human plasma-derived.

12. The composition for use according to any one of claims 1-11, wherein the composition further comprises a stabilizer, optionally proline or serine.

13. The composition for use according to any one of claims 1-12, wherein the IgG is at a concentration of 2-15%, in particular 7%.

14. The composition for use according to any one of claims 1-13, wherein the IgG has a purity of at least 95%, in particular at least 98%.

15. The composition for use according to any one of claims 1-14, wherein the composition is nebulized using a vibrating membrane nebulizer.