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[54] USE OF AEROSOLIZED LEVOFLOXACIN FOR TREATING CYSTIC FIBROSIS
霧化左氧氟沙星在治療囊胞性纖維症中的應用

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(54) **USE OF AEROSOLIZED LEVOFLOXACIN FOR TREATING CYSTIC FIBROSIS**

VERWENDUNG VON AEROSOLISIERTEM LEVOFLOXAZIN ZUR BEHANDLUNG VON ZYSTISCHER FIBROSE

UTILISATION DE LÉVOFLOXACINE EN AÉROSOL POUR TRAITER LA FIBROSE KYSTIQUE

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Description

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/240,092 filed on September 4, 2009, and U.S. Provisional Application No. 61/249,231 filed on October 6, 2009.

FIELD OF THE INVENTION

[0002] A composition for the use of aerosolized levofloxacin for treating cystic fibrosis in a human having a pulmonary infection comprising *P. aeruginosa* is provided.

BACKGROUND

[0003] Patients with cystic fibrosis (CF) suffer from chronic infections of the lower respiratory tract that can be caused by bacteria, including *Pseudomonas aeruginosa. Pseudomonas aeruginosa* has been particularly problematic to eradicate and has been implicated as the major cause of morbidity and mortality in CF patients.

[0004] Aerosol delivery of antibiotics directly to the lungs has the potential to increase the local concentration of antibiotic at the site of infection, thereby, enhancing bacterial killing compared with systemic administration. Currently, tobramycin solution for inhalation is the only aerosol antibiotic approved for the management of CF patients with bacteria such as *P aeruginosa.* Because of the development of resistance to tobramycin and the limited effect on reducing bacterial density in sputum, there is a need for improved therapies to treat CF patients with pulmonary infections caused by multidrug resistant bacteria, including *P aeruginosa.*

SUMMARY

[0005] The present invention relates to a solution comprising levofloxacin at a concentration between about 75 mg/ml to about 150 mg/ml, a magnesium chloride concentration between about 150 mM to about 250 mM; a pH between about 5 to about 7; an osmolality of between about 300 mOsmol/kg to about 500 mOsmol/kg, and lacking lactose for use in a method for treating cystic fibrosis in a human, wherein said human has a pulmonary infection comprising *P. aeruginosa,* and wherein the solution comprises about 240 mg levofloxacin and the solution is administered as an aerosol to said human twice daily.

[0006] In some embodiments, the solution is administered to said human in need thereof as an aerosol of the solution to achieve a reduction in the density of the *P. aeruginosa* in the sputum of said human by at least 40%, at least 44%, at least 70%, at least 90% and at least 97%. Some such embodiments include achieving a reduction in the density of the *P. aeruginosa* in the sputum of said human by at least 0.25 $\log_{10}$ CFU/g sputum, at least 0.50 $\log_{10}$ CFU/g sputum, at least 1.0 $\log_{10}$ CFU/g sputum, at least 1.5 $\log_{10}$ CFU/g sputum, and at least 1.8 $\log_{10}$ CFU/g sputum.

[0007] In some embodiments , the solution is administered to the human in need thereof as an aerosol of the solution to achieve an increase in FEV_1 of at least 2% and an increase in FEF 25-75 of at least 5%, an increase in FEV_1 of at least 5% and an increase in FEF 25-75 of at least 10%, an increase in FEV_1 of at least 7% and an increase in FEF 25-75 of at least 15%, and an increase in FEV_1 of at least 10%, and an increase in FEF 25-75 of at least 20%.

[0008] Some embodiments include achieving an increase in FEV_1 of at least 0.05 L and an increase in FEF 25-75 of at least 0.05 L, an increase in FEV_1 of at least 0.10 L and an increase in FEF 25-75 of at least 0.10 L, an increase in FEV_1 of at least 0.15 L and an increase in FEF 25-75 of at least 0.15 L, an increase in FEV_1 of at least 0.20 L and an increase in FEF 25-75 of at least 0.20 L, and an increase in FEV_1 of at least 0.25 L and an increase in FEF 25-75 of at least 0.25 L. Some embodiments include achieving an increase in FEF 25-75 of at least 0.27 L.

[0009] Some embodiments include administering to said human in need thereof an aerosol of the solution to achieve a hazard ratio less than 1.0, wherein the hazard ratio is indicative of a decreased need for other anti-pseudomonal antimicrobials. In some such embodiments, the hazard ratio is less than 0.8, less than 0.6, less than 0.4, and less than 0.3.

[0010] In some embodiments a human who has a pulmonary infection comprising *P. aeruginosa* and is being administered an agent by inhalation selected from the group consisting of one or more of dornase alpha, azithromycin, salbutamol, pancrelipase, sodium chloride, seretide, and ADEK, is administered an aerosol of the solution. In some embodiments, the agent is selected from the group consisting of salbutamol, pancrelipase, seretide, and ADEK. Some embodiments include achieving a reduction in the density of the *P. aeruginosa* in the sputum of said human by at least 0.25 $\log_{10}$ CFU/g sputum, at least 0.50 $\log_{10}$ CFU/g sputum, and at least 1.0 $\log_{10}$ CFU/g sputum.

[0011] Some embodiments include repeatedly administering to said human in need thereof an aerosol of the solution, wherein said repeated administration does not result in a greater than 16-fold increase in minimum inhibitory concentration (MIC) of the *P. aeruginosa* strain in said human having the highest MIC relative to other *P. aeruginosa* strains. In some

embodiments, the repeated administration does not result in a greater than 8-fold increase in minimum inhibitory concentration (MIC) of the P. aeruginosa strain in said human having the highest MIC relative to other *P. aeruginosa* strains. In some embodiments, repeated administration does not result in a greater than 4-fold increase in minimum inhibitory concentration (MIC) of the *P. aeruginosa* strain in said human having the highest MIC relative to other *P. aeruginosa* strains.

[0012] Some embodiments include repeatedly administering to said human in need thereof an aerosol of the solution to achieve an increase in a CFQ-R respiratory domain greater than 1, greater than 2, greater than 3, greater than 4, and greater than 5.

[0013] Some embodiments include decreasing small airway resistance in a human with cystic fibrosis, comprising administering to said human in need thereof an aerosol of the solution to achieve an increase in FEF 25-75 of at least 5%, at least 10%, at least 15%, and at least 20%. Some embodiments include, achieving an increase in FEF 25-75 of at least 0.05 L, at least 0.10 L, at least 0.15 L, at least 0.20 L, at least 0.25 L, and at least 0.27 L.

[0014] Some embodiments include repeatedly administering to said human an aerosol of the solution, wherein said repeated administration does not result in an incidence of arthralgia. In some embodiments, administering is repeated at least twice daily for 14 days, at least twice daily for 28 days, and at least twice daily for 35 days.

[0015] Some embodiments include use in a method for treating cystic fibrosis in a human in which the human has a pulmonary infection comprising *P. aeruginosa* and said human has a body surface area less than 1.5 m^2. Some such methods include administering to said human in need thereof an aerosol of the solution to achieve a dose-normalized serum AUC at least 20 (ng.h/L)/mg Dose. In some embodiments, the administering is repeated twice daily for at least 14 days the aerosol comprises an amount of levofloxacin of 240 mg. Some embodiments include achieving a dose-normalized serum AUC at least 20 (ng.h/L)/mg Dose, at least 40 (ng.h/L)/mg Dose, at least 60 (ng.h/L)/mg Dose, at least 80 (ng.h/L)/mg Dose, and at least 100 (ng.h/L)/mg Dose.

[0016] Some embodiments include use in a method for treating cystic fibrosis in a human in which the human has a pulmonary infection comprising *P. aeruginosa* and the human has a body surface area less than 1.5 m^2. Some such methods include administering to said human in need thereof an aerosol of the solution to achieve a dose-normalized serum C_{max} greater than 2 μg/L/mg administered dose greater than 4 μg/L/mg administered dose, greater than 6 μg/L/mg administered dose, greater than 8 μg/L/mg administered dose, and greater than 14 μ/L/mg administered dose. In some embodiments, the human is less than 15 years of age, less than 12 years of age, less than 10 years of age. In some embodiments, the human comprises a mass less than 55 kg, less than 45 kg, less than 35 kg, less than 25 kg.

[0017] In some of the foregoing embodiments, the solution consists essentially of levofloxacin and magnesium chloride.

[0018] The solution comprises no lactose.

[0019] In some of the foregoing embodiments, the solution comprises a magnesium chloride concentration from about 150 mM to about 250 mM, and a levofloxacin concentration from between about 90 mg/ml to about 125 mg/ml.

[0020] The solution comprises an osmolality from about 300 mOsmol/kg to about 500 mOsmol/kg, and a pH from about 5 to about 7.

[0021] In some of the foregoing embodiments, the solution comprises an osmolality from about 350 mOsmol/kg to about 425 mOsmol/kg, and a pH from about 5 to about 6.5.

[0022] In some of the foregoing embodiments, the solution comprises a pH from about 5.5 to about 6.5.

[0023] In some of the foregoing embodiments, the solution comprises a levofloxacin concentration between about 90 mg/ml to about 110 mg/ml, a magnesium chloride concentration between about 175 mM to about 225 mM, a pH between about 5 to about 7; an osmolarity of between about 300 mOsmol/kg to about 500 mOsmol/kg, and lacks lactose.

[0024] In some of the foregoing embodiments, the aerosol comprises a mass median aerodynamic diameter from about 2 microns to about 5 microns with a geometric standard deviation less than or equal to about 2.5 microns.

[0025] In some of the foregoing embodiments, the aerosol comprises a mass median aerodynamic diameter from about 2.5 microns to about 4.5 microns with a geometric standard deviation less than or equal to about 1.8 microns.

[0026] In some of the foregoing embodiments, the aerosol comprises a mass median aerodynamic diameter from about 2.8 microns to about 4.3 microns with a geometric standard deviation less than or equal to about 2 microns.

[0027] Some of the foregoing embodiments also include producing the aerosol with a vibrating mesh nebulizer. In some such embodiments, the vibrating mesh nebulizer is a PARI E-FLOW® nebulizer.

[0028] In some of the foregoing embodiments, the amount of levofloxacin administered to the lung is at least about 20 mg, at least about 100 mg, at least about 125 mg, and at least about 150 mg

[0029] In some of the foregoing embodiments, at least about 100 mg the aerosol is administered to the lung in less than about 10 minutes, less than about 5 minutes, less than about 3 minutes, less than about 2 minutes.

[0030] Some of the foregoing embodiments also include co-administering an additional active agent selected from the group consisting of antibiotics, bronchodilators, anticholinergics, glucocorticoids, eicosanoid inhibitors, and combinations thereof

[0031] In some embodiments, the antibiotic can include tobramycin, aztreonam, ciprofloxacin, azithromycin, tetracycline, quinupristin, linezolid, vancomycin, and chloramphenicol, colisitin and combinations thereof. In some embodiments,

the bronchodilator can include salbutamol, levosalbuterol, terbutaline, fenoterol, terbutlaine, pirbuterol, procaterol, bitolterol, rimiterol, carbuterol, tulobuterol, reproterol, salmeterol, formoterol, arformoterol, bambuterol, clenbuterol, indacterol, theophylline, roflumilast, cilomilast, and combinations thereof In some embodiments, the anticholinergic can include ipratropium, tiotropium, and combinations thereof. In some embodiments, the glucocorticoid can include prednisone, fluticasone, budesonide, mometasone, ciclesonide, beclomethasone, and combinations thereof in some embodiments, the eicosanoid can include montelukast, pranlukast, zafirlukast, zileuton, ramatroban, seratrodast, and combinations thereof. In some embodiments, co-administering comprises inhaling the additional active agent.

[0032] In some of the foregoing embodiments, the pulmonary infection further comprises one or more bacteria that can include *Pseudomonas fluorescens, Pseudomonas acidovorans, Pseudomonas alcaligenes,* and *Pseudomonas putida, Stenotrophomonas maltophilia, Aeromonas hydrophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholera, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Burkholderia cepacia, Francisella tularensis, Kingella, and Moraxella.*

[0033] In some of the foregoing embodiments, the pulmonary infection further comprises a gram-negative anaerobic bacteria.

[0034] In some of the foregoing embodiments, the pulmonary infection further comprises one or more of the bacteria that can include *Bacteroides fragilis, Bacteroides distasonis, Bacteroides* 3452A homology group, *Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, and Bacteroides splanchnicus.*

[0035] In some of the foregoing embodiments, the pulmonary infection further comprises a gram-positive bacteria.

[0036] In some of the foregoing embodiments, the pulmonary infection further comprises one or more of the bacteria that can include *Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus milleri; Streptococcus (Group G); Streptococcus (Group CIF); Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus subsP. hyicus, Staphylococcus haemolyticus, Staphylococcus hominis, and Staphylococcus saccharolyticus.*

[0037] In some of the foregoing embodiments, the pulmonary infection further comprises a gram-positive anaerobic bacteria.

[0038] In some of the foregoing embodiments, the pulmonary infection further comprises one or more bacteria that can include *Clostridium difficile, Clostridium perfringens, Clostridium tetini, and Clostridium botulinum.*

[0039] In some of the foregoing embodiments, the pulmonary infection further comprises an acid-fast bacteria.

[0040] In some of the foregoing embodiments, the pulmonary infection further comprises one or more bacteria that can include *Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, and Mycobacterium leprae.*

[0041] In some of the foregoing embodiments, the pulmonary infection further comprises an atypical bacteria.

[0042] In some of the foregoing embodiments, the pulmonary infection further comprises one or more bacteria that can include *Chlamydia pneumoniae and Mycoplasma pneumoniae.*

BRIEF DESCRIPTION OF THE DRAWINGS

[0043]

Figures 1A and 1B show graphs using linear axes and semi-logarithmic axes, respectively, of the arithmetic mean serum concentrations of levofloxacin after administration of single 180 mg doses as a 50 mg/ml and 100 mg/ml solution for inhalation and after administration of 240 mg as a 100 mg/ml solution for inhalation once daily for 7 days to patients with CF.

Figures 2A and 2B show graphs using linear axes and semi-logarithmic axes, respectively, of the arithmetic mean sputum concentrations of levofloxacin after administration of single 180 mg doses as a 50 mg/ml and 100 mg/ml solution for inhalation and after administration of 240 mg as a 100 mg/ml solution for inhalation once daily for 7 days to patients with CF.

Figure 3 shows a graph of the mean change in *P. aeruginosa* (log10 CFU/g sputum) over time for various treatment

arms in an EE patient population. Patients were administered: levofloxacin 120 mg QD, levofloxacin 240 mg QD, levofloxacin 240 mg BID, or placebo.

Figure 4 shows a graph of change in *P. aeruginosa* (log10 CFU/g sputum) over time for various treatment arms in a MITT patient population. Patients were administered: levofloxacin 120 mg QD, levofloxacin 240 mg QD, levofloxacin 240 mg BID, or placebo.

Figure 5 shows a graph of survival distribution function over time for various treatment groups in an EE population.

Figure 6 shows a graph of survival distribution function over time for various treatment groups in a MITT population.

Figure 7 shows a graph of percent change in FEV_1 (L) at Day 28 for the EE population treated with placebo, 120 mg QD, 240 mg QD, or 240 mg BID.

Figure 8 shows a graph of percent change in FEV_1 (L) vs. placebo at Day 28 for the EE population treated with 120 mg QD, 240 mg QD, or 240 mg BID. *p=0.0102.

Figure 9 shows a graph of the categorical change in percent predicted FEV_1 at Day 28 for the EE population treated with 120 mg QD, 240 mg QD, or 240 mg BID. *1)=0.0370, **p=0.0037.

Figure 10 shows a graph of dose normalized serum AUC (ng.h/L/mgDose) vs. pediatric CF patient body weight (■ 180 mg (n=7); ♦ 240 mg (n=18)). The mean value is shown for serum levofloxacin AUC in adult CF patients studied in another clinical trial (not shown) and based on a mean weight of 71 kg (▲; +/- standard deviation).

Figure 11A shows a graph of dose normalized serum AUC (ng.h/L/mgDose) vs. pediatric CF patient age (■ 180 mg; ♦ 240 mg). Figure 11B shows a graph of dose normalized serum AUC (ng.h/L/mg Dose) vs. BSA (body surface area) (■ 180 mg;¨ ♦ 240 mg). Figure 11C shows a graph of dose normalized serum C_{max} (μ/L/mg administered dose) vs. pediatric CF patient body weight (■ 180 mg; ♦ 240 mg). Figure 11D shows a graph of dose normalized serum C_{max} (μ/L/mg administered dose) vs. pediatric CF patient age (■ 180 mg; ♦ 240 mg). Figure 11E shows a graph of dose normalized serum C_{max} (μg/L/mg administered dose) vs. BSA (■ 180 mg; ♦ 240 mg).

DETAILED DESCRIPTION

[0044] The present invention relates to the use of particular formulations of levofloxacin solutions for inhalation and particular dosage and administration regimens for the treatment of cystic fibrosis in a human wherein said human has a pulmonary infection comprising *P. aeruginosa.* Methods described herein for treating cystic fibrosis can include administering formulations of levofloxacin. In some embodiments, methods for treating cystic fibrosis can also include achieving a reduction in the density of particular pathogens in the lungs of a subject. In some embodiments, methods for treating cystic fibrosis can also include improving pulmonary characteristics of a subject that can be measured with parameters such as FEV_1, FEF 25-72, and the like.

[0045] The present invention provides several advantages. For example, aerosol levofloxacin provides high doses of drug directly to the lung. High doses are advantageous in reducing the development of resistant strains. In addition, the present invention provides formulations with reduced adverse effects typically associated with fluoroquinolones, such as arthralgia. Some embodiments provide methods for treating cystic fibrosis that decrease the risk of acute exacerbations in CF patients at risk for exacerbations. More embodiments provide methods for increasing the airflow in the lungs of CF patients. In various embodiments, the above methods are achieved by administering aerosolized levofloxacin in dosages and administration schedules sufficient to achieve the recited result.

Definitions

[0046] The term "administration" or "administering" refers to a method of giving a dosage of an antimicrobial pharmaceutical composition to a vertebrate. The preferred method of administration can vary depending on various factors, e.g., the components of the pharmaceutical composition, the site of the potential or actual bacterial infection, the microbe involved, and the severity of an actual microbial infection. In some embodiments, administration can include loading an instrument to deliver a drug to a subject. In some such embodiments, administering can include loading a nebulizer with a drug to be delivered to a patient. Thus, the dosage administered may be the dosage loaded into the instrument (e.g., nebulizer).

[0047] A "carrier" or "excipient" is a compound or material used to facilitate administration of the compound, for example, to increase the solubility of the compound. Solid carriers include, e.g., starch, lactose, dicalcium phosphate, sucrose, and kaolin. Liquid carriers include, e.g., sterile water, saline, buffers, non-ionic surfactants, and edible oils such as oil, peanut and sesame oils. In addition, various adjuvants such as are commonly used in the art may be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, incorporated by reference herein in its entirety.

[0048] A "diagnostic" as used herein is a compound, method, system, or device that assists in the identification and

characterization of a health or disease state. The diagnostic can be used in standard assays as is known in the art.

[0049] The term "mammal" is used in its usual biological sense. Thus, it specifically includes humans, cattle, horses, dogs, and cats, but also includes many other species.

[0050] The term "microbial infection" refers to the undesired proliferation or presence of invasion of pathogenic microbes in a host organism. This includes the excessive growth of microbes that are normally present in or on the body of a mammal or other organism. More generally, a microbial infection can be any situation in which the presence of a microbial population(s) is damaging to a host mammal. Thus, a microbial infection exists when excessive numbers of a microbial population are present in or on a mammal's body, or when the effects of the presence of a microbial population(s) is damaging the cells or other tissue of a mammal.

[0051] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0052] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which are not biologically or otherwise undesirable. In many cases, the compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, naphtoic acid, oleic acid, palmitic acid, pamoic (emboic) acid, stearic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, ascorbic acid, glucoheptonic acid, glucuronic acid, lactic acid, lactobioic acid, tartaric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, histidine, arginine, lysine, benethamine, N-methyl-glucamine, and ethanolamine. Other acids include dodecylsufuric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, and saccharin.

[0053] "Solvate" refers to the compound formed by the interaction of a solvent and fluoroquinolone antimicrobial, a metabolite, or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

[0054] In the context of the response of a microbe, such as a bacterium, to an antimicrobial agent, the term "susceptibility" refers to the sensitivity of the microbe for the presence of the antimicrobial agent. So, to increase the susceptibility means that the microbe will be inhibited by a lower concentration of the antimicrobial agent in the medium surrounding the microbial cells. This is equivalent to saying that the microbe is more sensitive to the antimicrobial agent. In most cases the minimum inhibitory concentration (MIC) of that antimicrobial agent will have been reduced. The MIC_{90} can include the concentration to inhibit growth in 90% of organisms.

[0055] By "therapeutically effective amount" or "pharmaceutically effective amount" is meant a fluoroquinolone antimicrobial agent, as disclosed for this invention, which has a therapeutic effect. The doses of fluoroquinolone antimicrobial agent which are useful in treatment are therapeutically effective amounts. Thus, as used herein, a therapeutically effective amount means those amounts of fluoroquinolone antimicrobial agent which produce the desired therapeutic effect as judged by clinical trial results and/or model animal infection studies. In particular embodiments, the fluoroquinolone antimicrobial agent are administered in a predetermined dose, and thus a therapeutically effective amount would be an amount of the dose administered. This amount and the amount of the fluoroquinolone antimicrobial agent can be routinely determined by one of skill in the art, and will vary, depending on several factors, such as the particular microbial strain involved. This amount can further depend upon the patient's height, weight, sex, age and medical history. For prophylactic treatments, a therapeutically effective amount is that amount which would be effective to prevent a microbial infection.

[0056] A "therapeutic effect" relieves, to some extent, one or more of the symptoms of the infection, and includes curing an infection. "Curing" means that the symptoms of active infection are eliminated, including the total or substantial elimination of excessive members of viable microbe of those involved in the infection to a point at or below the threshold of detection by traditional measurements. However, certain long-term or permanent effects of the infection may exist even after a cure is obtained (such as extensive tissue damage). As used herein, a "therapeutic effect" is defined as a statistically significant reduction in bacterial load in a host, emergence of resistance, or improvement in infection symptoms as measured by human clinical results or animal studies.

[0057] "Treat," "treatment," or "treating," as used herein refers to administering a pharmaceutical composition for

prophylactic and/or therapeutic purposes. The term "prophylactic treatment" refers to treating a patient who is not yet infected, but who is susceptible to, or otherwise at risk of, a particular infection such that there is a reduced onset of infection. The term "therapeutic treatment" refers to administering treatment to a patient already suffering from an infection. Thus, in preferred embodiments, treating is the administration to a mammal (either for therapeutic or prophylactic purposes) of therapeutically effective amounts of a fluoroquinolone antimicrobial agent.

[0058] Pharmacokinetics (PK) is concerned with the time course of antimicrobial concentration in the body. Pharmacodynamics (PD) is concerned with the relationship between pharmacokinetics and the antimicrobial efficacy *in vivo*. PK/PD parameters correlate antimicrobial exposure with antimicrobial activity. The rate of killing by antimicrobial is dependent on antimicrobial mode of action and is determined by either the length oftime necessary to kill (time-dependent) or the effect of increasing concentrations (concentration-dependent). To predict the therapeutic efficacy of antimicrobials with diverse mechanisms of action different PK/PD parameters may be used. PK/PD parameters may be used to determine the bioavailability of antimicrobial compositions, for example, bioavailability of a composition in the pulmonary system, and/or bioavailability of a composition in plasma/serum.

[0059] "AUC/MIC ratio" is one example of a PK/PD parameter. AUC is defined as the area under the plasma/serum or site-of-infection concentration-time curve of an antimicrobial agent in vivo (in animal or human). For example, the site of infection and/or the site where concentration is measured can include portions of the pulmonary system, such as bronchial fluid and/or sputum. Accordingly, AUC may include serum AUC, and pulmonary AUC. $AUC_{(0\text{-}t)}$ can include the area under curve for time zero to a specific time 't.' $AUC_{(0\text{-}inf)}$ can include the area under curve from time zero to infinity. AUC/MIC ratio is determined by dividing the 24-hour-AUC for an individual antimicrobial by the MIC for the same antimicrobial determined *in vitro*. Activity of antimicrobials with the dose-dependent killing (such as fluoroquinolones) is well predicted by the magnitude of the AUC/MIC ratio.

[0060] "C_{max}:MIC" ratio is another PK:PD parameter. It describes the maximum drug concentration in plasma or tissue relative to the MIC. Fluoroquinolones and aminoglycosides are examples where C_{max}:MIC may predict *in vivo* bacterial killing where resistance can be suppressed.

[0061] "Time above MIC" (T>MIC) is another PK/PD parameter. It is expressed a percentage of a dosage interval in which the plasma or site-of-infection level exceeds the MIC. Activity of antimicrobials with the time-dependent killing (such as beta-lactams or oxazolidinones) is well predicted by the magnitude of the T>MIC ratio.

[0062] The term "dosing interval" refers to the time between administrations of the two sequential doses of a pharmaceutical's during multiple dosing regimens. For example, in the case of orally administered ciprofloxacin, which is administered twice daily (traditional regimen of 400 mg b.i.d) and orally administered levofloxacin, which is administered once a day (500 mg or 750 mg q.d.), the dosing intervals are 12 hours and 24 hours, respectively.

[0063] As used herein, the "peak period" of a pharmaceutical's in vivo concentration is defined as that time of the pharmaceutical dosing interval when the pharmaceutical concentration is not less than 50% of its maximum plasma or site-of-infection concentration. In some embodiments, "peak period" is used to describe an interval of antimicrobial dosing.

[0064] The "respirable delivered dose" is the amount of drug inhaled during the inspiratory phase of the breath simulator that is equal to or less than 5 microns using a simulator programmed to the European Standard pattern of 15 breaths per minute, with an inspiration to expiration ratio of 1:1.

Pharmaceutical Compositions

[0065] The solution comprising levofloxacin at a concentration between about 75 mg/ml to about 150 mg/ml and a magnesium chloride concentration between about 150 mM to about 250 mM may be administered as an aerosol using an inhaler. In some embodiments, the solution is suitable for aerosol formation and has good taste, storage stability, and patient safety and tolerability. In some embodiments, the isoform content of levofloxacin may be optimized for tolerability, antimicrobial activity and stability.

[0066] The solution comprises magnesium chloridein a concentration of from about 150 mM to about 250 mM. In some embodiments, the magnesium chloride concentration is from about 175 mM to about 225 mM, from about 180 mM to about 220 mM, or from about 190 mM to about 210 mM.

[0067] The solution has a levofloxacin concentration of from about 75 mg/ml to about 150 mg/ml. In some embodiments, the solution has a levofloxacin concentration of from about 80 mg/ml to about 125 mg/ml, from about 80 mg/ml to about 120 mg/ml, from about 90 mg/ml to about 125 mg/ml, from about 90 mg/ml to about 120 mg/ml, or from about 90 mg/ml to about 110 mg/ml.

[0068] The solution has an osmolality from about 300 mOsmol/kg to about 500 mOsmol/kg. In some embodiments, the solution has an osmolality of from about 325 mOsmol/kg to about 450 mOsmol/kg, from about 350 mOsmol/kg to about 425 mOsmol/kg, and from about 350 mOsmol/kg to about 400 mOsmol/kg. In some embodiments, the osmolality of the solution is greater than about 300 mOsmol/kg, about 325 mOsmol/kg, about 350 mOsmol/kg, about 375 mOsmol/kg, about 400 mOsmol/kg, about 425 mOsmol/kg, about 450 mOsmol/kg, about 475 mOsmol/kg, and about 500 mOsmol/kg.

[0069] The solution has a pH from about 5.0 to about 7.0. In some embodiments, the solution has a pH from about

5.0 to about 6.5, from about 5.5 to about 6.5, and from 6.0 to about 6.5.

[0070] The solution lacks lactose but can comprise any other conventional pharmaceutical carrier, excipient or the like (e.g., mannitol, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium crosscarmellose, glucose, gelatin, sucrose, magnesium carbonate, and the like), or auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like (e.g., sodium acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate, and the like). In some embodiments, the solution can lack a conventional pharmaceutical carrier, excipient or the like. In some embodiments, the solution can consist essentially of levofloxacin and magnesium chloride.

[0071] The solution comprises a levofloxacin concentration between about 75 mg/ml to about 150 mg/ml, a magnesium chloride concentration between about 150 mM to about 250 mM, a pH between about 5 to about 7; an osmolality of between about 300 mOsmol/kg to about 500 mOsmol/kg, and lacks lactose.

[0072] In some embodiments, the solution comprises a levofloxacin concentration about 100 mg/ml, a magnesium chloride concentration about 200 mM, a pH about 6.2 an osmolality about 383 mOsmol/kg, and lacks lactose. In some embodiments, the solution consists essentially of a levofloxacin concentration about 100 mg/ml, a magnesium chloride concentration about 200 mM, a pH about 6.2 an osmolality about 383 mOsmol/kg, and lacks lactose. In some embodiments, the solution consists of a levofloxacin concentration about 100 mg/ml, a magnesium chloride concentration about 200 mM, a pH about 6.2 an osmolality about 383 mOsmol/kg, and lacks lactose.

[0073] In some embodiments, the aerosol levofloxacin therapy may be administered as a treatment or prophylaxis in combination or alternating therapeutic sequence with other aerosol, oral or parenteral antibiotics. By non-limiting example this may include tobramycin and/or other aminoglycoside, aztreonam, carumonam and tigemonam and/or other beta or mono-bactam, ciprofloxacin and/or other fluoroquinolones, azithromycin and/or other macrolides or ketolides, tetracycline and/or other tetracyclines, quinupristin and/or other streptogramins, linezolid and/or other oxazolidinones, vancomycin and/or other glycopeptides, and chloramphenicol and/or other phenicols, and colisitin and/or other polymyxins. In more embodiments, the antibiotic can include quinolones, tetracyclines, glycopeptides, aminoglycosides, β-lactams, rifamycins, macrolides/ketolides, oxazolidinones, coumermycins, chloramphenicol, streptogramins, trimethoprim, sulfamethoxazole, or polymyxins. In particular embodiments, an antibiotic of the above classes can be, for example, one of the following. In some embodiments, any of the foregoing antibiotics can be administered by any acceptable method or route, for example, by aerosol, orally or parenterally.

Beta-Lactam Antibiotics

[0074] Beta-lactam antibiotics include, but are not limited to, imipenem, meropenem, biapenem, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefixime, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefpimizole, cefpiramide, cefpodoxime, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephaacetrile, cephalexin, cephaloglycin, cephaloridine, cephalothin, cephapirin, cephradine, cefmetazole, cefoxitin, cefotetan, azthreonam, carumonam, flomoxef, moxalactam, amidinocillin, amoxicillin, ampicillin, azlocillin, carbenicillin, benzylpenicillin, carfecillin, cloxacillin, dicloxacillin, methicillin, mezlocillin, nafcillin, oxacillin, penicillin G, piperacillin, sulbenicillin, temocillin, ticarcillin, cefditoren, SC004, KY-020, cefdinir, ceftibuten, FK-312, S-1090, CP-0467, BK-218, FK-037, DQ-2556, FK-518, cefozopran, ME1228, KP-736, CP-6232, Ro 09-1227, OPC-20000, and LY206763.

Macrolides

[0075] Macrolides include, but are not limited to, azithromycin, clarithromycin, erythromycin, oleandomycin, rokitamycin, rosaramicin, roxithromycin, and troleandomycin.

Ketolides

[0076] Ketolides include, but are not limited to, telithromycin and cethrimycin.

Quinolones

[0077] Quinolones include, but are not limited to, amifloxacin, cinoxacin, ciprofloxacin, enoxacin, fleroxacin, flumequine, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, levofloxacin, oxolinic acid, pefloxacin, rosoxacin, temafloxacin, tosufloxacin, sparfloxacin, clinafloxacin, moxifloxacin; gemifloxacin; garenofloxacin; PD131628, PD138312, PD140248, Q-35, AM-1155, NM394, T-3761, rufloxacin, OPC-17116, DU-6859a (see, *e.g.*, Sato, K. et al., 1992, Antimicrob Agents Chemother. 37:1491-98), and DV-7751a (see, e.g., Tanaka, M. et al., 1992, Antimicrob. Agents Chemother. 37:2212-18).

Tetracyclines, Glycylcyclines and Oxazolidinones

[0078] Tetracyclines, glycylcyclines, and oxazolidinones include, but are not limited to, chlortetracycline, demeclocycline, doxycycline, lymecycline, methacycline, minocycline, oxytetracycline, tetracycline, tigecycline, linezolide, and eperozolid.

Aminoglycosides

[0079] Aminoglycosides include, but are not limited to amikacin, arbekacin, butirosin, dibekacin, fortimicins, gentamicin, kanamycin, meomycin, netilmicin, ribostamycin, sisomicin, spectinomycin, streptomycin, and tobramycin.

Lincosamides

[0080] Lincosamides include, but are not limited to, clindamycin and lincomycin.

Streptogramins

[0081] Streptogramins include, but are not limited to quinupristin.

Glycopeptides

[0082] Glycopeptides include, but are not limited to vancomycin.

Polymyxins

[0083] Polymyxins include but are not limited to colisitin.

[0084] More examples include fosfomycin, penicillins, cephalosporins, carbapenems, penems, and carbacephems.

[0085] In some embodiments, a formulation can include a fluoroquinolone in combination with an additional active agent. As discussed herein, some such additional active agents can include antibiotics. More additional active agents can include bronchodilators, anticholinergics, glucocorticoids, eicosanoid inhibitors, and combinations thereof. Examples of bronchodilators include salbutamol, levosalbuterol, terbutaline, fenoterol, terbutlaine, pirbuterol, procaterol, bitolterol, rimiterol, carbuterol, tulobuterol, reproterol, salmeterol, formoterol, arformoterol, bambuterol, clenbuterol, indacterol, theophylline, roflumilast, cilomilast. Examples of anticholinergics include pratropium, and tiotropium. Examples of glucocorticoids include prednisone, fluticasone, budesonide, mometasone, ciclesonide, and beclomethasone. Examples of eicosanoids include montelukast, pranlukast, zafirlukast, zileuton, ramatroban, and seratrodast. More additional active agents can include pulmozyme, hypertonic saline, agents that restore chloride channel function in CF, inhaled beta-agonists, inhaled antimuscarinic agents, inhaled corticosteroids, and inhaled phosphodiesterase inhibitors. In some embodiments, the aerosol antibiotic therapy administered as a treatment or prophylaxis may be used in combination or alternating therapeutic sequence with an additional active agent. In more embodiments, the additional active agent may be administered as a treatment, alone, co-formulated, or administered with the aerosol antibiotic therapy.

Administration

[0086] The solution of levofloxacin and magnesium chloride comprises about 240 mg levofloxacin and is administered as an aerosol to said human twice daily. In some embodiments, therapy is administered for at least 28 days.

[0087] Administration of the solution is by aerosol inhalation. Methods, devices and compositions for delivery are described in U.S. Patent Application Publication No. 2006-0276483.

[0088] Pharmaceutically acceptable compositions include solid, semi-solid, liquid and aerosol dosage forms, such as, for example, powders, liquids, suspensions, complexations, liposomes, particulates, or the like. Preferably, the compositions are provided in unit dosage forms suitable for single administration of a precise dose.

[0089] The solution comprising levofloxacin and magnesium chloride and lacking lactose can be administered either alone or in some alternatives, in combination with a conventional pharmaceutical carrier, excipient or the like (e.g., mannitol, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium crosscarmellose, glucose, gelatin, sucrose, magnesium carbonate, and the like). If desired, the pharmaceutical composition can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like (e.g., sodium acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate, and the like). Generally, depending on the intended mode of administration, the pharmaceutical formulation will contain about 0.005% to 95%, preferably about 0.5% to 50% by weight of levofloxacin. Actual

methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania.

[0090] In one preferred embodiment, the compositions will take the form of a unit dosage form such as vial containing a liquid, solid to be suspended, dry powder, lyophilate, or other composition and thus the composition may contain, along with the active ingredient, a diluent such as sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like.

[0091] Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. the active compound as defined above and optional pharmaceutical adjuvants in a carrier (e.g., water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) to form a solution or suspension. Solutions to be aerosolized can be prepared in conventional forms, either as liquid solutions or suspensions, as emulsions, or in solid forms suitable for dissolution or suspension in liquid prior to aerosol production and inhalation. The percentage of active compound contained in such aerosol compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.01% to 90% in solution are employable, and will be higher if the composition is a solid, which will be subsequently diluted to the above percentages. In some embodiments, the composition will comprise 1.0%-50.0% of the active agent in solution.

[0092] In some embodiments of the methods, compositions, and uses provided herein, the duration of a therapy, e.g., an aerosolized antibiotic therapy can include at least about 1 day /month, at least about 2 days /month, at least about 3 days /month, at least about 4 days /month, at least about 5 days /month, at least about 6 days /month, at least about 7 days /month, at least about 8 days /month, at least about 9 days /month, at least about 10 days /month, at least about 11 days /month, at least about 12 days /month, at least about 13 days /month, at least about 14 days /month, at least about 15 days /month, at least about 16 days /month, at least about 17 days /month, at least about 18 days /month, at least about 19 days /month, at least about 20 days /month, at least about 21 days /month, at least about 22 days /month, at least about 23 days /month, at least about 24 days /month, at least about 25 days /month, at least about 26 days /month, at least about 27 days /month, at least about 28 days /month, at least about 29 days /month, at least about 30 days /month, and at least about 31 days /month.

[0093] The solution is administered twice daily.

Aerosol delivery

[0094] For pulmonary administration, the upper airways are avoided in favor of the middle and lower airways. Pulmonary drug delivery may be accomplished by inhalation of an aerosol through the mouth and throat. Particles having a mass median aerodynamic diameter (MMAD) of greater than about 5 microns generally do not reach the lung; instead, they tend to impact the back of the throat and are swallowed and possibly orally absorbed. Particles having diameters of about 2 to about 5 microns are small enough to reach the upper- to mid-pulmonary region (conducting airways), but are too large to reach the alveoli. Smaller particles, i.e., about 0.5 to about 2 microns, are capable of reaching the alveolar region. Particles having diameters smaller than about 0.5 microns can also be deposited in the alveolar region by sedimentation, although very small particles may be exhaled.

[0095] In one embodiment, a nebulizer is selected on the basis of allowing the formation of an aerosol of levofloxacin disclosed herein having an MMAD predominantly between about 2 to about 5 microns. In one embodiment, the delivered amount of levofloxacin provides a therapeutic effect for respiratory infections. The nebulizer can deliver an aerosol comprising a mass median aerodynamic diameter from about 2 microns to about 5 microns with a geometric standard deviation less than or equal to about 2.5 microns, a mass median aerodynamic diameter from about 2.5 microns to about 4.5 microns with a geometric standard deviation less than or equal to about 1.8 microns, and a mass median aerodynamic diameter from about 2.8 microns to about 4.3 microns with a geometric standard deviation less than or equal to about 2 microns. In some embodiments, the aerosol can be produced using a vibrating mesh nebulizer. An example of a vibrating mesh nebulizer includes the PART E-FLOW® nebulizer. More examples of nebulizers are provided in U.S. Patent Nos. 4,268,460; 4,253,468; ,046,146; 3,826,255; 4,649,911; 4,510,929; 4,624,251; 5,164,740; 5,586,550; 5,758,637; 6,644,304; 6,338,443; 5,906,202; 5,934,272; 5,960,792; 5,971,951; 6,070,575; 6,192,876; 6,230,706; 6,349,719; 6,367,470; 6,543,442; 6,584,971; 6,601,581; 4,263,907; 5,709,202; 5,823,179; 6,192,876; 6,644,304; 5,549,102; 6,083,922; 6,161,536; 6,264,922; 6,557,549; and 6,612,303. More commercial examples of nebulizers that can be used with the formulations described herein include Respirgard II®, Aeroneb®, Aeroneb® Pro, and Aeroneb® Go produced by Aerogen; AERx® and AERx EssenceTM produced by Aradigm; Porta-Neb®, Freeway Freedom™, Sidestream Ventstream and I-neb produced by Respironics, Inc.; and PARI LC-Plus®, PARI LC-Star®, produced by PART, GmbH. By further non-limiting example, U.S. Patent No. 6,196,219, is hereby incorporated by reference in its entirety.

[0096] The amount of levofloxacin that is administered as an aerosol (as a respirable dose, nebulizer loaded dose and/or deposited dose) includes about 240 mg.

[0097] The aerosol can be administered to the lungs in less than about 10 minutes, about 5 minutes, about 4 minutes, about 3 minutes, about 2 minutes, and about 1 minute.

Indications

[0098] The solution described herein can be used to treat cystic fibrosis in a human, wherein said human has a pulmonary infection comprising *P. aeruginosa*. Some embodiments include treating a pulmonary infection comprising *P. aeruginosa* and one or more additional bacteria that can include *Pseudomonas fluorescens, Pseudomonas acidovorans, Pseudomonas alcaligenes, Pseudomonas putida, Stenotrophomonas sp., e.g., Stenotrophomonas maltophilia, Aeromonas hydrophilia, Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholera, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Burkholderia sp., e.g., Burkholderia cepacia, Francisella tularensis, Kingella, and Moraxella.* In some embodiments, the pulmonary infection can include a gram-negative anaerobic bacteria. In more embodiments, the pulmonary infection can include one or more of the bacteria selected from the group consisting of *Bacteroides fragilis, Bacteroides distasonis, Bacteroides* 3452A homology group, *Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, and Bacteroides splanchnicus.* In some embodiments, the pulmonary infection can include a gram-positive bacteria. In some embodiments, the pulmonary infection can include one or more of the bacteria selected from the group consisting of *Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus milleri; Streptococcus (Group G); Streptococcus (Group C/F); Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus subsP. hyicus, Staphylococcus haemolyticus, Staphylococcus hominis, and Staphylococcus saccharolyticus.* In some embodiments, the pulmonary infection can include a gram-positive anaerobic bacteria. In some embodiments, the pulmonary infection can include one or more bacteria selected from the group consisting of *Clostridium difficile, Clostridium perfringens, Clostridium tetini, and Clostridium botulinum.* In some embodiments, the pulmonary infection can include an acid-fast bacteria. In some embodiments, the pulmonary infection can include one or more bacteria selected from the group consisting of *Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, and Mycobacterium leprae.* In some embodiments, the pulmonary infection can include an atypical bacteria. In some embodiments, the pulmonary infection can include one or more bacteria selected from the group consisting of *Chlamydia pneumoniae and Mycoplasma pneumoniae.* In some embodiments, the pulmonary infection can comprise a non-fermenting gram-negative bacteria (NFGNB). Examples of NFGNB can include *Burkholeria spp., stenotrophomonas spp., acinetobacter spp., pseudomonas spp., and Achromobacter spp.* More example of bacteria useful in the methods and compositions provided herein can be found in 'Bergey's Manual of Systematic Bacteriology,' Editor-in-chief: Garrity, George M. Boone, David R.; Castenholz, Richard W. (Eds.) Originally published by Williams & Wilkins, 1984, 2nd ed., (2001).

[0099] Some compositions provided here can be especially appropriate for the treatment of pulmonary infections and disorders that include microbial strains that can be difficult to treat using an antimicrobial agent delivered parenterally due to the need for high parenteral dose levels, which can cause undesirable side effects, or due to lack of any clinically effective antimicrobial agents. For example, administration of an aerosol levofloxacin directly to the site of infection may reduce systemic exposure and can maximize the amount of levofloxacin to the site of microbial infection. Such methods can be appropriate for treating infections involving microbes that are susceptible to levofloxacin as a way of reducing the frequency of selection of resistant microbes.

[0100] In some embodiments, the aerosol levofloxacin formulated with magnesium chloride is administered at a level sufficient to overcome the emergence resistance in bacteria or increase killing efficiency such that resistance does not have the opportunity to develop.

[0101] Some embodiments of the compositions described herein include achieving a reduction in a pulmonary infection. A reduction in a pulmonary infection can be measured using a variety of different methods. For example, in a pulmonary infection comprising one or more organisms, a reduction in the density of the organism can be measured. In some embodiments, treatment can achieve a reduction in the density of an organism by at least about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, and about 100%. In some

embodiments, treatment can achieve a reduction in the density of an organism by at least about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, and about 100%.

[0102] The density of an organism can be measured in a sample taken from a subject, for example, bronchial alveolar lavage, sputum, and serum. In some embodiments the density of an organism can be reduced by at least about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.8, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5 $\log_{10}$ CFU/g sputum, or more.

[0103] Some embodiments of the compositions described herein can include achieving an improvement in a pulmonary function parameter. Examples of such parameters can include FEV (forced expiratory volume), FEV_1 (forced expiratory volume in 1 second), and FEF 25-75 (forced expiratory flow 25-75%). In some embodiments, the FEV_1 of a subject can be increased using the methods and compositions described herein, by at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, and more. In some embodiments, the FEVI of a subject can be increased using the methods and compositions described herein, by at least about 0.01 L, 0.02 L, 0.03 L, 0.04 L, and 0.05 L, and by at least about 0.1 L, 0.2 L, 0.3 L, 0.4 L, 0.5 L, 0.6 L, 0.7 L, 0.8 L, 0.9L, 1.0 L, and more.

[0104] In some embodiments, the FEF 25-75 of a subject can be increased using the compositions described herein, by at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, and 25%. In some embodiments, the FEF 25-75 of a subject can be increased using the methods and compositions described herein, by at least about 0.01 L, 0.02 L, 0.03 L, 0.04 L, and 0.05 L, and by at least about 0.1 L, 0.2 L, 0.3 L, 0.4 L, 0.5 L, 0.6 L, 0.7 L, 0.8 L, 0.9L, 1.0 L, and more.

[0105] Some embodiments of the compositions described herein can include reducing the need for a subject to need other inhaled or systemic antibiotics, such as anti-pseudomonal antimicrobials. Such a reduction can be measured by a variety of methods, for example, by the increase in time to need other inhaled or systemic antibiotics. A reduction in such a need can be measured by a variety of statistical means. For example, hazard ratios may be used in a survival analysis. In some embodiments, the hazard ratio is less than about 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, and less.

[0106] Some embodiments of the compositions described herein can include decreasing the frequency of exacerbations, the severity of exacerbations, the duration of exacerbations, or the likelihood that an exacerbation will occur. An exacerbation can be defined by any of several methods and criteria provided by such methods. In some embodiments, a patient can concurrently meet at least 4 symptoms/signs of the Fuchs definition of an exacerbation (Fuchs HJ, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. N Engl J Med 1994;331:637-642). The symptoms/signs defined by the Fuchs criteria include: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 % or more from a previously recorded value; and radiographic changes indicative of pulmonary infection

[0107] In some embodiments, a patient with an improved exacerbation profile can have at least 1, at least 2, at least 3, and at least 4 of the following signs/symptoms, where changes can be relative to a patient's typical experience, for example daily experience, and weekly experience.

(1) Change in sputum, e.g., for sputum production: patients have no change, a little less or much less amounts of sputum when coughing up, or for change in sputum appearance: for sputum thickness, patients have a little thinner or much thinner sputum; for sputum color, patients have a better color of sputum (better increases from brown -> green -> yellow -> clear).

(2) Hemoptysis, e.g., patients have a little decrease or a large decrease in the amount of blood coughed up.

(3) Cough, e.g., for intensity of cough, patients have a little lighter, or much lighter coughs; for frequency of cough, patients cough a little less often or much less often.

(4) Dyspnea, e.g., for dyspnea with exertion, patients breathe a little easier or much easier when performing daily activities.

(5) Malaise, fatigue or lethargy, e.g., patients have a little more energy or much more energy, and/or patients perform daily activities, e.g., climbing stairs, a little easier, or much easier.

(6) Temperature, e.g., patients have normal healthy temperature e.g., about 37°C, or patients have no recent history of fever.

(7) Anorexia or weight loss, e.g., patients have no change in weight, or a little weight gain, and/or patients have a little increase in appetite

(8) Sinus pain or tenderness, e.g., patient has no sinus pain or tenderness, or less sinus pain or tenderness.

(9) Change in sinus discharge, e.g., patients have better sinus discharge (a decrease in thickness and/or better color).

(10) Change in physical examination of the chest, e.g., patients have improved signs on examination of the chest and may report for example, a little decrease chest congestion, or a large decrease in chest congestion.

(11) Pulmonary function by 10 % or more from a previously recorded value, e.g., patients have improved pulmonary function in pulmonary function tests.

(12) Radiographic changes indicative of pulmonary infection, e.g. patients show improved radiographic changes indicating reduced pulmonary infection.

[0108] In some embodiments, exercise tolerance and/or absenteeism from scheduled events, e.g., school or work can be measured as signs/symptoms of exacerbations.

[0109] Table 1 summarizes a variety of methods useful to measure exacerbations.

TABLE 1

Sign/Symptom	Method / Protocol						
	Fuchs	Ramsey	CFF	Rosenfeld (Seattle)[A]	Kraynack[B]	Rabin	Blummer
Cough	X	X	X	X	X	X	X
Sputum	X	X	X	X	X	X	X
Hemoptysis	X				X	X	
Dyspnea	X				X		X
Exercise Tolerance			X	X	X		X
Absenteeism		X	X	X	X		
Fatigue	X				X		X
Fever	X	X	X		X		
Decreased/Loss Appetite	X	X	X	X	X	X	X
Sinus pain	X	X					
Sinus discharge	X						
Chest exam	X		X	X	X	X	X
Tachypnea		X	X				X
Lung function	X	X	X	(X)	X	X	X
CXR	X		X		X		X
SaO2			X		X		
Neutrophila		X					
Criteria	4/12 plus antibiotics	2/5 plus 1/3	3/11	Score	Score	3/4	¾
A: Rosenfeld M. et al., Defining a pulmonary exacerbation in cystic fibrosis. J. of Pediatrics 139:359-365(2001), incorporated by reference in its entirety.							

(continued)

Sign/Symptom	Method / Protocol						
	Fuchs	Ramsey	CFF	Rosenfeld (Seattle)[A]	Kraynack[B]	Rabin	Blummer
B: Kraynack N.C. et al., Improving care at cystic fibrosis centers through quality improvement. Semin Respir Crit Care Med. 2009 Oct;30(5):547-58), incorporated by reference in its entirety.							

[0110] Some embodiments of any of the above uses include administering levofloxacin in combination with magnesium chloride in a dosage amount, administration schedule, and/or method of administration sufficient to achieve the above recited outcomes.

Pediatric patient populations

[0111] The solution provided herein relates to the use of the solution for treating cystic fibrosis in a human having a pulmonary infection comprising *P. aeruginosa*. In some embodiments, the human is a pediatric patient. In some embodiments, the human has an age less than about 18 years, less than about 17 years, less than about 16 years, less than about 15 years, less than about 14 years, less than about 13 years, less than about 12 years, less than about 11 years, less than about 10 years, less than about 9 years, less than about 8 years, less than about 7 years, less than about 6 years, less than about 5 years, less than about 4 years, less than about 3 years, less than about 2 years, and less than about 1 year.

[0112] Dosages of aerosol levofloxacin for pediatric subjects can be less than the dosage for an adult subject. In some embodiments, dosage can be determined, in part, due to the weight of a subject. For example, a subject having a weight from about 14 kg to about 21 kg can receive a dose of about 120 mg, a subject having a weight from about 22 kg to about 30 kg can receive a dose of about 180 mg dose, and a subject having a weight more than about 30 kg can receive a dose of about 240 mg. The aerosol levofloxacin is administered twice daily. In some embodiments, the aerosol levofloxacin can be administered for a period of at least about 1 day, 3 days, 5 days, 10 days, 15 days, 20 days, and 30 days. In particular embodiments, the aerosol levofloxacin is administered twice daily for 14 days.

[0113] In some embodiments, the human has a body weight less than about 70 kg, less than about 60 kg, less than about 50 kg, less than about 40 kg, less than about 30 kg, less than about 20 kg, and less than about 10 kg.

[0114] In some embodiments, the human has a body surface area less than about 1.8 m^2, less than about 1.6 m^2, less than about 1.4 m^2, less than about 1.2 m^2, less than about 1.0 m^2, less than about 0.8 m^2, less than about 0.6 m^2, and less than about 0.4 m^2.

[0115] In some embodiments, treating one of the above humans comprises achieving a dose-normalized serum AUC at least about 5 (ng.h/L)/mg Dose, at least about 10 (ng.h/L)/mg Dose, at least about 20 (ng.h/L)/mg Dose, at least about 40 (ng.h/L)/mg Dose, at least about 60 (ng.h/L)/mg Dose, at least about 80 (ng.h/L)/mg Dose, and at least about 100 (ng.h/L)/mg Dose.

[0116] In some embodiments, treating one of the above humans comprises achieving a dose-normalized serum C_{max} greater than about 1 μg/L/mg administered dose, greater than about 2 μg/L/mg administered dose, greater than about 3 μg/L/mg administered dose, greater than about 4 μg/L/mg administered dose, greater than about 5 μg/L/mg administered dose, greater than about 6 μg/L/mg administered dose, greater than about 7 μg/L/mg administered dose, greater than about 8 μg/L/mg administered dose, greater than about 9 μg/L/mg administered dose, greater than about 10 μg/L/mg administered dose, greater than about 11 μg/L/mg administered dose, greater than about 12 μg/L/mg administered dose, greater than about 13 μg/L/mg administered dose, greater than about 14 μg/L/mg administered dose, greater than about 15 μg/L/mg administered dose, and greater than about 16 μg/L/mg administered dose.

[0117] Some embodiments of any of the above methods for treating the recited humans include administering levofloxacin in combination with magnesium chloride in a dosage amount, administration schedule, and/or method of administration sufficient to achieve the recited outcomes.

EXAMPLES

Example 1-Phase 1b clinical study with levofloxacin

[0118] A Phase 1 b single-blind, placebo-control, dose-escalating multicenter study was carried out to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of aerosolized levofloxacin administered to stable CF patients. All patients had had *P. aeruginosa* cultured from sputum within the previous 24 months and at the screening visit. Study drug was administered twice daily for up to 14 days at three doses by aerosol using a PART eFlow device. Respirable

delivered doses (RDD) were approximately 40 mg, 80 mg, and 120 mg per treatment, corresponding to loaded doses of 78 mg, 175 mg, and 260 mg, respectively. Thus, the estimated total daily RDDs were 80 mg, 160 mg, and 240 mg. Study drugs were administered at 30 mg/ml (for 40 mg dose) or 50 mg/ml (for 80 mg and 120 mg doses). Table 2 shows the formulations of the study drugs.

TABLE 2

	30 mg/ml Levofloxacin solution	50 mg/ml Levofloxacin solution	Placebo
Levofloxacin, mg/ml mM)	30 (81.6)	50 (136)	0
Magnesium, mg/ml (mM)	1.5 (60)	2.4 (100)	2.4 (100)
Chloride, mg/ml (mM)	4.3 (120)	7.1 (200)	7.1 (200)
Lactose, mg/ml (mM)	51.4 (150)	51.4 (150)	51.4 (150)
pH	6.3	6.3	6.5
Osmolality, mOsm/kg	314	400	424

[0119] All patients used at least 1 concomitant medication during the study. Concomitant medications are those medications taken after the first dose of Study Drug regardless of medication start date. Concomitant medications used by at least 20% of patients included Salbutamol, Dornase alfa, Azithromycin, Seretide, Pancrelipase, Adeks, Hypertonic solutions, and Nortase.

Efficacy results

[0120] Table 3 summarizes the results for pulmonary function tests for FEV_1 measurements. The greatest relative improvement in FEV_1 after 7 and 14 days of dosing was observed in the 120 mg RDD (260 mg loaded) levofloxacin cohort, with a mean improvement of 14.79% and 17.58%, respectively. A mean improvement of 8.90% persisted over the 2 weeks to the follow-up visit. In addition, there appeared to be a dose response in patients receiving levofloxacin with patients in the 80 mg and 120 mg dose groups having an improvement in the FEV_1, while those in the 40-mg dose group did not. All 9 patients in the 120 mg dose group had a relative increase in FEV_1, with 4 of 9 patients having at least a 20% increase.

TABLE 3

	Median FEVi change (%) for each Treatment Group			
Time point	Placebo	40 mg RDD Levofloxacin	80 mg RDD Levofloxacin	120mg. RDD Levofloxacin
Day 7	n=10 5.75	n=10 -0.75	n=10 6.15	n=9 10.20
Day 14	n=8 1.20	n=10 -1.55	n=10 2.95	n=9 16.90

[0121] Table 4 show the relative changes from baseline across visits (Day 1, 2, 7, 14, and 21) in pulmonary function tests for FEV_1. In Table 3, relative change from baseline (CBG) was calculated as 'Result' FEV_1 minus 'Baseline' FEV_1 divided by 'Baseline' FEV_1.

TABLE 4

	FEV_1 (L) for each Treatment Group			
Time point	Placebo N=10	40 mg RDD Levofloxacin N=10	80 mg RDD Levofloxacin N=10	120mg. RDD Levofloxacin N=10
Day 1 Predose (Baseline)				
n	10	10	10	10

(continued)

	FEV_1 (L) for each Treatment Group			
Time point	**Placebo N=10**	**40 mg RDD Levofloxacin N=10**	**80 mg RDD Levofloxacin N=10**	**120mg. RDD Levofloxacin N=10**
Day 1 Predose (Baseline)				
Mean (SD)	2.62 (1.150)	2.26 (0.534)	2.06 (0.649)	2.56 (1.121)
Median	2.46	2.30	1.95	2.23
Minimum, maximum	1.31,4.90	1.58, 3.50	1.17,3.19	1.43, 4.71
Day 2 Predose Result				
n	10	10	10	10
Mean (SD)	2.75 (1.310)	2.31 (0.594)	2.10 (0.709)	2.73 (1.132)
Median	2.43	2.32	2.00	2.38
Minimum, maximum	1.33, 5.50	1.57, 3.60	1.13, 3.46	1.40, 4.72
Day 2 Relative CFB (%)				
n	10	10	10	10
Mean (SD)	3.85 (6.627)	1.92 (8.315)	1.57 (5.149)	7.29 (10.081)
Median	2.00	-0.30	1.90	6.60
Minimum, maximum	-7.10, 12.20	-6.30, 21.70	-7.60, 8.90	-4.70, 23.90
Day 7 Result				
n	10	10	10	9
Mean (SD)	2.82 (1.361)	2.30 (0.544)	2.26 (0.831)	3.07 (1.220)
Median	2.35	2.30	2.08	2.40
Minimum, maximum	1.39, 5.20	1.49, 3.48	1.20, 3.79	1.79, 4.99
Day 7 Relative CFB (%)				
n	10	10	10	9
Mean (SD)	5.86 (10.196)	1.60 (6.985)	9.42 (18.911)	14.79 (12.865)
Median	5.75	-0.75	6.15	10.20
Minimum, maximum	-6.50, 29.40	-5.70, 17.90	-7.40, 59.90	3.40, 37.70
Day 14 Predose Result				
n	8	10	10	9
Mean (SD)	2.99 (1.272)	2.26 (0.524)	2.09 (0.616)	3.12 (1.173)

(continued)

Day 14 Predose Result				
Median	3.11	2.30	2.10	2.57
Minimum, maximum	1.47, 5.20	1.55, 3.38	1.19, 3.21	1.74, 4.78
Day 14 Relative CFB (%)				
n	8	10	10	9
Mean (SD)	2.00 (5.529)	0.21 (8.440)	2.69 (10.125)	17.58 (15.089)
Median	1.20	-1.55	2.95	16.90
Minimum, maximum	-6.70, 8.80	-8.70,23.10	-19.40, 19.10	1.50, 41.50
Day 21/ET Result				
n	10	10	10	10
Mean (SD)	2.75 (1.327)	2.16 (0.517)	2.03 (0.632)	2.75 (1.155)
Median	2.28	2.07	2.04	2.48
Minimum, maximum	1.17, 5.10	1.46, 3.42	1.06, 2.82	1.49, 4.87
Day 21/ET Relative CFB (%)				
n	10	10	10	10
Mean (SD)	3.20 (10.157)	-4.25 (7.092)	-1.03 (8.880)	8.90 (15.789)
Median	1.75	-5.80	-3.10	10.10
Minimum, maximum	-10.70, 20.60	-12.70, 11.80	-11.60, 12.90	-15.90, 38.70
ET = early termination.				

[0122] Colony-forming units of P aeruginosa at Day 1 were compared with colony-forming units at Day 7 and 14. Table 5 summarizes the percentage change in sputum P. aeruginosa (log CFU/g) in treatment groups. Declines in sputum *P. aeruginosa* were observed over all days of dosing.

TABLE 5

Time point	**Median Change in sputum *P. aeruginosa* (log CFU/g) for Treatment Group**	
	Placebo	**Levofloxacin solution**
Day 7	0.04 (n=9)	-0.50 (n=21)
Day 14	0.04 (n=9)	-1.23 (n=21)

Safety results

[0123] No study drug-related serious adverse events were reported. Most adverse events were mild or moderate in severity and self-limiting. The majority of adverse events were mild, with taste complaints, cough and headache as the most commonly observed adverse events. No patients receiving levofloxacin solution for inhalation met drug intolerability criteria. Adverse events reported in more than 1 patient receiving levofloxacin included abdominal pain, cough, disease

progression (acute exacerbation), dysgeusia (bad taste), haemoptysis, headache, nasal congestion, nasopharyngeal pain (sore throat), respiratory tract congestion, and wheezing. Table 6 summarizes adverse events observed in more than one CF patient receiving levofloxacin. Accordingly, these results demonstrated the safety and tolerability of levofloxacin with multiple doses over 14 days.

TABLE 6

Adverse event	Treatment group			
	40 mg Levofloxacin (N=10)	80 mg Levofloxacin (N=10)	120mg. Levofloxacin (N=10)	Placebo (N=10)
Abdominal pain	1 (10%)	--	1 (10%)	--
Alopecia	--	1 (10%)	--	--
Blood blister	--	--	1 (10%)	--
Breath sounds abnormal		--	1 (10%)	--
Chest discomfort	--	1 (10%)	--	1 (10%)
Cough	--	4 (40%)	4 (40%)	1 (10%)
Diarrhoea	1 (10%)	--	--	--
Disease progression	--	--	2 (20%)	1 (10%)
Drooling		1 (10%)		
Dysguesia	3 (30%)	6 (60%)	5 (50%)	1 (10%)
Dyspnoea	1 (10%)	--	--	--
Fatigue	--	1 (10%)	--	--
Flank pain	1 (10%)	--	--	--
Forced expired volume decreased	--	1 (10%)	--	1 (10%)
Hemoptysis	--	1 (10%)	1 (10%)	--
Headache	--	2 (20%)	2 (20%)	--
Migraine	--	1 (10%)	-	--
Nasal congestion	--	1 (10%)	1 (10%)	--
Non-cardiac chest pain	--	1 (10%)	--	--
Oral candidiasis	--	1 (10%)	--	--
Paraethesia oral	--	--	1 (10%)	--
Pharyngolaryngeal pain	--	--	2 (20%)	--
Pulmonary function test decreased	--	--	1 (10%)	--
Pyrexia	--	--	1 (10%)	--
Rash erythematous	--	--	1 (10%)	--
Respiratory tract congestion	--	--	2 (20%)	--
Retching	--	1 (10%)	--	--
Rhinorrhoea	--	1 (10%)	--	--
Thirst	--	1 (10%)	--	--

(continued)

Adverse event	Treatment group			
	40 mg Levofloxacin (N=10)	80 mg Levofloxacin (N=10)	120mg. Levofloxacin (N=10)	Placebo (N=10)
Upper respiratory tract infection	1 (10%)	--	--	1 (10%)
Wheezing	1 (10%)	--	1 (10%)	--

Example 2-Phase 2 clinical study with levofloxacin

[0124] A phase 2, multi-center, randomized, double-blind, placebo-controlled study was carried out to evaluate the safety, tolerability and efficacy of three dosage regimens of levofloxacin formulated with $MgCl_2$ administered for 28 days to stable CF patients. The following dosage regimens (as nebulizer loaded doses) were evaluated: 120 mg QD (daily); 240 mg QD (daily); and 240 mg BID (twice daily). Based on aerosol characterization studies of the 100 mg/ml formulation, these loaded doses of 120 and 240 mg correspond estimated respirable delivered doses (RDDs) using a PART eFlow nebulizer of about 65 and 130 mg, respectively. The plasma levofloxacin Cm. and AUC with all dosage regimens chosen for this study should provide concentrations in pulmonary tissues well in excess of those associated with bactericidal activity against CF pathogens (data not shown).

[0125] The formulation of levofloxacin solution and placebo is shown in Table 7. Study drug was administered by aerosol using the PARI eFlow® device with a mesh to deliver a particle size smaller than approximately 3.5 μm - 4.0 μm.

TABLE 7

	Levofloxacin	Placebo
Levofloxacin, mg/ml (mM)	100 (272)	0
Mg, mg/ml (mM)	5.0 (200)	0
Cl, mg/ml (mM)	14.4 (400)	0
pH	5 - 7	6 - 8
Osmolality, mOsm/kg	350 - 500	300 - 500
Saline	-	0.9 %

[0126] Patient inclusion criteria included: (1) at least 16 years of age; (2) clinically diagnosed with CF; (3) able to elicit an $FEV_1 \geq 25\%$ but $\leq 85\%$ predicted value at Screening; (4) received at least 3 courses of inhaled antimicrobials over the preceding 12 months and had received at least 1 course of inhaled tobramycin/(TOB®)/colistin in the 2 months prior to Visit 1 (Day 1), but none in the 28 days prior to Visit 1 (Day 1); (5) had a sputum specimen at Screening positive for *P. aeruginosa* and a history of at least 1 positive sputum culture positive for *P. aeruginosa* within the last 18 months; and (6) clinically stable with no significant changes in health status within the last 30 days.

[0127] Patient exclusion criteria included: (1) use of an investigational agent within 30 days prior to Visit 1 (Day 1); (2) use of any nebulized or systemic antibiotics active against *P. aeruginosa* within 28 days prior to Visit 1 (Day 1), other than maintenance oral azithromycin, which must have been initiated at least 30 days prior to Visit 1 (Day 1); (3) hypersensitivity to fluoroquinolones or excipients of levofloxacin formulated with $MgCl_2$; (4) intolerance to bronchodilators or unwilling to use a bronchodilator during the study; (5) use of oral corticosteroids in doses exceeding the equivalent of 10 mg prednisone/day or 20 mg prednisone every other day; (6) changes in physiotherapy technique or schedule within 14 days prior to Visit 1 (Day 1); (7) changes in medical regimen for treatment of CF (e.g., introduction, dose escalation, or elimination of therapies such as dornase alfa, nonsteroidal anti-inflammatory agents, azithromycin, hypertonic saline, or inhaled corticosteroids) within 30 days of Visit 1 (Day 1); (8) history of lung transplantation; (9) evidence of acute upper respiratory tract infection within 10 days or lower respiratory tract infection within 30 days prior to Visit 1 (Day 1); (10) pregnancy, breastfeeding, or unwilling to practice birth control or abstinence during participation in the study (women only); (11) history of seizures or low seizure threshold (e.g., epilepsy); (12) renal dysfunction (calculated creatinine clearance [CrCl] < 50 mL/min) at Screening; (13) aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥ 3 x upper limit of normal (ULN) at Screening or evidence of severe liver disease (e.g., cirrhosis, portal hypertension); (14) history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection/seropositivity;

(15) history of hemoptysis ≥ 30 mL over any 24-hour period during the 30 days prior to Visit 1; (16) oxygen saturation < 90% on room air at Screening or Visit 1 (Day 1); and (17) > 15% relative decline in FEV_1 (L) from Screening to Visit 1 (Day 1).

[0128] Patients were assessed on Day 1, 7, 14, and 28, and then up to 28 days after completion of study drug, namely, Days 42 and 56. The formulation of study drug, i.e., levofloxacin, is shown in Table 7. The end of the study was defined as the last visit of the last patient. Study populations included: (1) safety/modified intent to treat (MITT) population which included all patients enrolled in the study that receive at least one dose of study drug; (2) efficacy evaluable (EE) population which included all patients enrolled in the study without major protocol violations that receive at least 80% of study drug doses during the 28 days of study drug therapy; and (3) pharmacokinetic (PK) population which included all patients that receive at least one dose of study drug and have at least one PK blood sample collected.

[0129] Approximately 32 patients per treatment arm provided 80% power to detect a difference between treatment arms using a 2-sided analysis of covariance (ANCOVA), with a 5% alpha, assuming a standard deviation (SD) of 1.5 and a mean log CFU change in P. aeruginosa of 0.75 decrease, 0.75 decrease, no change and 0.25 increase for the levofloxacin 240 mg BID, levofloxacin 240 mg QD, levofloxacin 120 mg QD, and placebo treatment arms, respectively. Sample size calculations assumed a 10% discontinuation rate from the study; therefore patients who discontinue the study were not replaced.

[0130] Efficacy was evaluated by microbiologic assessment of sputum samples, time to need for anti-pseudomonal antimicrobials, the Cystic Fibrosis Questionaire-Revised (CFQ-R), and pulmonary function tests. In addition, a primary efficacy comparison tested Ho: the average decline in log CFUs of *P. aeruginosa* from the start of levofloxacin or placebo administration (Day 1) to four weeks later is equal for all four groups, versus H_1: the average decline in log CFUs is different for at least one of the four groups using a repeated-measures mixed effects model adjusting for baseline levofloxacin minimum inhibitory concentration (MIC) as a continuous variable (log base 2 transformed), baseline lung function, and geographical region (U.S. versus ex-U.S.). Pair-wise comparisons between all the treatment arms were conducted as secondary analyses.

[0131] Efficacy endpoints including clinical endpoints, pulmonary function tests, and additional microbiological parameters were assessed as change from Day 1 to subsequent visits where the endpoint data was collected. Time to need for intravenous/oral/inhaled anti-pseudomonal antimicrobials were assessed from Day 1 until final visit using survival analysis. The primary population for efficacy analysis was the EE population, but efficacy endpoints were also analyzed using the MITT population.

[0132] Patients enrolled in the study had a median of 5 courses of aerosolized antibiotics over the previous 12 months. The baseline FEV_1 (as percent predicted) was 53% across the entire study and not different among groups. The median baseline MICs of all isolates of *Pseudomonas aeruginosa* recovered from all patients (n=592) to levofloxacin was 4 mg/L and the MIC90 was 16, also similar across all groups. These MICs are indicative of baseline non-susceptibility/resistance to levofloxacin, as defined by CLSI reference methods and the US FDA.

[0133] Concomitant medication used by patients during the study included Dornase alfa, Azithromycin, Salbutamol, Pancrelipase, hypertonic sodium chloride, Seretide, and ADEK, and are summarized for the EE population in Table 8. Table 9 summarizes patient disposition in the study. The results of the study showed were statistically significant advantages of aerosol levofloxacin compared to the placebo in several clinical and microbiological measures, despite the use of concomitant medications, resistance to levofloxacin, and previous use of other aerosolized antibiotics, including tobramycin and colistin.

TABLE 8

Medication	Placebo (N= 37)	Levofloxacin 120mg QD (N= 38)	Levofloxacin 240mg QD (N= 37)	Levofloxacin 240mg BID (N= 39)	Total (N=151)
Dornase alpha	31 (83.8%)	27 (71.1%)	33 (89.2%)	29 (74.4%)	120 (79.5%)
Azithromycin	25 (67.6%)	29 (76.3%)	26 (70.3%)	32 (82.1%)	112 (74.2%)
Salbutamol	25 (67.6%)	29 (76.3%)	25 (67.6%)	23 (59.0%)	102 (67.5%)
Pancrelipase	9 (51.14%)	21 (55.3%)	22 (59.5%)	21 (53.8%)	83 (55.0%)
Sodium chloride	22 (59.5%)	13 (34.2%)	13 (35.1%)	22 (56.4%)	70 (46.4%)

(continued)

Medication	Placebo (N= 37)	Levofloxacin 120mg QD (N= 38)	Levofloxacin 240mg QD (N= 37)	Levofloxacin 240mg BID (N= 39)	Total (N=151)
Seretide	9 (51.14%)	20 (52.6%)	16 (43.2%)	15 (38.5%)	70 (46.4%)
ADEK	10 (27.0%)	13 (34.2%)	10 (27.0%)	13 (33.3%)	46 (30.5%)

TABLE 9

Disposition		Placebo	Levofloxacin 120mg. QD	Levofloxacin 240mg QD	Levofloxacin 240mg BID	Total
Patients Enrolled		37	38	37	39	151
Safety/MITT population		37				
(100.0%)		38 (100.0%)	37 (100.0%)	39 (100.0%)	151 (100.0%)	
Efficacy Evaluable population		32 (86.5%)	35 (92.1%)	35 (94.6%)	34 (87.2%)	136 (90.1%)
PK population		37 (100.0%)	37 (97.4%)	37 (100.0%)	39 (100.0%)	150 (99.3%)
Completed Study		35 (94.6%)	37 (97.4%)	35 (94.6%)	36 (92.3%)	143 (94.7%)
Discontinued from Study		2 (5.4%)	1 (2.6%)	2 (5.4%)	3 (7.7%)	8 (5.3%)
	Adverse Event	2 (5.4%)	1 (2.6%)	1 (2.7%)	2 (5.1%)	6 (4.0%)
Primary Reason for Discontinuation from Study	Withdrawal of consent	0 (0.0%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	1 (0.7%)
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (0.7%)
	Primary Reason for Study Drug Discontinuation[a]	5 (13.5%)	3 (7.9%)	1 (2.7%)	2 (5.1%)	11 (7.3%)
	Adverse Event[a]	4 (10.8%)	3 (7.9%)	1 (2.7%)	2 (5.1%)	10 (6.6%)
	Other	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
a: Patients could be included in both discontinuation from study and Study Drug categories.						

Microbiological evaluations

[0134] Changes in *P. aeruginosa* density (loglo CFU/g sputum) for sputum samples taken from the EE and MITT populations are summarized in Tables 10 and 11, respectively (SD = standard deviation). Changes in MIC for *P. aeruginosa* density (log^{10} CFU/g sputum) to levofloxacin (all organisms) for EE and MITT populations are shown in Tables 12 and 13, respectively. In addition, changes in the highest MIC values for *P. aeruginosa* isolates to levofloxacin were determined for EE and MITT populations, and are summarized in Tables 14 and 15, respectively. Tables 16 and 17 summarize the percentage of EE and MITT populations, respectively, with categorical changes in highest MIC values for *P. aeruginosa* isolates to levofloxacin. Tables 18 and 19 summarize changes in non-fermenting gram negative bacilli density (NFGNB), excluding *P. aeruginosa*, with only patients with positive NFGNB counts at baseline, for EE and MITT populations, respectively. Tables 20 and 21 summarize changes for presumptive S. aureus density (log_{10} CFU/g sputum) for only patients with positive *S. aureus* counts at baseline, for EE and MITT populations, respectively.

TABLE 10

		EE population - *P. aeruginosa* density (log_{10} CFU/g sputum)				
		Placebo (N=32)	**Levofloxacin 120mg. QD (N=35)**	**Levofloxacin 240mg QD (N=35)**	**Levofloxacin 240mg BID (N=34)**	**Combined Levofloxacin 240mg QD and BID (N=69)**
Day 1	Mean (SD)	7.49 (1.674)	7/43 (1.622)	7.16 (1.597)	7.26 (1.433)	7.21 (1.508)
	Median	8.11	8.17	7.97	7.84	7.90
Day 7	Mean (SD)	7.37 (1.746)	6.64 (1.818)	6.94 (1.783)	6.23 (1.850)	6.59 (1.838)
	Median	8.14	6.86	7.15	6.52	6.77
Change from Baseline to Day 7	Mean (SD)	-0.12 (1.422)	-0.76 (1.263)	-0.25 (1.789)	-1.03 (1.921)	-0.64 (1.833)
	Median	0.09	-0.58	-0.18	-0.88	-0.37
	P-value		0.0277	0.5892	0.0051	0.0533
Day 14	Mean (SD)	7.48 (1.616	7.32 (1.643)	6.69 (1.628(	6.43 (1.725)	6.56 (1.669)
	Median	7.85	8.00	6.46	6.81	6.78
Change from Baseline to Day 14	Mean (SD)	0.03 (1.355)	-0.10 (1.240)	-0.47 (1.905)	-0.83 (1.901)	-0.65 (1.898)
	Median	-0.01	0.00	-0.11	-0.91	-0.46
	P-value		0.3929	0.0998	0.0047	0.0105
Day 28	Mean (SD)	7.85 (1.050)	7.25 (1.431)	6.78 (1.896)	6.65 (1.440)	6.72 (1.683)
	Median	8.28	7.78	7.38	6.40	6.90
Change from Baseline to Day 28	Mean (SD)	0.36 (1.329)	-0.31 (1.050)	-0.38 (1.780)	-0.74 (1.488)	-0.55 (1.645)
	Median	0.00	-0.20	-0.52	-0.68	-0.58
	P-Value		0.0093	0.0075	0.0002	0.0002

TABLE 11

		MITT population - *P. aeruginosa* density (log_{10} CFU/g sputum)				
		Placebo (N=37)	**Levofloxacin 120mg. QD (N=38)**	**Levofloxacin 240mg QD (N=37)**	**Levofloxacin 240mg BID (N=39)**	**Combined Levofloxacin 240mg QD and BID (N=76)**
Day 1	Mean (SD)	7.45 (1.656)	7.43 (1.571)	7.08 (1.742)	7.17 (1.726)	7.12 (1.723)
	Median	8.10	8.16	7.97	7.90	7.91
Day 7	Mean (SD)	7.21 (1.750)	6.68 (1.778)	6.79 (1.854)	6.16 (1.969)	6.47 (1.927)
	Median	7.97	6.98	6.95	6.53	6.69

(continued)

		MITT population - *P. aeruginosa* density (log_{10} CFU/g sputum)				
		Placebo (N=37)	**Levofloxacin 120mg. QD (N=38)**	**Levofloxacin 240mg QD (N=37)**	**Levofloxacin 240mg BID (N=39)**	**Combined Levofloxacin 240mg QD and BID (N=76)**
Change from Baseline to Day 7	Mean (SD)	-0.24 (1.429)	-0.70 (1.257)	-0.31 (1.823)	-0.97 (1.846)	-0.65 (1.852)
	Median	0.00	-0.53	-0.18	-0.76	-0.35
	P-value		0.1091	0.6986	0.0124	0.0956
Day 14	Mean (SD)	7.33 (1.651)	7.33 (1.602)	6.63 (1.744)	6.32 (1.875)	6.48 (1.806)
	Median	7.85	8.00	6.46	6.70	6.61
Change from Baseline to Day 14	Mean (SD)	0.07 (1.373)	-0.07 (1.213)	-0.44 (1.855)	-0.81 (1.838)	-0.63 (1.843)
	Median	-0.02	0.00	-0.10	-0.79	-0.40
	P-value		0.7941	0.1972	0.0091	0.0251
Day 28	Mean (SD)	7.66 (1.236)	7.26 (1.394)	6.82 (1.869)	6.58 (1.704)	6.70 (1.781)
	Median	8.26	7.78	7.38	6.48	6.90
Change from Baseline to Day 28	Mean (SD)	0.21 (1.377)	-0.27 (1.035)	-0.25 (1.857)	-0.66 (1.422)	-0.46 (1.658)
	Median	0.00	-0.20	-0.39	-0.56	-0.5
	P-Value		0.0728	0.0698	0.0014	0.0039

TABLE 12

		EE population - MIC of *P. aeruginosa* to levofloxacin (all organisms) (μg/ml)				
		Placebo (N=37)	**Levofloxacin 120mg. QD**	**Levofloxacin 240mg QD**	**Levofloxacin 240mg BID**	**Combined Levofloxacin 240mg QD and BID**
Day 1	N	124	140	140	136	276
	Mean (SD)	6.0 (5.00)	11.5 (21.98)	6.3 (8.85)	6.8 (8.80)	6.5 (8.82)
	MIC_{50}	4	4	4	4	4
	MIC_{90}	16	32	16	16	16
Day 7	N	124	136	132	132	264
	Mean (SD)	6.6 (6.73)	9.9 (17.28)	6.8 (16.13)	8.8 (17.28)	7.8 (16.71)
	Min, Max	0.25,32	0.13, 128	0.13, 128	0.13, 128	0.13, 128
	MIC_{50}	4	4	2	4	4
	MIC_{90}	8	16	16	16	16

(continued)

		EE population - MIC of *P. aeruginosa* to levofloxacin (all organisms) (μg/ml)				
		Placebo (N=37)	**Levofloxacin 120mg. QD**	**Levofloxacin 240mg QD**	**Levofloxacin 240mg BID**	**Combined Levofloxacin 240mg QD and BID**
Day 14	N	120	140	136	132	268
	Mean (SD)	5.6 (6.79)	13.0 (29.34)	6.6 (9.44)	8.4 (14.47)	7.5 (12.19)
	MIC_{50}	4	4	4	4	4
	MIC_{90}	8	32	16	16	16
Day 28	N	128	132	136	124	260
	Mean (SD)	5.0 (3.97)	8.9 (13.47)	6.0 (7.57)	10.1 (16.32)	8.0 (12.67)
	MIC_{50}	4	4	4	4	4
	MIC_{90}	8	16	16	32	16

TABLE 13

r		MITT population - MIC of *P. aeruginosa* to levofloxacin (all organisms) (μg/ml)				
		Placebo	**Levofloxacin 120mg. QD**	**Levofloxacin 240mg QD**	**Levofloxacin 240mg BID**	**Combined Levofloxacin 240mg QD and BID**
Day 1	N	140	152	148	152	300
	Mean (SD)	6.1 (5.40)	11.0 (21.17)	6.1 (8.64)	6.8 (8.47)	6.4 (8.55)
	MIC_{50}	4	4	4	4	4
	MIC_{90}	16	32	16	16	16
Day 7	N	136	144	140	140	280
	Mean (SD)	6.8(7.33)	9.6 (16.83)	6.7 (15.69)	8.6 (16.82)	7.6 (16.27)
	MIC_{50}	4	4	4	4	4
	MIC_{90}	16	16	16	16	16
Day 14	N	128	144	144	140	284
	Mean (SD)	5.8	12.9 (28.95)	6.5 (9.23)	8.2 (14.11)	7.3 (11.90)
	MIC_{50}	4	6	4	4	4
	MIC_{90}	16	32	16	16	16
Day 28	N	132	136	140	132	272
	Mean (SD)	4.9 (3.97)	8.8 (13.32)	5.9 (750)	9.9 (15.98)	7.9 (12.51)
	MIC_{50}	4	4	4	4	4
	MIC_{90}	8	16	16	32	16

TABLE 14

		EE population - MIC of *P. aeruginosa* to levofloxacin (all organisms) (μg/ml)				
		Placebo (N=32)	**Levofloxacin 120mg. QD (N=35)**	**Levofloxacin 240mg QD (N=35)**	**Levofloxacin 240mg BID (N=34)**	**Combined Levofloxacin 240mg QD and BID (N=69)**
Day 1	Mean (SD)	8.79 (6.661)	14.98 (22.383)	9.35 (12.991)	11.58 (13.399)	10.46 (13.144)
	MIC_{50}	8	8	4	6	4
	MIC_{90}	16	32	32	32	32
Day 7	Mean (SD)	8.77 (7.455)	15.71(22.523)	10.86 (22.222)	13.05 (22.838)	11.95 (22.385)
	MIC_{50}	8	8	4	4	4
	MIC_{90}	16	32	16	32	32
Day 14	Mean (SD)	8.42 (11.437)	21.16 (43.639)	9.56 (12.409)	15.18 (25.541)	12.33 (20.032)
	MIC_{50}	6	8	8	4	8
	MIC_{90}	16	32	16	32	32
Day 28	Mean (SD)	7.31 (4.961)	12.91 (15.669)	9.42 (11.658)	17.97 (26.008)	13.56 (20.252)
	MIC_{50}	8	8	8	8	8
	MIC_{90}	16	32	16	32	32

TABLE 15

		MITT population - Highest MIC of *P. aeruginosa* to levofloxacin (μg/ml)				
		Placebo (N= 37)	**Levofloxacin 120mg. QD (N= 38)**	**Levofloxacin 240mg QD (N= 37)**	**Levofloxacin 240mg BID (N= 39)**	**Combined Levofloxacin 240mg QD and BID (N= 76)**
Day 1	Mean (SD)	9.04 (7.593)	14.32 (21.583)	9.06 (12.685)	11.41 (12.816)	10.25 (12.720
	MIC_{50}	8	8	4	6	4
	MIC_{90}	16	32	32	32	32
Day 7	Mean (SD)	9.06 (8.203)	15.17 (21.991)	10.53 (21.615)	12.96 (21.902)	11.76 (21.639)
	MIC_{50}	8	8	4	6	4
	MIC_{90}	16	32	16	32	16
Day 14	Mean (SD)	8.78 (11.554)	20.34 (42.555)	9.28 (12.136)	14.86 (24.522)	12.07 (19.415)
	MIC_{50}	6	8	8	6	8
	MIC_{90}	16	32	16	32	32

(continued)

		MITT population - Highest MIC of *P. aeruginosa* to levofloxacin (μg/ml)				
		Placebo (N= 37)	**Levofloxacin 120mg. QD (N= 38)**	**Levofloxacin 240mg QD (N= 37)**	**Levofloxacin 240mg BID (N= 39)**	**Combined Levofloxacin 240mg QD and BID (N= 76)**
Day 28	Mean (SD)	7.78 (6.334)	12.74 (15.286)	9.17 (11.389)	17.91 (25.067)	13.48 (19.734)
	MIC_{50}	8	8	8	8	8
	MIC_{90}	16	32	16	16	32

TABLE 16

		EE population - Categorical change in highest MIC of *P. aeruginosa* to levofloxacin (% population)				
		Placebo (N= 32)	**Levofloxacin 120mg. QD (N=35)**	**Levofloxacin 240mg QD (N= 35)**	**Levofloxacin 240mg BID (N= 34)**	**Combined Levofloxacin 240mg QD and BID (N= 69)**
Change from Baseline to Day 7	>=4 fold increase	6.5%	2.9%	12.1%	9.1%	10.6%
	<4 fold increase	93.5%	97.1%	87.9%	90.9%	89.4%
Change from Baseline to Day 14	>=4 fold increase	10.0%	11.4%	5.9%	18.2%	11.9%
	<4 fold increase	90.0%	88.6%	94.1%	81.8%	88.1%
Change from Baseline to Day 28	>=4 fold increase	9.4%	9.1%	8.8%	15.6%	10.6%
	<4 fold increase	90.6%	90.9%	91.2%	84.4%	87.9%
Change from Baseline to Day 56/Early Term	>=4 fold increase	22.6%	6.2%	5.7%	15.2%	10.3%
	<4 fold increase	77.4%	93.6%	94.3%	84.8%	89.7%

TABLE 17

		MITT population - Categorical change in highest MIC of *P. aeruginosa* to levofloxacin (% population)				
		Placebo (N= 37)	**Levofloxacin 120mg. QD (N= 38)**	**Levofloxacin 240mg QD (N=37)**	**Levofloxacin 240mg BID (N= 39)**	**Combined Levofloxacin 240mg QD and BID (N= 76)**
Change from Baseline to Day 7	>=4 fold increase	5.7%	2.8%	11.4%	8.3%	9.9%
	<4 fold increase	94.3%	97.2%	88.6%	91.7%	90.1%

(continued)

		MITT population - Categorical change in highest MIC of *P. aeruginosa* to levofloxacin (% population)				
		Placebo (N= 37)	**Levofloxacin 120mg. QD (N= 38)**	**Levofloxacin 240mg QD (N=37)**	**Levofloxacin 240mg BID (N= 39)**	**Combined Levofloxacin 240mg QD and BID (N= 76)**
Change from Baseline to Day 14	> = 4 fold increase	8.8%	10.8%	5.6%	16.7%	11.1%
	< 4 fold increase	91.2%	89.2%	94.4%	83.3%	88.9%
Change from Baseline to Day 28	> = 4 fold increase	8.3%	8.6%	8.3%	14.3%	11.3%
	< 4 fold increase	91.7%	91.4%	91.7%	85.7%	88.7%
Change from Baseline to Day 56/Early Term	> = 4 fold increase	20.0%	5.9%	5.4%	13.9%	9.6%
	< 4 fold increase	80.0%	94.1%	94.6%	86.1%	90.4%

TABLE 18

		EE population - Change in non-fermenting gram negative bacilli density (log_{10} CFU/g sputum)					
		Placebo (N= 5)	**Levofloxacin 120mg. QD (N= 5)**	**Levofloxacin 240mg QD (N= 5)**	**Levofloxacin 240mg BID (N= 4)**	**Combined Levofloxacin 240mg QD and BID (N= 9)**	**Combined Levofloxacin (N= 14)**
Day 1	Mean (SD)	6.60 (1.113)	5.69 (2.674)	4.65 (2.271)	5.52 (2.291)	5.03 (2.182)	5.27 (2.288)
Day 7	Mean (SD)	6.26 (3.018)	4.54 (2.361)	2.18 (1.614)	5.01 (3.068)	3.44 (2.657)	3.83 (2.522)
Change from Baseline to Day 7	Mean (SD)	-0.34 (2.610)	-1.15 (1.607)	-2.47 (3.346)	-0.51 (3.184)	-1.60 (3.235)	-1.44 (2.699)
	P-value		0.1206	0.0476	0.7552	0.1755	0.1178
Day 14	Mean (SD)	5.94 (3.002)	3.15 (3.122)	2.04 (2.315)	6.02 (1.894)	3.80 (2.903)	3.57 (2.880)
Change from Baseline to Day 28	Mean (SD)	-0.66 (2.315)	-2.54 (3.057)	-2.61 (3.222)	0.50 (1.638)	-1.23 (2.980)	-1.70 (2.961)
	P-value		0.0894	0.1571	0.5983	0.5932	0.2824
Day 28	Mean (SD)	5.60 (3.012)	5.10 (2.938)	1.36 (0.808)	5.01 (2.758)	2.98 (2.621)	3.63 (2.787)
Change from	Mean (SD)	-1.00 (3.262)	-1.44 (4.739)	-3.29 (2.401)	-0.51 (1.438)	-2.05 (2.407)	-1.87 (3.092)
Baseline to Day 28	P-value		0.2997	0.0479	0.9881	0.2237	0.1956

TABLE 19

		MITT population - Change in non-fermenting gram negative bacilli density (log_{10} CFU/g sputum)					
		Placebo (N= 6)	**Levofloxacin 120mg. QD (N= 5)**	**Levofloxacin 240mg QD (N= 7)**	**Levofloxacin 240mg BID (N= 5)**	**Combined Levofloxacin 240mg QD and BID (N= 12)**	**Combined Levofloxacin (N= 17)**
Day 1	Mean (SD)	5.88 (2.018)	5.69 (2.674)	5.26 (2.203)	6.05 (2.317)	5.59 (2.184)	5.62 (2.251)
Day 7	Mean (SD)	5.44 (3.375)	4.54 (2.361)	2.52 (1.997)	5.63 (3.004)	3.82 (2.832)	4.03 (2.650)
Change from Baseline to Day 7	Mean (SD)	-0.45 (2.350)	-1.15 (1.607)	-2.73 (2.882)	-0.42 (2.765)	-1.77 (2.955)	-1.59 (2.594)
	P-value		0.2680	0.0485	0.6562	0.3749	0.2748
Day 14	Mean (SD)	5.17 (3.286)	3.25 (3.122)	3.08 (2.599)	6.50 (1.964)	4.50 (2.862)	4.11 (2.911)
Change from Baseline to Day 28	Mean (SD)	-0.72 (2.075)	-2.54 (3.057)	-2.18 (2.784)	0.45 (1.423)	-1.08 (2.605)	-1.51 (2.733)
	P-value		0.1020	0.1924	0.2832	0.9333	0.4410
Day 28	Mean (SD)	4.88 (3.215)	5.10 (2.938)	2.77 (2.505)	5.63 (2.762)	3.96 (2.892)	4.24 (2.850)
Change from Baseline to Day 28	Mean (SD)	-1.00 (2.917)	-1.44 (4.739)	-2.49 (2.538)	-0.43 (1.260)	1.63 (2.284)	-1.58 (2.885)
	P-value		0.5733	0.1606	0.4532	0.7266	0.6211

TABLE 20

		EE population - Change for presumptive *S. aureus* density (log_{10} CFU/g sputum)					
		Placebo (N= 16)	**Levofloxacin 120mg. QD (N= 16)**	**Levofloxacin 240mg QD (N= 19)**	**Levofloxacin 240mg BID (N= 13)**	**Combined Levofloxacin 240mg QD and BID (N= 32)**	**Combined Levofloxacin (N= 48)**
Day 1	Mean (SD)	5.67 (2.125)	5.72 (1.871)	5.64 (1.985)	5.68 (2.196)	5.65 (2.038)	5.68 (1.964)
Day 7	Mean (SD)	5.53 (2.152)	4.53 (2.272)	5.34 (2.321)	4.96 (2.992)	5.18 (2.574)	4.97 (2.473)
Change from Baseline to Day 7	Mean (SD)	-0.14 (0.968)	-1.19 (1.722)	-0.30 (1.579)	-0.72 (1.159)	-0.47 (1.419)	-0.71 (1.546)
	P-value		0.0347	0.5969	0.2039	0.2891	0.1059
Day 14	Mean (SD)	5.35 (2.469)	5.30 (2.543)	5.14 (2.594)	4.70 (2.829)	4.96 (2.656)	5.08 (2.597)
Change from Baseline to Day 28	Mean (SD)	-0.32 (1.259)	-0.42 (1.273)	-0.50 (1.766)	-0.98 (0.998)	-0.69 (1.502)	-0.60 (1.422)
	P-value		0.6684	0.5883	0.1593	0.2497	0.3259
Day 28	Mean (SD)	5.46 (2.647)	5.31 (2.482)	4.56 (2.724)	5.42 (2.973)	4.89 (2.806)	5.04 (2.680)
Change from Baseline to Day 28	Mean (SD)	-0.21 (1.137)	-0.41 (1.146)	-1.08 (2.622)	-0.38 (1.144)	-0.81 (2.173)	-0.67 (1.882)
	P-value		0.6124	0.1186	0.6403	0.2589	0.3159

TABLE 21

		EE population - Change for presumptive *S. aureus* density (log_{10} CFU/g sputum)					
		Placebo (N= 19)	**Levofloxacin 120mg. QD (N= 17)**	**Levofloxacin 240mg QD (N= 21)**	**Levofloxacin 240mg BID (N= 16)**	**Combined Levofloxacin 240mg QD and BID (N= 37)**	**Combined Levofloxacin (N= 54)**
Day 1	Mean (SD)	6.06 (2.152)	5.89 (1.941)	5.63 (1.894)	5.51 (2.318)	5.58 (2.058)	5.68 (2.009)
Day 7	Mean (SD)	5.78 (2.071)	4.75 (2.382)	5.23 (2.249)	4.65 (2.954)	4.99 (2.543)	4.91 (2.472)
Change from Baseline to Day 7	Mean (SD)	-0.28 (0.985)	-1.14 (1.681)	-0.40 (1.615)	-0.66 (1.243)	-0.51 (1.458)	-0.71 (1.545)
	P-value		0.0563	0.6856	0.3058	0.3995	0.1653
Day 14	Mean (SD)	5.64 (2.387)	5.48 (2.568)	4.97 (2.579)	4.32 (2.820)	4.70 (2.662)	4.95 (2.633)
Change from Baseline to Day 28	Mean (SD)	-0.42 (1.216)	-0.41 (1.233)	-0.66 (1.907)	-0.99 (0.981)	-0.80 (1.578)	-0.68 (1.475)
	P-value		0.8238	0.5691	0.2231	0.2393	0.4058
Day 28	Mean (SD)	5.65 (2.511)	5.49 (2.510)	4.48 (2.633)	4.95 (3.018)	4.66 (2.760)	4.93 (2.684)
Change from Baseline to Day 28	Mean (SD)	-0.41 (1.240)	-0.41 (1.110)	-1.15 (2.578)	-0.44 (1.150)	-0.87 (2.131)	-0.72 (1.860)
	P-value		0.8341	0.1623	0.7846	0.3528	0.4572

[0135] *P. aeruginosa* densities were reduced from baseline values on (Day 1) over the course of the study in all three levofloxacin treatment groups in both the EE and MITT populations. Figures 3 and 4 show mean changes in *P. aeruginosa* densities over time for each treatment group.

[0136] In the EE population, there was a decrease of *P. aeruginosa* density in patients administered levofloxacin 240 mg BID from a median value of 7.84 $\log_{10}$ CFU/g sputum on Day 1 to a median value of 6.40 $\log_{10}$ CFU/g sputum on Day 28, representing a reduction in *P. aeruginosa* density in sputum of approximately 96%. In patients administered levofloxacin 240 mg QD, there was a decrease in *P. aeruginosa* density from a median value of 7.97 $\log_{10}$ CFU/g sputum on Day 1 to a median value of 7.38 $\log_{10}$ CFU/g sputum on Day 28, representing a reduction in *P. aeruginosa* density in sputum of approximately 74%. In patients administered levofloxacin 120 mg QD, there was a decrease in *P. aeruginosa* density from a median value of 8.17 $\log_{10}$ CFU/g sputum on Day 1 to a median value of 7.78 $\log_{10}$ CFU/g sputum on Day 28, representing a reduction in *P. aeruginosa* density in sputum of approximately 59%. The largest differences for *P. aeruginosa* density in sputum between patients administered placebo and patients administered levofloxacin were 1.62 $\log_{10}$ CFU/g sputum on Day 7, 1.39 $\log_{10}$ CFU/g sputum on Day 14, and 1.88 $\log_{10}$ CFU/g sputum on Day 28.

[0137] In the MITT population, there was a decrease of *P. aeruginosa* density in patients administered levofloxacin 240 mg BID from a median value of 7.90 $\log_{10}$, CFU/g sputum on Day 1 to a median value of 6.48 $\log_{10}$ CFU/g sputum on Day 28, representing a reduction in *P. aeruginosa* density in sputum of approximately 96%. In patients administered levofloxacin 240 mg QD, there was a decrease in *P. aeruginosa* density from a median value of 7.97 $\log_{10}$ CFU/g sputum on Day 1 to a median value of 7.38 $\log_{10}$ CFU/g sputum on Day 28, representing a reduction in *P. aeruginosa* density in sputum of approximately 74%. In patients administered levofloxacin 120 mg QD, there was a decrease in *P. aeruginosa* density from a median value of 8.16 $\log_{10}$ CFU/g sputum on Day 1 to a median value of 7.78 $\log_{10}$ CFU/g sputum on Day 28, representing a reduction in *P. aeruginosa* density in sputum of approximately 58%. The largest differences for *P. aeruginosa* density in sputum between patients administered placebo and patients administered levofloxacin were 1.44 $\log_{10}$ CFU/g sputum on Day 7, 1.39 $\log_{10}$ CFU/g sputum on Day 14, and 1.78 $\log_{10}$ CFU/g sputum on Day 28.

[0138] For the EE and MITT populations, baseline MIC50 values for *P. aeruginosa* isolates from patients administered placebo, 120 mg QD, 240 mg QD, and 240 mg BID were 8 μg/ml, 8, 4 μg/ml, and 6 μg/ml, respectively. On Day 28, MIC_{50} values for *P. aeruginosa* isolates from patients administered placebo, 120 mg QD, 240 mg QD, and 240 mg BID were 8 μg/ml, 8 μg/ml, 8 μg/ml, and 8 μg/ml, respectively. Baseline MIC_{90} values for *P. aeruginosa* isolates from patients administered placebo, 120 mg QD, 240 mg QD, and 240 mg BID were 16 μg/ml, 32 μg/ml, 32 μg/ml, and 32 μg/ml, respectively. On Day 28, MIC_{90} values for *P. aeruginosa* isolates from patients administered placebo, 120 mg QD, 240 mg QD, and 240 mg BID were 16 μg/ml, 32 μg/ml, 16 μg/ml, and 32 μg/ml, respectively.

[0139] The similarity of corresponding MIC_{50} and MIC_{90} values between Day 1 and Day 28 for the EE and MITT populations indicates that *P. aeruginosa* cultures from patients did not develop any significant resistance to levofloxacin.

Clinical evaluations-CFQ-R questionnaire

[0140] Patients completed the CFQ-R questionnaire with domains that included: respiratory, body image, digestion, eating, emotion, health perception, physical, role/school, social, treatment burden, vitality, and weight. Tables 22 and 23 summarize results for the respiratory domain of the CFQ-R for EE and MITT populations, respectively. Table 24 summarizes changes in score for various domains of the CFQ-R from baseline to visit 4 in the MITT population.

TABLE 22

		EE population - Respiratory domain of CFQ-R				
		Placebo (N= 32)	**Levofloxacin 120mg. QD (N= 35)**	**Levofloxacin 240mg QD (N= 35)**	**Levofloxacin 240mg BID (N= 34)**	**Combined Levofloxacin 240mg QD and BID (N= 69)**
Day 1	Mean (SD)	66.7 (14.39)	63.5 (15.84)	60.8 (15.83)	60.3 (16.42)	60.5 (16.00)
	Median	66.7	66.7	61.1	61.1	61.1
Day 14	Mean (SD)	66.7 (15.84)	67.8 (13.79)	63.2 (19.34)	68.8 (19.15)	66.0 (19.31)
	Median	63.9	66.7	66.7	72.2	66.7

(continued)

		EE population - Respiratory domain of CFQ-R				
		Placebo (N= 32)	**Levofloxacin 120mg.QD (N= 35)**	**Levofloxacin 240mg QD (N= 35)**	**Levofloxacin 240mg BID (N= 34)**	**Combined Levofloxacin 240mg QD and BID (N= 69)**
Change from Baseline to Day 14	Mean (SD)	-0.0 (11.20)	4.3 (9.82)	2.1 (16.41)	8.5 (15.55)	5.3 (16.19)
	Median	0.0	5.5	0.0	5.6	5.6
	P-value		0.3953	0.9534	0.0374	0.2171
Day 28	Mean (SD)	64.9 (18.53)	65.1 (17.28)	61.7 (19.37)	66.0 (19.68)	63.8 (19.49)
	Median	63.9	66.7	66.7	72.2	66.7
Change from Baseline to Day 28	Mean (SD)	-1.7 (14.90)	1.6 (12.32)	1.0 (14.91)	5.2 (17.56)	3.0 (16.27)
	Median	0.0	0.0	0.0	5.5	0.0
	P-value		0.6183	0.8145	0.0924	0.2690

TABLE 23

		MITT population - Respiratory domain of CFQ-R				
		Placebo (N= 37)	**Levofloxacin 120mg.QD (N= 38)**	**Levofloxacin 240mg QD (N= 37)**	**Levofloxacin 240mg BID (N= 39)**	**Combined Levofloxacin 240mg QD and BID (N= 76)**
Day 1	Mean (SD)	64.9 (14.17)	62.3 (15.88)	61.3 (15.52)	60.5 (16.31)	60.9 (15.83)
	Median	66.7	61.1	61.1	61.1	61.1
Day 14	Mean (SD)	64.6 (15.84)	67.1 (13.70)	63.0 (19.74)	68.4 (19.51)	65.8 (19.68)
	Median	61.1	66.7	66.7	72.2	69.4
Change from Baseline to Day 14	Mean (SD)	-0.3 (10.79)	4.5 (9.78)	1.4 (17.54)	7.5 (15.30)	4.5 (16.59)
	Median	0.0	5.5	0.0	5.6	5.5
	P-value		0.2559	0.8964	0.0334	0.1937
Day 28	Mean (SD)	63.1 (18.01)	64.6 (16.94)	61.6 (19.74)	64.4 (20.39)	63.0 (19.98)
	Median	61.1	66.7	66.7	72.2	66.7
	Min, Max	22, 94	17, 100	17, 89	22, 94	17, 94
Change from	Mean (SD)	-1.8 (14.11)	2.0 (12.23)	0.3 (16.14)	3.0 (19.18)	1.7 (17.66)

(continued)

		MITT population - Respiratory domain of CFQ-R				
		Placebo (N= 37)	Levofloxacin 120mg. QD (N= 38)	Levofloxacin 240mg QD (N= 37)	Levofloxacin 240mg BID (N= 39)	Combined Levofloxacin 240mg QD and BID (N= 76)
Baseline to Day 28	Median	0.0	0.0	0.0	0.0	0.0
	P-value		0.5029	0.8365	0.2174	0.4069

TABLE 24

CFQ-R Scale	LS Mean Change from Baseline		LS Mean Difference (95% CI)	P-Value
	Placebo (N= 37)	Levofloxacin 240mg. BID (N= 39)		
Respiratory	-0.44	4.06	4.50 (-2.68, 11.67)	0.2174
Body Image	0.59	0.34	-0.25 (-6.00, 5.50)	0.9315
Digestion	-1.35	1.11	2.46 (-3.27, 8.18)	0.3975
Eating	-3.29	2.41	5.70 (0.78, 10.62)	0.0235
Emotion	2.32	2.22	-0.09 (-4.34, 4.15)	0.9651
Health Perception	-2.1	0.52	2.58 (-3.70, 8.86)	0.4117
Physical	-2.80	3.14	5.94 (0.75, 11.13)	0.0252
Role/School	-1.41	-1.94	-0.53 (-5.43, 4.38)	0.8324
Social	-1.68	0.69	2.37 (-2.66, 7.40)	0.3530
Treatment Burden	-0.99	-0.93	0.06 (-5.84, 5.95)	0.9851
Vitality	-1.88	1.23	3.11 (-2.91, 9.13)	0.3085
Weight	4.72	10.06	5.4 (-4.38, 15.06)	0.2792

[0141] For the EE population, mean changes from baseline to Day 28 for respiratory factors measured by the CFQ-R for patient administered placebo, 120 mg QD, 240 mg QD, and 240 mg BID treatment groups were 1.6, 1.0, 5.2, and 3.0 units, respectively. For the MITT population, mean changes from baseline to Day 28 for respiratory factors for patient administered placebo, 120 mg QD, 240 mg QD, and 240 mg BID treatment groups were 2.0, 0.3, 3.0, and 1.7 units, respectively. The 240mg BID group in the EE population demonstrated a statistically significant improvement in respiratory score on Day 14.

[0142] The CFQ-R eating score also showed improvement with the difference in the 240mg BID group in the MITT population showing statistically significant improvement at Day 28.

Time to patient need for anti-pseudomonal antimicrobials

[0143] Time to administration of intravenous/oral/inhaled anti-pseudomonal antimicrobials from Day 1 until Final visit was measured for patients with at least one of the following: decreased exercise tolerance, increased cough, increased sputum/chest congestion, and decreased appetite. The proportion of patients requiring anti-pseudomonal antimicrobials (inhaled or systemic) over time was analyzed using a Cox proportional hazards model. Table 25 summarizes results for time to need for anti-pseudomonal antimicrobials for EE and MITT populations.

TABLE 25

		EE and MITT populations - Parameters for time to need anti-pseudomonal antimicrobials				
		Placebo (N= 32)	**Levofloxacin 120mg. QD (N= 35)**	**Levofloxacin 240mg QD (N= 35)**	**Levofloxacin 240mg BID (N= 34)**	**Combined Levofloxacin 240mg QD and BID (N= 69)**
EE population	Patients Requiring Anti-Pseudomonal Antimicrobials	40.6%	20.0%	25.7%	20.6%	23.2%
	Hazard Ratio [95%CI]		0.39 [0.15, 1.01]	0.48 [0.20, 1.17]	0.26 [0.10, 0.69]	0.37 [0.17, 0.81]
	P-value		0.0522	0.1050	0.0067	0.0123
MITT population	Number (%) of Patients Requiring Anti-Pseudomonal Antimicrobials	48.6%	18.4%	27.0%	20.5%	23.7%
	Hazard Ratio [95% CI]		0.29 [0.12, 0.71]	0.39 [0.17, 0.87]	0.21 [0.09, 0.52]	0.30 [0.15, 0.60]
	P-value		0.0069	0.0215	0.0007	0.0007

[0144] The measured need for additional anti-pseudomonal microbials was reduced in all levofloxacin treatment groups. In addition, significant hazard ratios were observed in all levofloxacin treatment groups. Hazard ratios are related to the relative risk that an event may occur. The hazard ratios were 0.29 for the levofloxacin 120 mg QD group, 0.39 for the levofloxacin 240 mg QD group, and 0.21 for the levofloxacin 240 mg BID group in the MITT Population compared to the placebo group, and were statistically significant compared to placebo. Figures 5 and 6 are plots of survival distribution function over time for each treatment group and show that the survival distribution function for patients treated with placebo begins to fall at a shorter time than patients treated with levofloxacin. In sum, at least 240 mg BID showed significant efficacy over placebo at Day 28 in time to need for anti-pseudomonal antimicrobials.

Pulmonary function evaluations

[0145] Changes in FEV_1 (forced expiratory volume in 1 second), FVC (forced vital capacity) and FEF 25-75 (forced expiratory flow 25-75%) from Day 1 to all subsequent visits were determined for patients. Tables 26 and 27 summarize the results for FEV_1 measurements in EE and MITT populations, respectively. Figures 7 and 8 show graphs of percent change in FEV_1 (L) and percent change in FEV_1 (L) vs. placebo, respectively, at Day 28 for the EET population treated with placebo, 120 mg QD, 240 mg QD, or 240 mg BID. Figure 9 shows a graph of the categorical change in percent predicted FEV_1 at Day 28 for the EET population treated with 120 mg QD, 240 mg QD, or 240 mg BID. Tables 28 and 29 summarize the results for predicted FEVI measurements in EE and MITT populations, respectively. Tables 30 and 31 summarize results for FEF 25-75 measurements in EE and MITT populations, respectively.

TABLE 26

		EE population-Changes in FEV_1 values				
		Placebo (N= 32)	**Levofloxacin 120mg. QD (N= 35)**	**Levofloxacin 240mg QD (N= 35)**	**Levofloxacin 240mg BID (N= 34)**	**Combined Levofloxacin 240mg QD and BID (N= 69)**
Day 1	Mean (SD)	1.98 (0.61)	1.99 (0.83)	2.09 (0.75)	1.86 (0.68)	1.98 (0.72)
	Median	2.01	1.87	2.02	1.70	1.81
Day 14	Mean (SD)	1..97 (0.63)	2.00 (0.83)	2.16 (0.78)	2.02 (0.76)	2.09 (0.77)
	Median	1.93	1.82	2.09	1.88	2.03
Percent Change from Baseline to Day 14	Mean (SD)	-0.89 (6.86)	1.13 (7.48)	3.84 (10.23)	8.87 (12.42)	6.32 (11.56)
	Median	-0.17	0.56	1.92	7.51	3.94
	P-value vs. Placebo		0.4940	0.0737	0.001	0.0013
Day 28	Mean (SD)	1.95 (0.65)	2.03 (0.89)	2.13 (0.76)	1.90 (0.68)	2.02 (0.73)
	Median	1.91	1.91	2.15	1.79	1.98
Percent Change from Baseline to Day 28	Mean (SD)	-2.55 (10.37)	1.71 (9.37)	2.51 (13.25)	5.05 (11.49)	3.75 (12.40)
	Median	-3.91	1.60	1.28	4.55	2.80
	P-value vs. Placebo		0.1726	0.1121	0.0102	0.0168

TABLE 27

		MITT population-Changes in FEV_1 values				
		Placebo (N= 37)	**Levofloxacin 120mg. QD (N= 38)**	**Levofloxacin 240mg QD (N= 37)**	**Levofloxacin 240mg BID (N= 39)**	**Combined Levofloxacin 240mg QD and BID (N= 76)**
Day 1	Mean (SD)	1.94 (0.61)	1.95 (0.81)	2.05 (0.75)	1.88 (0.68)	1.96 (0.71)
	Median	1.97	1.83	1.90	1.70	1.80
Day 14	Mean (SD)	1.92 (0.63)	1.97 (0.81)	2.12 (0.78)	2.04 (0.77)	2.08 (0.77)
	Median	1.92	1.79	2.04	1.90	1.97
Percent Change from Baseline to Day 14	Mean (SD)	-1.21 (6.46)	1.87 (9.41)	3.81 (10.32)	9.34 (13.72)	6.61 (12.40)
	Median	-0.90	0.56	1.92	7.51	3.94
	P-value		0.2873	0.0497	<.0001	0.0005

(continued)

		MITT population-Changes in FEV_1 values				
		Placebo (N= 37)	**Levofloxacin 120mg. QD (N= 38)**	**Levofloxacin 240mg QD (N= 37)**	**Levofloxacin 240mg BID (N= 39)**	**Combined Levofloxacin 240mg QD and BID (N= 76)**
Day 28	Mean (SD)	1.89 (0.64)	1.99 (0.88)	2.09(0.76)	1.93 (0.69)	2.01 (0.73)
	Median	1.85	1.83	2.10	1.82	1.95
Percent Change from Baseline to Day 28	Mean (SD)	-2.96 (9.81)	1.92 (9.95)	2.35 (13.03)	5.93 (15.07)	4.14 (14.11)
	Median	-3.92	1.60	1.28	3.55	2.50
	P-value		0.1292	0.0831	0.0026	0.0063

TABLE 28

		EE population-Changes in % predictedFEV_1				
		Placebo (N= 32)	**Levofloxacin 120mg. QD (N= 35)**	**Levofloxacin 240mg QD (N= 35)**	**Levofloxacin 240mg BID (N= 34)**	**Combined Levofloxacin 240mg QD and BID (N= 69)**
Day 1	Mean (SD)	54.4 (12.93)	54.0 (17.79)	55.9 (14.60)	48.2 (14.88)	52.1 (15.13)
	Median	54.5	53.0	56.0	45.5	51.0
Day 14	Mean (SD)	53.9 (13.21)	54.7 (17.61)	57.7 (15.19)	51.7 (16.93)	54.7 (16.23)
	Median	54.5	53.0	62.0	49.5	52.0
Relative Percent	Mean (SD)	-0.77 (6.85)	1.77 (6.08)	3.57 (10.75)	7.67 (14.70)	5.59 (12.92)
Change from Baseline to Day 14	Median	0.00	1.15	1.52	7.42	69) 4.00
Day 28	Mean (SD)	53.1 (14.05)	55.0 (19.30)	57.3 (15.52)	50.5 (15.36)	54.0 (15.71)
	Median	55.0	52.0	58.0	49.0	54.0
Relative Percent Change from Baseline to Day 28	Mean (SD)	-2.47 (10.34)	1.82 (9.81)	2.99 (14.54)	7.39 (17.48)	5.13 (16.06)
	Median	-3.74	2.30	0.00	4.88	4.00
	P-value		0.2655	0.1411	0.0034	0.0113

TABLE 29

		MITT population-Changes in % predictedFEV_1				
		Placebo (N= 37)	**Levofloxacin 120mg. QD (N= 38)**	**Levofloxacin 240mg QD (N= 37)**	**Levofloxacin 240mg BID (N= 39)**	**Combined Levofloxacin 240mg QD and BID (N= 76)**
Day 1	Mean (SD)	52.4 (13.42	52.9 (17.68)	55.4 (14.41)	48.8 (15.15)	52.0 (15.07)
	Median	53.0	53.0	56.0	46.0	51.0
Day 14	Mean (SD)	51.7 (13.84)	53.9 (17.42)	57.1 (14.96)	52.1 (17.16)	54.6 (16.20)
	Median	53.0	53.0	61.0	49.55555	52.0
	Mean (SD)	-0.68 (3.37)	0.81 (3.24)	1.70(5.39)	3.66 (7.49)	2.69 (6.57)
	Median	-1.00	1.00	1.00	2.50	2.00
Relative Percent Change from Baseline to Day 14	Mean (SD)	-1.30 (6.58)	2.46 (8.47)	3.51 (10.83)	8.30 (15.80)	5.93 (13.70)
	Median	-1.89	1.15	1.52	7.42	4.00
	P-value		0.2284	0.0780	0.0005	0.0025
Day 28	Mean (SD)	50.9 (14.46)	54.1 (19.19)	56.7 (15.33)	50.8 (15.40)	53.8 (15.54)
	Median	52.0	50.0	54.0	49.0	53.5
Relative Percent Change from Baseline to Day 28	Mean (SD)	-3.08 (9.82)	2.00 (10.07)	2.77 (14.30)	7.97 (19.49)	5.37(17.18)
	Median	-3.77	2.30	0.00	4.44	3.85
	P-value		0.1759	0.0888	0.0008	0.0036

TABLE 30

		EE population-Changes in FEF 25-75 values				
		Placebo (N= 32)	**Levofloxacin 120mg. QD (N= 35)**	**Levofloxacin 240mg QD (N= 35)**	**Levofloxacin 240mg BID (N= 34)**	**Combined Levofloxacin 240mg QD and BID (N= 69)**
Day 1	Mean (SD)	1.02 (0.57)	1.17 (0.78)	1.22 (0.84)	0.85 (0.53)	1.04(0.72
	Median	0.94	0.98	1.10	0.68	0.83
Day 14	Mean (SD)	1.03 (0.64)	1.18 (0.83)	1.33 (0.93)	1.00 (0.78)	1.17 (0.87)
	Median	0.86	0.99	1.11	0.78	0.92
Percent Change	Mean (SD)	1.95 (19.45)	0.41 (12.28)	9.58 (21.16)	16.99 (32.60)	13.23 (27.45)

(continued)

		EE population-Changes in FEF 25-75 values				
		Placebo (N= 32	Levofloxacin 120mg. QD (N= 35)	Levofloxacin 240mg QD (N= 35)	Levofloxacin 240mg BID (N= 34)	Combined Levofloxacin 240mg QD and BID (N= 69)
from Baseline to Day 14	Median	-1.72	0.45	4.41	11.66	8.79
	P-value		0.6634	0.2532	0.0072	0.0275
Day 28	Mean (SD)	1.00 (0.64)	1.23 (0.93)	1.27(0.88)	0.93 (0.59)	1.10 (0.77)
	Median	0.94	1.03	1.15	0.78	0.97
Percent Change from Baseline to Day 28	Mean (SD)	-2.73 (16.74)	0.73 (15.76)	4.70 (16.11)	13.11 (28.50)	8.78 (23.19)
	Median	-4.61	2.70	5.77	5.71	5.74
	P-value,		0.6038	0.2223	0.0007	0.0076

TABLE 31

		MITT population-Changes in FEF 25-75 values				
		Placebo (N= 37)	Levofloxacin solution 120mg. QD (N= 38)	Levofloxacin solution240mg QD (N= 37)	Levofloxacin solution240mg BID (N= 39)	Combined Levofloxacin solution 240mg QD and BID (N= 76)
Day 1	Mean (SD)	0.98 (0.55)	1.12 (0.77)	1.18 (0.83)	0.87 (0.53)	1.02 (0.71)
	Median	0.92	0.89	1.09	0.68	0.83
Day 14	Mean (SD)	0.97 (0.63)	1.15 (0.82)	1.29 (0.92)	1.01 (0.78)	1.15 (0.86)
	Median	0.81	0.85	1.08	0.78	0.90
Percent Change from Baseline to Day 14	Mean (SD)	-1.78 (22.86)	1.73 (13.76)	9.53 (20.70)	16.70 (31.72)	13.16 (26.92)
	Median	-4.46	1.35	4.41	11.66	8.79
	value		0.5910	0.0699	0.0007	0.0027
Day 28	Mean (SD)	0.94 (0.62)	1.20(0.92)	1.23 (0.87)	0.95 (0.61)	1.09 (0.76)
	Median	0.91	0.83	1.12	0.82	0.93
Percent Change from Baseline to Day 28	Mean (SD)	-6.40 (20.27)	1.94 (16.55)	5.02 (15.98)	14.19 (28.56)	9.61 (23.44)
	Median	-8.66	3.38	5.77	7.46	5.88
	P-value		0.1241	0.0489	<.0001	0.0003

[0146] In the EE population, FEV_1 values for patients administered levofloxacin 240 mg BID increased from a median value of 1.70 L at Day 1 (baseline) to 1.79 L at Day 28, representing an increase in FEV_1 of approximately 5%. In patients administered levofloxacin 240 mg QD, FEV_1 values increased from a median value of 2.02 L on Day 1 to a median value

of 2.15 L on Day 28, representing an increase in FEV_1 of approximately 6%. In patients administered levofloxacin 120 mg QD, FEV_1 values increased from a median value of 1.87 L on Day 1 to a median value of 1.91 L on Day 28, representing an increase in FEV_1 of approximately 2%. The largest differences for FEV_1 between patients administered placebo and patients administered levofloxacin were 0.16 L on Day 14, and 0.24 L on Day 28.

[0147] In the MITT population, FEV_1 values for patients administered levofloxacin 240 mg BID increased from a median value of 1.70 L at Day 1 (baseline) to 1.82 L at Day 28, representing an increase in FEV_1 of approximately 7%. In patients administered levofloxacin 240 mg QD, FEV_1 values increased from a median value of 1.90 L on Day 1 to a median value of 2.10 L on Day 28, representing an increase in FEVI of approximately 10%. The largest differences for FEV_1 between patients administered placebo and patients administered levofloxacin were 0.12 L on Day 14, and 0.25 L on Day 28.

[0148] FEF 25-75 values relate to the average flow of air coming out of the lungs during the middle portion of the expiration. In small airway diseases this value can be reduced. In the EE population, FEF 25-75 values for patients administered levofloxacin 240 mg BID increased from a median value of 0.68 at Day 1 (baseline) to 0.78 at Day 28, representing an increase in FEF 25-75 of approximately 15%. In patients administered levofloxacin 240 mg QD, FEF 25-75 values increased from a median value of 1.10 on Day 1 to a median value of 1.15 on Day 28, representing an increase in FEF 25-75 of approximately 4%. In patients administered levofloxacin 120 mg QD, FEF 25-75 values increased from a median value of 0.98 on Day 1 to a median value of 1.03 on Day 28, representing an increase in FEF 25-75 of approximately 5%. The largest differences for FEF 25-75 between patients administered placebo and patients administered levofloxacin were 0.25 L on Day 14, and 0.21 L on Day 28.

[0149] In the MITT population, FEF 25-75 values for patients administered levofloxacin 240 mg BID increased from a median value of 0.68 at Day 1 (baseline) to 0.82 at Day 28, representing an increase in FEF 25-75 of approximately 20%. In patients administered levofloxacin 240 mg QD, FEF 25-75 values increased from a median value of 1.09 on Day 1 to a median value of 1.12 on Day 28, representing an increase in FEF 25-75 of approximately 3%. The largest differences for FEF 25-75 between patients administered placebo and patients administered levofloxacin were 0.27 L on Day 14, and 0.21 L on Day 28.

Safety evaluations

[0150] Adverse events and drug intolerability from Day 1 through the end of study were evaluated. No significant adverse events were reported.

[0151] Flouroquinolone-induced arthralgia and myalgia have been previously reported in the use of some fluoroquinolones, for example in the treatment of sinusitis (0-Lee T., et al "Fluoroquinolone-induced arthralgia and myalgia in the treatment of sinusitis" Am. J. Rhinol. (2005) 19:395-9, incorporated by reference in its entirety). In this study, Arthralgia was reported in 5.4% of patients administered with placebo. No arthralgia was reported in patients administered any levofloxacin formulations.

Example 3-Phase I Clinical Study in Pediatric CF Patients

[0152] A Phase 1 multicenter, open-label study was carried out to evaluate the safety, tolerability and pharmacokinetics of weight-adjusted doses of levofloxacin formulated with $MgCl_2$ administered once daily for 14 days to stable pediatric CF patients. Patients were divided into 2 groups based on their age: 6-11 years of age and 12-16 years of age. The daily dose administered of levofloxacin formulated with $MgCl_2$ was divided as follows: patients that weighed 14-21 kg received a 120 mg dose, patients that weighed 22-30 kg received a 180 mg dose, and patients that weighed more than 30 kg received a 240 mg dose. A total of 27 patients were enrolled and all patients completed the study. There were 14 patients in the 6-11 years of age group and 13 patients in the 12-16 years of age group. Seven patients (all in the 6-11 age group) received 180 mg QD levofloxacin formulated with $MgCl_2$ and the remaining 20 patients received 240 mg QD levofloxacin formulated with $MgCl_2$. Figure 10 shows a graph of dose normalized serum AUC in pediatric CF patients vs. patient body weight. Figures 11A-9B show graphs of dose normalized serum AUC in pediatric CF patients vs. patient age, and vs. BSA, respectively. Figures 11C-9E show graphs of dose normalized serum Cmax in pediatric CF patients vs. patient body weight, vs. patient age, and vs. BSA, respectively.

[0153] Serum levofloxacin exposures with either the 180 or 240 mg dose of levofloxacin formulated with $MgCl_2$ appear to be in the ranges observed in adults CF patients studied in a related clinical trial (data not shown).

Example 4-Phase III Clinical Study

[0154] A Phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of levofloxacin formulated with $MgCl_2$ in stable CF patients is performed. Following a 14-day screening period, patients are randomized at Visit 1/Day 1 in a 2:1 ratio to receive levofloxacin formulated with $MgCl_2$ or placebo. Randomization is stratified by geographic region (US vs. non-US), age (12-18 years vs. >18 years of age) and by FEV_1

percent predicted (< 55% vs. > 55%). Patients receive 28 days of either levofloxacin formulated with $MgCl_2$ or placebo followed by 28 days of observation. Patients should remain off anti-pseudomonal antimicrobials, other than Study Drug (levofloxacin formulated with $MgCl_2$ or placebo) and maintenance oral azithromycin (if applicable), for the duration of the study unless they meet the protocol defined definition of an exacerbation or unless determined to be necessary for safety reasons by the Investigators. The end of the study is defined as the last visit of the last patient.

[0155] Levofloxacin formulated with $MgCl_2$ (levofloxacin inhalation solution, Aeroquin™) will be provided in single use ampules ready for administration. Each ampule contains 240 mg of levofloxacin formulated with $MgCl_2$ in 2.4 mL (100 mg/mL). A 240 mg dose (1 ampule) is administered using a PART investigational eFlow® nebulizer twice daily (BID) approximately 8-12 hours apart. Placebo is riboflavin 5'-phosphate (solubilized form of vitamin B2) in 0.9% saline provided in single use ampules ready for administration. Each ampule contains 9.6 lag of riboflavin 5'-phosphate in a volume of 2.4 mL. A PART investigational eFlow® nebulizer is optimized and customized for use only with levofloxacin formulated with $MgCl_2$. Both levofloxacin formulated with $MgCl_2$ and the placebo control are administered using this nebulizer system. Analysis populations include: (1) safety/modified intent to treat (MITT) population (all patients enrolled in the study who receive at least one dose of Study Drug (levofloxacin formulated with $MgCl_2$ or placebo); (2) efficacy evaluable Population (all patients enrolled in the study, without major protocol violations, who receive at least 80% of Study Drug (levofloxacin formulated with $MgCl_2$/placebo) doses); and (3) pharmacokinetic population (all patients who receive a least one dose of Study Drug (levofloxacin formulated with $MgCl_2$/placebo) and have at least one pharmacokinetic (PK) blood or sputum sample collected).

[0156] Inclusion criteria for study patients included: at least 12 years of age; weigh at least 30 kg or 66 pounds; and have documented CF diagnosis as evidenced by one or more clinical features consistent with the CF phenotype. Exclusion criteria for study patients included: use of an investigational agent within 28 days prior to Visit 1; use of any nebulized or systemic antimicrobials active against *P. aeruginosa* within 28 days prior to Visit 1, other than maintenance oral azithromycin, which must have been initiated at least 28 days prior to Visit 1; and use of oral corticosteroids in doses exceeding the equivalent of 10 mg prednisone/day or 20 mg prednisone every other day at Screening or Visit 1.

Primary Efficacy Evaluations

[0157] The primary endpoint includes the time (in days) to an exacerbation from Baseline (Visit 1/Day 1) until Final Visit. To meet the endpoint a patient must concurrently meet 4 of the 12 symptoms/signs that make up the Fuchs definition of an exacerbation (Fuchs HJ, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. N Engl J Med 1994;331:637-642, incorporated by reference in its entirety).

[0158] The 12 symptoms/signs defined by the Fuchs criteria include: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 % or more from a previously recorded value; and radiographic changes indicative of pulmonary infection

[0159] The above symptoms associated with an exacerbation are recorded from each patient using a standardized questionnaire, the Respiratory and Systemic Symptoms Questionnaire (RSSQ) at patient visits. Changes the patient experiences are relative to what the patient considers normal on a day-to-day basis. It is anticipated that patients administered aerosolized levofloxacin formulated with $MgCl_2$ provide the following signs/symptoms that are included in the Fuchs criteria and that are recorded using the RSSQ:

(1) Increased sputum production: patients have no change, a little less or much less amounts of sputum when coughing up.
(2) Change in sputum appearance: for sputum thickness, patients have a little thinner or much thinner sputum; for sputum color, patients have a better color of sputum (better increases from brown -> green -> yellow -> clear).
(3) Increased chest congestion: patients have a little decrease, or a large decrease in chest congestion.
(4) New or increased coughing up of blood: patients have a little decrease or a large decrease in the amount of blood coughed up.
(5) Increased cough: for intensity of cough, patients have a little lighter, or much lighter coughs; for frequency of cough, patients cough a little less often or much less often.
(6) Decreased exercise tolerance: patients perform daily activities, e.g., climbing stairs, a little easier, or much easier.
(7) Increased dyspnea with exertion: patients breathe a little easier or much easier when performing daily activities
(8) Malaise, fatigue or lethargy: patients have a little more energy or much more energy since last visit.
(9) Fever: patients have no fever since last visit
(10) Weight loss: patients have no change in weight, or a little weight gain.
(11) Sinus pain and tenderness: patient has no pain or tenderness.
(12) Change in sinus discharge: patient has better sinus discharge (a decrease in thickness and/or better color).

(13) School or work absenteeism (due to illness): patient has no absenteeism from schedules activities.
(14) Decreased appetite: patient has a little increase in appetite.

Secondary Efficacy Evaluations

[0160] Secondary Endpoints include clinical, pulmonary function, microbiology, and patient reported outcome characteristics.

Clinical characteristics

[0161] Clinical characteristics include the time (in days) to administration of systemic (oral or IV) and/or inhaled anti-pseudomonal antimicrobials from Baseline (Visit 1/Day 1) until Final Visit. To meet this endpoint, patients must have at least one of four worsening respiratory symptoms (increased cough, increased sputum/chest congestion, decreased exercise tolerance, decreased appetite) at the time of administration of the anti-pseudomonal antimicrobial agent. Clinical characteristics also include the proportion of patients who miss at least 1 day of school/work secondary to worsening respiratory status.

[0162] It is anticipated that patients administered aerosolized levofloxacin formulated with $MgCl_2$ have an increased time to administration of systemic (oral or IV) and/or inhaled anti-pseudomonal antimicrobials from Baseline (Visit 1/Day 1) until Final Visit compared to patients administered placebo. In addition, the proportion of patients administered aerosolized levofloxacin formulated with $MgCl_2$ who miss at least 1 day of school/work secondary to worsening respiratory status is less than the proportion of patients administered placebo who miss at least 1 day of school/work secondary to worsening respiratory status.

Pulmonary Function characteristics

[0163] Pulmonary function characteristics include: percent change in FEV_1 (L) from Baseline to Day 28; relative change in FEV_1 (percent predicted) from Baseline to Day 28; percent change in FEF25-75 (L/s) from Baseline to Day 28; percent change in FVC (L) from Baseline to Day 28; and categorical assessment of percent change in FEV_1 (L) and relative change in percent predicted FEV_1 from Baseline to Day 28.

[0164] It is anticipated that patients administered aerosolized levofloxacin formulated with $MgCl_2$ have more advantageous pulmonary function characteristics compared to patients administered placebo.

Microbiology characteristics

[0165] Microbiology characteristics include: change in *P. aeruginosa* density (log10 colony-forming units [CFU] per gram sputum) from Baseline to Day 28; categorical assessment of change in *P. aeruginosa* density (log10 colony-forming units [CFU] per gram sputum) from Baseline to Day 28; and change in *Stenotrophomonas sp., Achromobacter sp., Burkholderia sP. and S. aureus density* (1og 10 colony-forming units [CFU] per gram sputum) from Baseline to Day 28.

[0166] It is anticipated that patients administered aerosolized levofloxacin formulated with $MgCl_2$ have more advantageous microbiology characteristics, e.g., decreased *P. aeruginosa* sputum density, decreased *Stenotrophomonas sp., Achromobacter sp., Burkholderia sP. and S. aureus sputum density*, compared to patients administered placebo.

Patient reported outcome characteristics

[0167] Patient reported outcome characteristics include: change in the respiratory domain of the CFQ-R from Baseline to Day 28; and categorical assessment of change in the respiratory domain of the CFQ-R from Baseline to Day 28.

[0168] It is anticipated that patients administered aerosolized levofloxacin formulated with $MgCl_2$ have more advantageous patient reported outcome characteristics than patients administered placebo.

Example *5-In vivo* antibacterial activity of levofloxacin inhalation solution against *Burkholderia cepacia*

[0169] *Burkholderia cepacia* is an opportunistic pathogen capable of causing pulmonary infection in CF patients. Infections with certain strains of *B. cepacia* cause "cepacia syndrome" which is characterized by progressive and invasive necrotizing pneumonia and septicemia. Most *B. cepacia* have high MICs to many antibiotics. Aerosolized levofloxacin formulated with $MgCl_2$ enables aerosol delivery of high drug concentrations to the lung.

[0170] Five *B. cepacia* strains with levofloxacin MICs ranging between 0.25 - 8 mg/L were tested in a mouse model of pulmonary infection. Female BALB/c mice were injected with 150 mg/kg of cyclophosphamide 3 days prior to infection. On day 4, the mice were infected with 50 ul of bacterial suspension (~10^6 CFU/ml) using a curved bead-tipped oral

gavage syringe under isoflurane anesthesia. Treatment with levofloxacin formulated with $MgCl_2$ (60 mg/kg BID) or saline only was initiated 72 hours post-infection and continued twice daily for four days using a microspray aerosol device. Sixteen hours after the last treatment, mice were sacrificed, lungs harvested, homogenized, and plated to determine colony counts (CFU).

[0171] As part of a Phase 2b trial of aerosolized levofloxacin formulated with $MgCl_2$ in CF patients, a 16 year old male patient infected with *B. cepacia* (levofloxacin MIC = >128 mg/L) received levofloxacin formulated with $MgCl_2$ 240 mg QD for 28 days.

[0172] Aerosolized levofloxacin formulated with $MgCl_2$ produced at least one log CFU of bacterial killing for all strains in the mouse infection model (Table 32). In the CF patient, a 1.7 log CFU decrease in bacterial counts was observed over 28 days.

TABLE 32

	Genomovar II			Genomovar III	
Strains	BC1012	BC1013	BC1014	BC1020	BC1021
MIC (mg/L)	4	0.25	1	8	8
Mean Change in Log CFU/Lungs	-1.03	-2.08	-1.47	-1.11	-1.35

[0173] An increase in the CF patient's FEV_1 was observed. On day 1 of the study, the patient's FEV_1 was 1.21L, this increased to 1.30L on day 28, a 7% improvement. From a population model, Cmax and AUC values were calculated to be approximately 12,900 mg/L and 4,400 mg*h/L, respectively.

[0174] Aerosol administration of levofloxacin formulated with $MgCl_2$ produced significant bacterial killing in strains with a wide range of MICs. The non-clinical and clinical data support the future clinical evaluation of levofloxacin formulated with $MgCl_2$ in the management of chronic pulmonary infections due to *B. cepacia*.

[0175] To the extent publications and patents or patent applications incorporated by reference herein contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

[0176] Unless otherwise defined, all terms (including technical and scientific terms) are to be given their ordinary and customary meaning to a person of ordinary skill in the art, and are not to be limited to a special or customized meaning unless expressly so defined herein.

[0177] The presence in some instances of broadening words and phrases such as 'one or more', 'at least', 'but not limited to', or other like phrases shall not be read to mean that the narrower case is intended or required in instances where such broadening phrases may be absent.

[0178] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term 'about.' Accordingly, unless indicated to the contrary, the numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of any claims in any application claiming priority to the present application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0179] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it is apparent to those skilled in the art that certain changes and modifications may be practiced.

Claims

1. A solution comprising levofloxacin at a concentration between about 75 mg/ml to about 150 mg/ml, a magnesium chloride concentration between about 150 mM to about 250 mM; a pH between about 5 to about 7; an osmolality of between about 300 mOsmol/kg to about 500 mOsmol/kg, and lacking lactose for use in a method for treating cystic fibrosis in a human, wherein said human has a pulmonary infection comprising *P. aeruginosa* and wherein the solution comprises about 240 mg levofloxacin and is administered as an aerosol to said human twice daily.

2. The solution for the use of claim 1 wherein the solution comprises a levofloxacin concentration between about 90 mg/ml to about 110 mg/ml; a magnesium chloride concentration between about 175 mM to about 225 mM; a pH between about 5 to about 7; an osmolality of between about 300 mOsmol/kg to about 500 mOsmol/kg, and lacks lactose.

3. The solution for the use of claim 1 wherein the solution comprises a levofloxacin concentration of 100 mg/ml; a magnesium concentration of 200 mM; a chloride concentration of 400 mM; a pH of from 5 to 7; and an osmolality of from 350 to 500 mOsmol/kg.

4. The solution for the use of claim 1 wherein the solution consists of levofloxacin at a concentration of about 100 mg/ml; magnesium chloride at a concentration of about 200 mM; a pH of about 6.2; an osmolality of about 383 mOsmol/kg, and lacks lactose.

5. The solution for the use of any of claims 1 to 4, wherein the aerosol is administered to the human twice daily for at least 14 days /month.

6. The solution for the use of any of claims 1 to 4, wherein the aerosol is administered to the human twice daily for at least 28 days /month.

7. The solution for the use of any of claims 1 to 4, wherein the aerosol is administered to the human twice daily for 14 days.

8. The solution for the use of any of claims 1 to 4, wherein the aerosol is administered to the human twice daily for 28 days.

9. The solution for the use of any of claims 1 to 8, wherein the aerosol is administered to the human twice daily with an interval between doses of 8 to 12 hours.

10. The solution for the use of any of claims 1 to 9, wherein the aerosol is produced using a vibrating mesh nebulizer.

11. The solution for the use of any of claims 1 to 10, wherein the aerosol is administered to the human in less than about 10 minutes, for example less than about 5 minutes.

12. The solution for the use of any of claims 1 to 11, wherein the human is treated concomitantly with a medication selected from dornase alfa, azithromycin, salbutamol, pancrelipase, hypertonic sodium chloride, seretide, and ADEK.

13. The solution for the use of any of claims 1 to 4, wherein the aerosol is administered to the human at least twice daily for 14 days.

14. The solution for the use of any of claims 1 to 4, wherein the aerosol is administered to the human at least twice daily for 28 days.

Patentansprüche

1. Lösung, umfassend Levofloxacin in einer Konzentration zwischen ungefähr 75 mg/ml und ungefähr 150 mg/ml, eine Magnesiumchloridkonzentration zwischen ungefähr 150 mM und ungefähr 250 mM; einen pH zwischen ungefähr 5 und ungefähr 7; eine Osmolalität zwischen ungefähr 300 mOsmol/kg und ungefähr 500 mOsmol/kg, und wobei ihr Lactose abgeht, zur Verwendung in einem Verfahren zur Behandlung von zystischer Fibrose bei einem Menschen, wobei der Mensch eine Lungeninfektion aufweist, die *P. aeruginosa* umfasst und wobei die Lösung ungefähr 240 mg Levofloxacin umfasst und dem Menschen zweimal täglich als ein Aerosol verabreicht wird.

2. Lösung zur Verwendung nach Anspruch 1, wobei die Lösung eine Levofloxacin-Konzentration zwischen ungefähr 90 mg/ml und ungefähr 110 mg/ml; eine Magnesiumchloridkonzentration zwischen ungefähr 175 mM und ungefähr 225 mM; einen pH zwischen ungefähr 5 und ungefähr 7; eine Osmolalität zwischen ungefähr 300 mOsmol/kg und ungefähr 500 mOsmol/kg umfasst und ihr Lactose abgeht.

3. Lösung zur Verwendung nach Anspruch 1, wobei die Lösung eine Levofloxacin-Konzentration von 100 mg/ml; eine Magnesiumkonzentration von 200 mM; eine Chloridkonzentration von 400 mM; einen pH von 5 bis 7 und eine Osmolalität von 350 bis 500 mOsmol/kg umfasst.

4. Lösung zur Verwendung nach Anspruch 1, wobei die Lösung aus Levofloxacin in einer Konzentration von ungefähr 100 mg/ml; Magnesiumchlorid in einer Konzentration von ungefähr 200 mM; einem pH von ungefähr 6,2; einer Osmolalität von ungefähr 383 mOsmol/kg besteht und ihr Lactose abgeht.

5. Lösung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das Aerosol dem Menschen zweimal täglich über zumindest 14 Tage/Monat verabreicht wird.

6. Lösung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das Aerosol dem Menschen zweimal täglich über zumindest 28 Tage/Monat verabreicht wird.

7. Lösung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das Aerosol dem Menschen zweimal täglich über 14 Tage verabreicht wird.

8. Lösung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das Aerosol dem Menschen zweimal täglich über 28 Tage verabreicht wird.

9. Lösung zur Verwendung nach einem der Ansprüche 1 bis 8, wobei das Aerosol dem Menschen zweimal täglich mit einem Intervall zwischen Dosen von 8 bis 12 Stunden verabreicht wird.

10. Lösung zur Verwendung nach einem der Ansprüche 1 bis 9, wobei das Aerosol unter Verwendung eines Rüttelgitterzerstäubers erzeugt wird.

11. Lösung zur Verwendung nach einem der Ansprüche 1 bis 10, wobei das Aerosol dem Menschen in weniger als ungefähr 10 Minuten, zum Beispiel weniger als ungefähr 5 Minuten verabreicht wird.

12. Lösung zur Verwendung nach einem der Ansprüche 1 bis 11, wobei der Mensch gleichzeitig mit einem Medikament behandelt wird, das aus Dornase alfa, Azithromycin, Salbutamol, Pancrelipase, hypertonischem Natriumchlorid, Seretid und ADEK ausgewählt ist.

13. Lösung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das Aerosol dem Menschen zumindest zweimal täglich über 14 Tage verabreicht wird.

14. Lösung zur Verwendung nach einem der Ansprüche 1 bis 4, wobei das Aerosol dem Menschen zumindest zweimal täglich über 28 Tage verabreicht wird.

Revendications

1. Solution comprenant de la lévofloxacine à une concentration entre environ 75 mg/ml à environ 150 mg/ml, une concentration de chlorure de magnésium entre environ 150 mM à environ 250 mM ; un pH entre environ 5 à environ 7 ; une osmolalité entre environ 300 mOsmol/kg à environ 500 mOsmol/kg, et étant exempte de lactose destinée à être utilisée dans un procédé destiné au traitement de la mucoviscidose chez un humain, dans laquelle ledit humain a une infection pulmonaire comprenant *P. aeruginosa* et dans laquelle la solution comprend environ 240 mg de lévofloxacine et est administrée sous forme d'un aérosol audit humain deux fois par jour.

2. Solution destinée à être utilisée selon la revendication 1 dans laquelle la solution comprend une concentration de lévofloxacine entre environ 90 mg/ml à environ 110 mg/ml ; une concentration de chlorure de magnésium entre environ 175 mM à environ 225 mM ; un pH entre environ 5 à environ 7 ; une osmolalité entre environ 300 mOsmol/kg à environ 500 mOsmol/kg, et est exempte de lactose.

3. Solution destinée à être utilisée selon la revendication 1 dans laquelle la solution comprend une concentration de lévofloxacine 100 mg/ml ; une concentration de magnésium de 200 mM ; une concentration de chlorure de 400 mM ; un pH allant de 5 à 7 ; et une osmolalité allant de 350 à 500 mOsmol/kg.

4. Solution destinée à être utilisée selon la revendication 1 dans laquelle la solution est constituée par de la lévofloxacine à une concentration d'environ 100 mg/ml ; du chlorure de magnésium à une concentration d'environ 200 mM ; un pH d'environ 6,2 ; une osmolalité d'environ 383 mOsmol/kg, et est exempte de lactose.

5. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 4, dans laquelle l'aérosol est administré à l'humain deux fois par jour pendant au moins 14 jours/mois.

6. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 4, dans laquelle l'aérosol est administré

à l'humain deux fois par jour pendant au moins 28 jours/mois.

7. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 4, dans laquelle l'aérosol est administré à l'humain deux fois par jour pendant 14 jours.

8. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 4, dans laquelle l'aérosol est administré à l'humain deux fois par jour pendant 28 jours.

9. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 8, dans laquelle l'aérosol est administré à l'humain deux fois par jour avec un intervalle entre les doses de 8 à 12 heures.

10. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 9, dans laquelle l'aérosol est produit en utilisant un nébuliseur à mailles vibrant.

11. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 10, dans laquelle l'aérosol est administré à l'humain en moins d'environ 10 minutes, par exemple moins d'environ 5 minutes.

12. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 11, dans laquelle l'humain est traité de manière concomitante avec un médicament sélectionné parmi la dornase alfa, l'azithromycine, le salbutamol, la pancrélipase, le chlorure de sodium hypertonique, le sérétide, et l'ADEK.

13. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 4, dans laquelle l'aérosol est administré à l'humain au moins deux fois par jour pendant 14 jours.

14. Solution destinée à être utilisée selon l'une quelconque des revendications 1 à 4, dans laquelle l'aérosol est administré à l'humain au moins deux fois par jour pendant 28 jours.

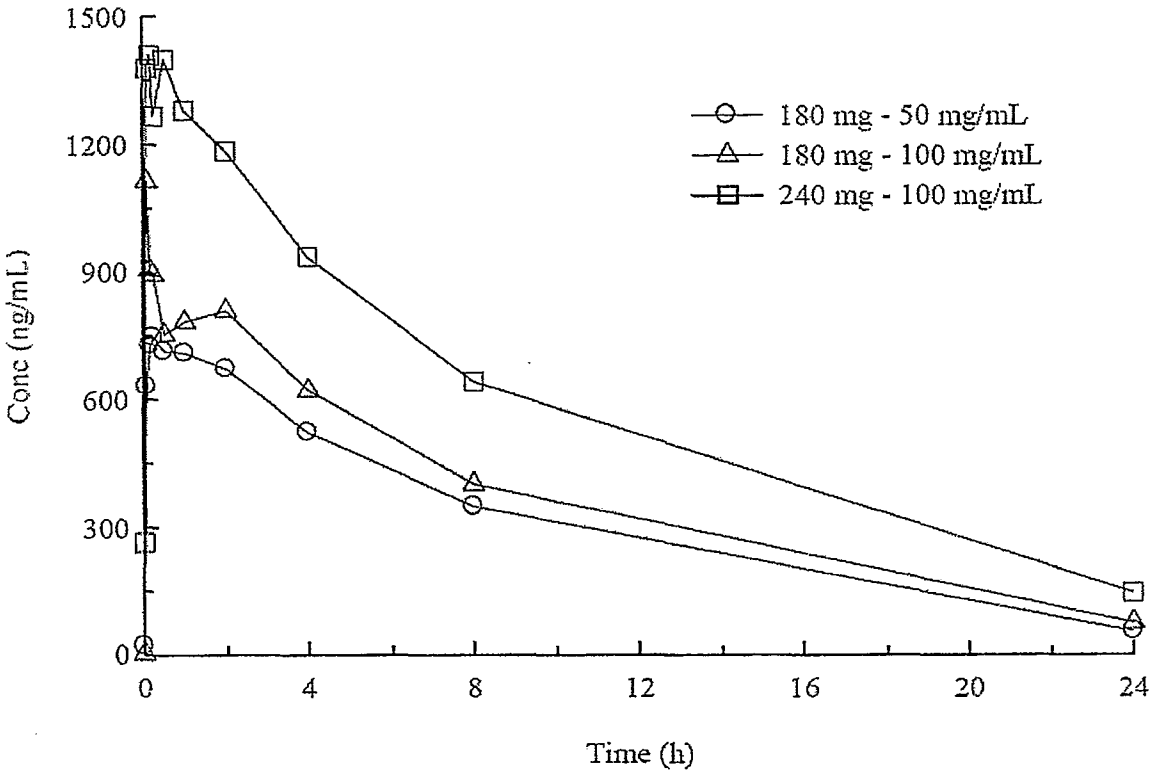
1500
1200
900
600
300
0
Conc (ng/mL)
0
4
8
12
16
20
24
Time (h)
180 mg - 50 mg/mL
180 mg - 100 mg/mL
240 mg - 100 mg/mL

FIGURE 1A

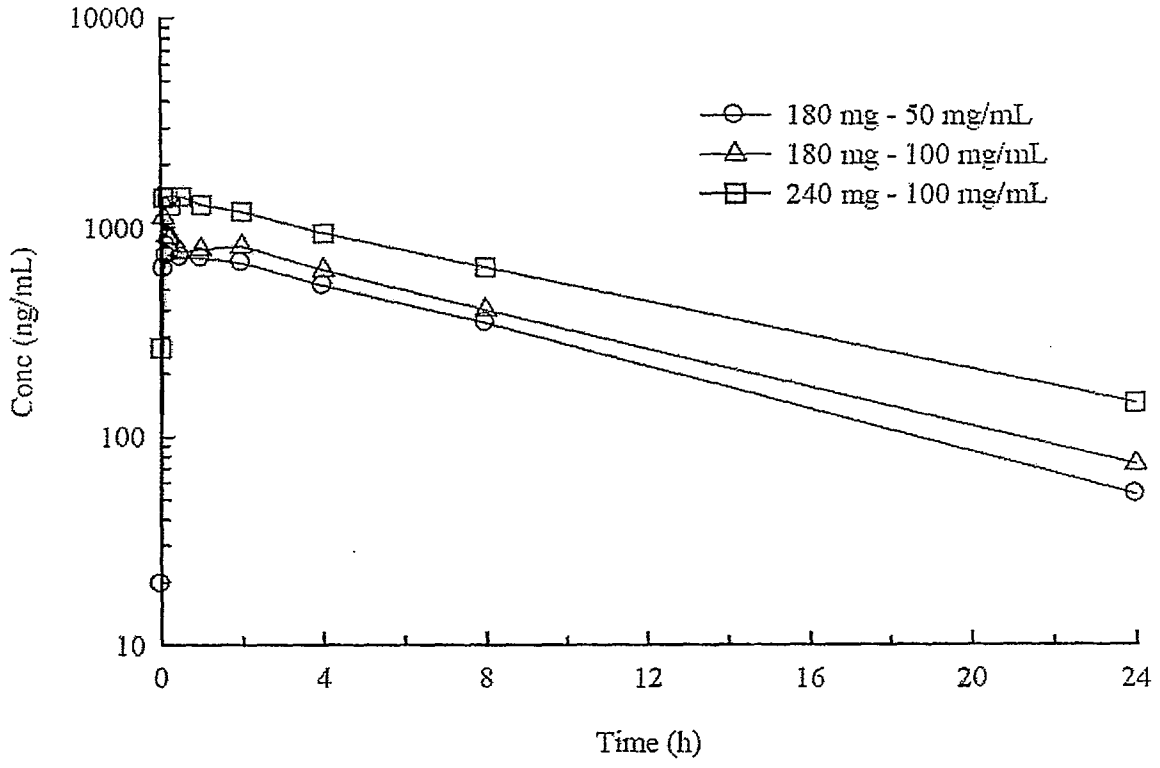
10000
1000
100
10
Conc (ng/mL)
0
4
8
12
16
20
24
Time (h)
180 mg - 50 mg/mL
180 mg - 100 mg/mL
240 mg - 100 mg/mL

FIGURE 1B

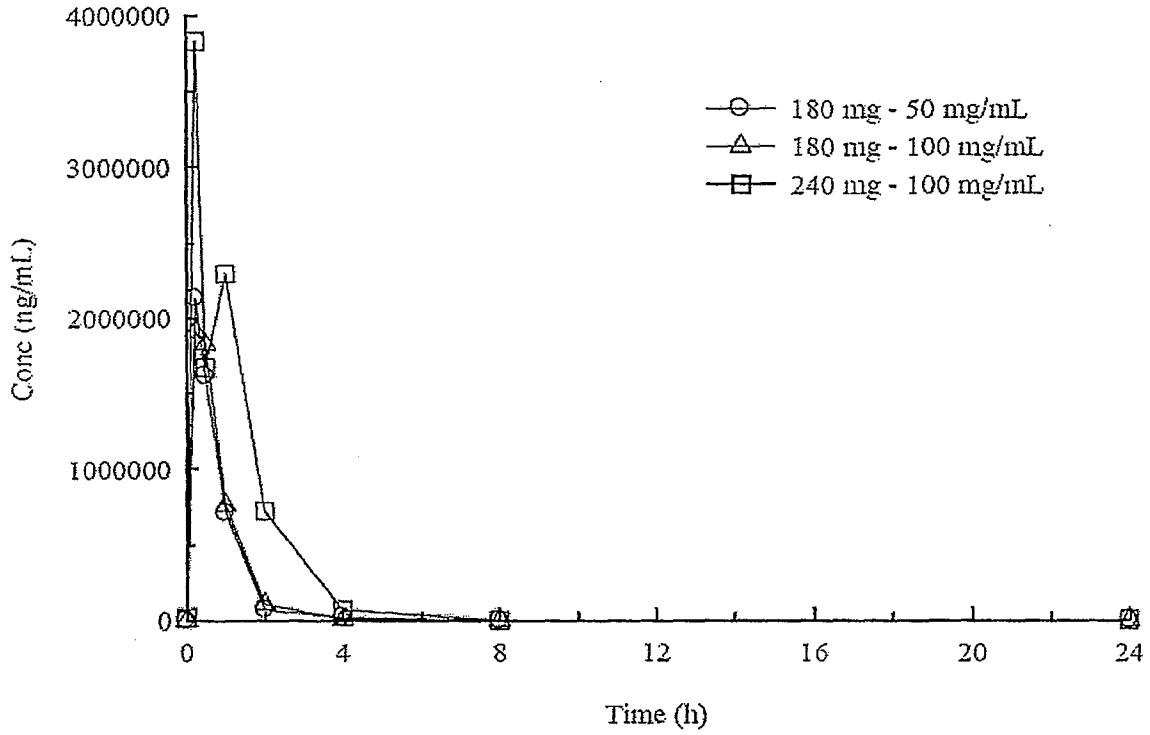
4000000
3000000
2000000
1000000
0
Conc (ng/mL)
0
4
8
12
16
20
24
Time (h)
180 mg - 50 mg/mL
180 mg - 100 mg/mL
240 mg - 100 mg/mL

FIGURE 2A

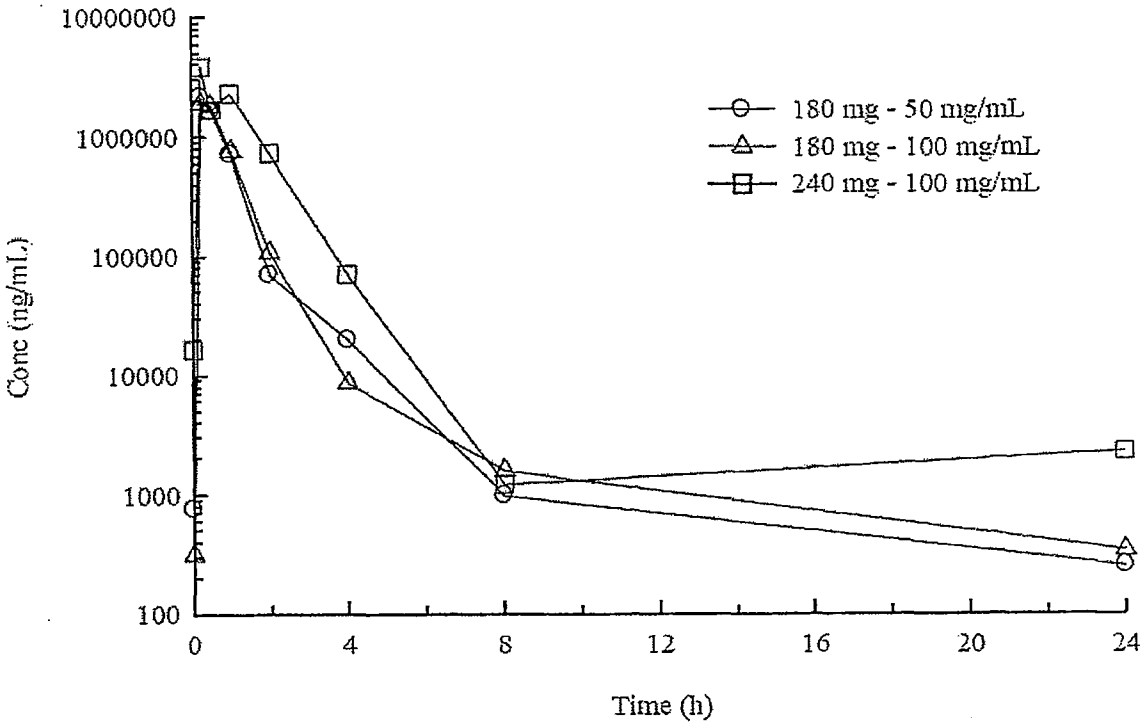
10000000
1000000
100000
10000
1000
100
Conc (ng/mL)
0
4
8
12
16
20
24
Time (h)
180 mg - 50 mg/mL
180 mg - 100 mg/mL
240 mg - 100 mg/mL

FIGURE 2B

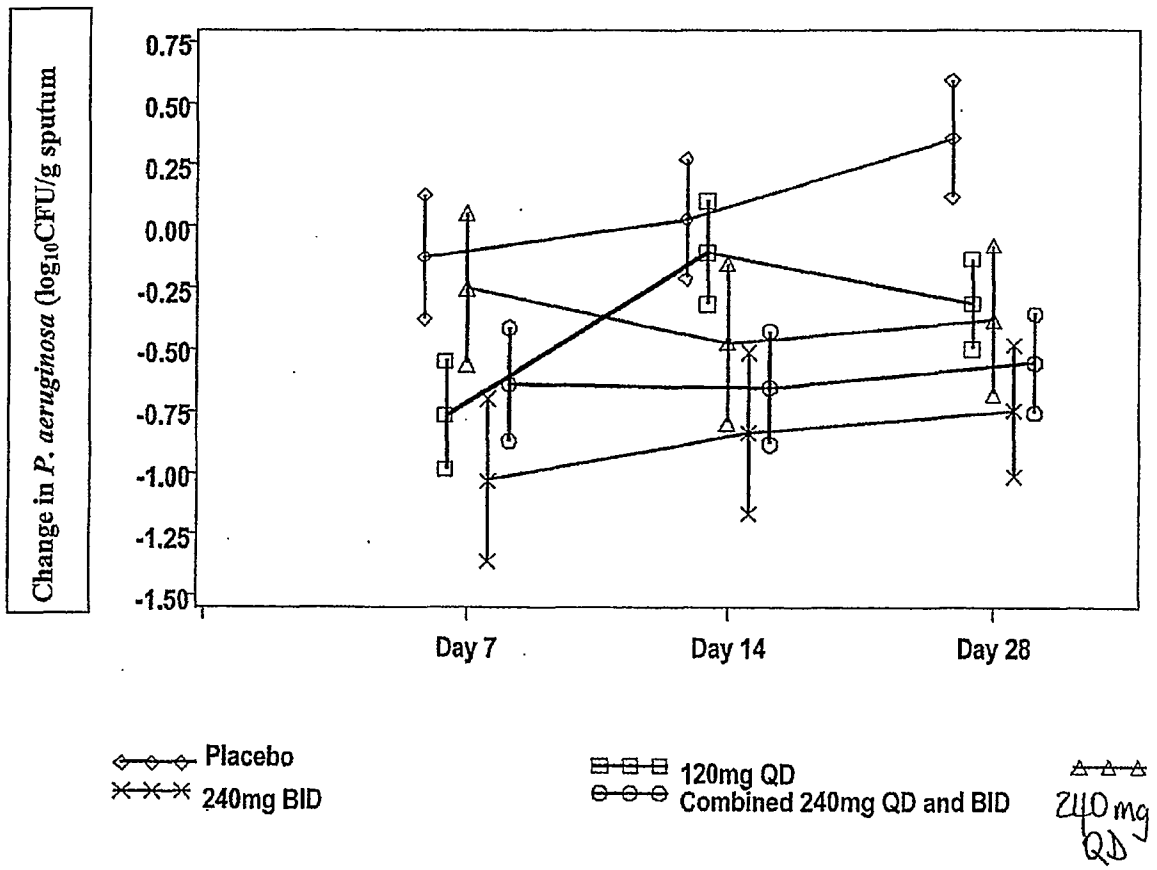
Change in P. aeruginosa (log10CFU/g sputum
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
-1.25
-1.50
Day 7
Day 14
Day 28
Placebo
240mg BID
120mg QD
Combined 240mg QD and BID
240 mg QD

FIGURE 3

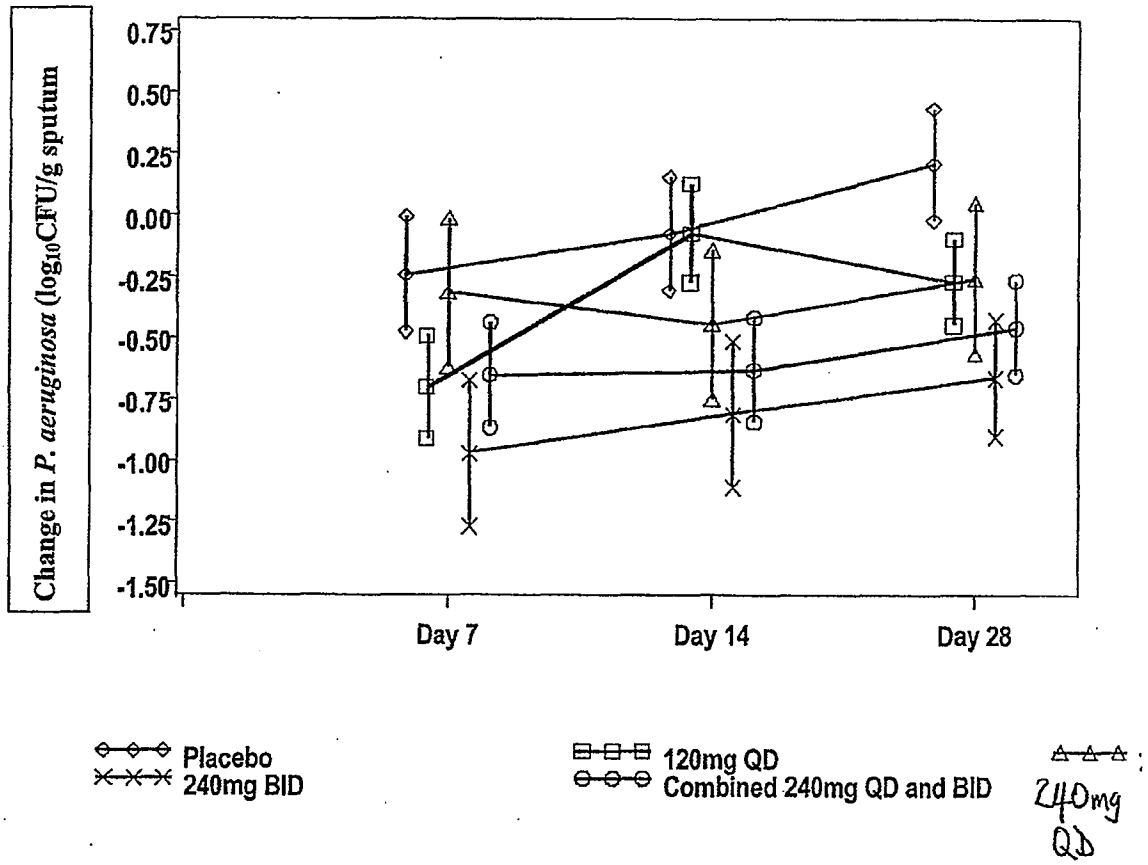
Change in P. aeruginosa (log10CFU/g sputum
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
-1.25
-1.50
Day 7
Day 14
Day 28
Placebo
240mg BID
120mg QD
Combined 240mg QD and BID
240mg QD

FIGURE 4

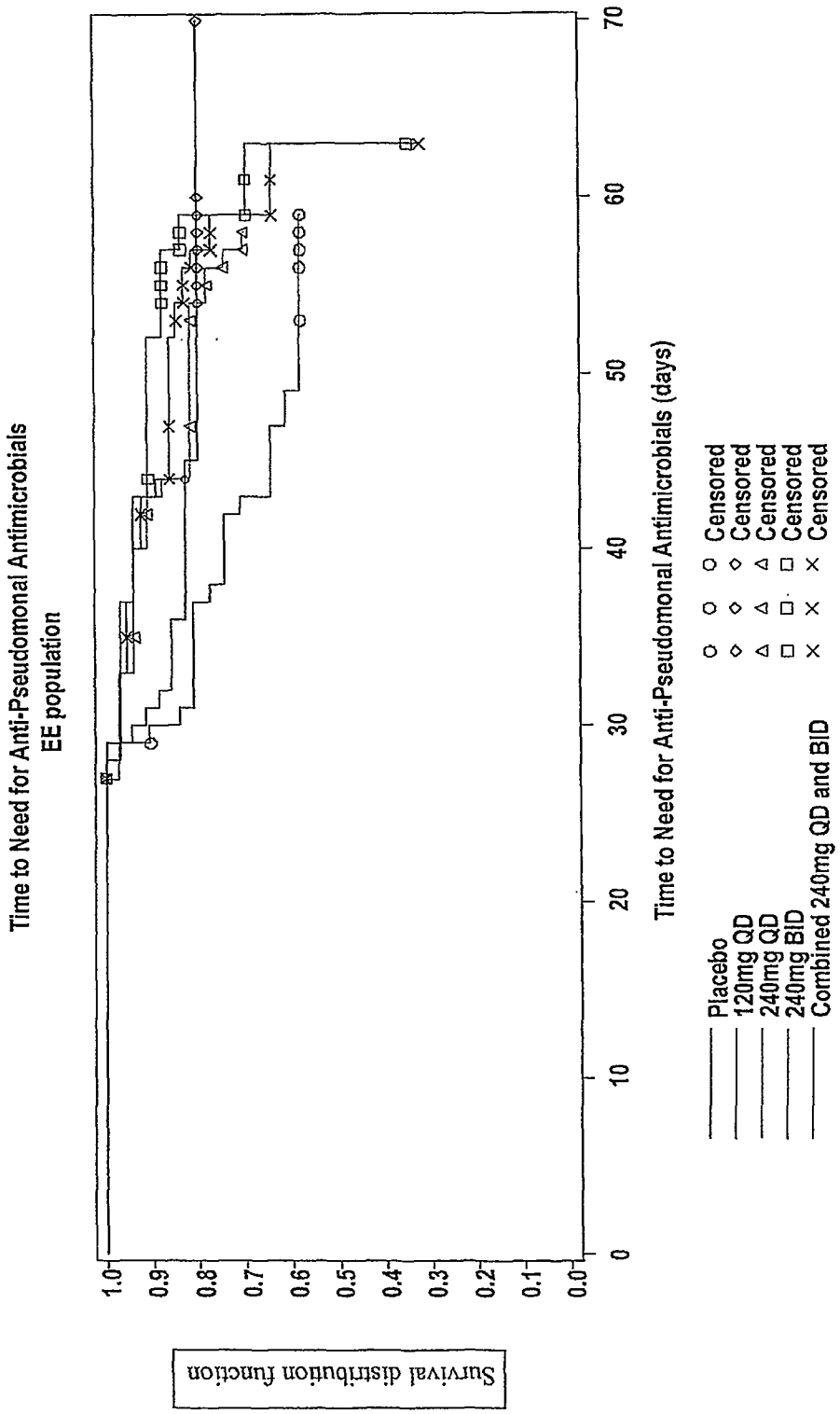
Time to Need for Anti-Pseudomonal Antimicrobials
EE population
Survival distribution function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
Time to Need for Anti-Pseudomonal Antimicrobials (days)
Placebo
120mg QD
240mg QD
240mg BID
Combined 240mg QD and BID
Censored
Censored
Censored
Censored
Censored

FIGURE 5

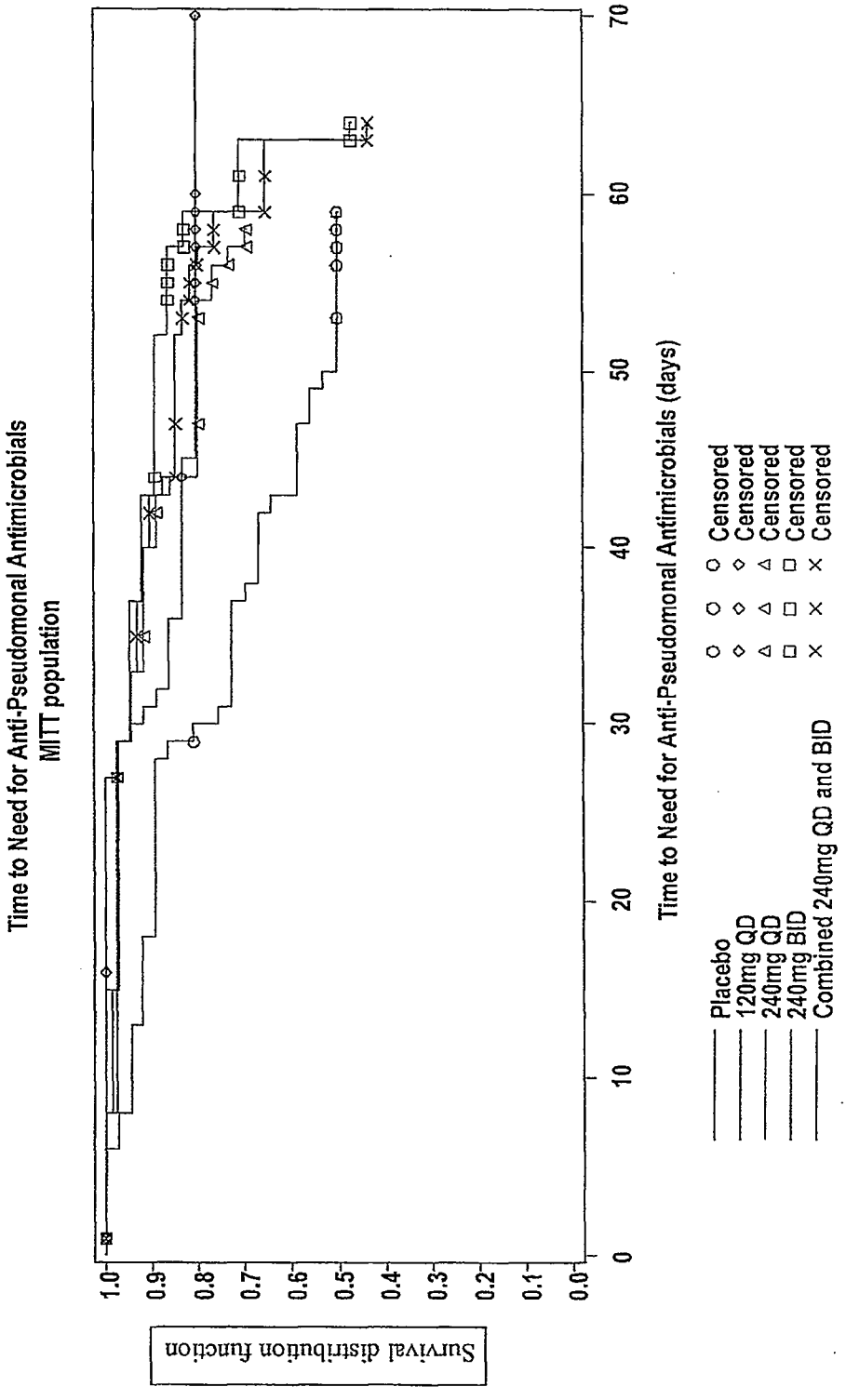
Time to Need for Anti-Pseudomonal Antimicrobials
MITT population
Survival distribution function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
Time to Need for Anti-Pseudomonal Antimicrobials (days)
Placebo
120mg QD
240mg QD
240mg BID
Combined 240mg QD and BID
Censored
Censored
Censored
Censored
Censored

FIGURE 6

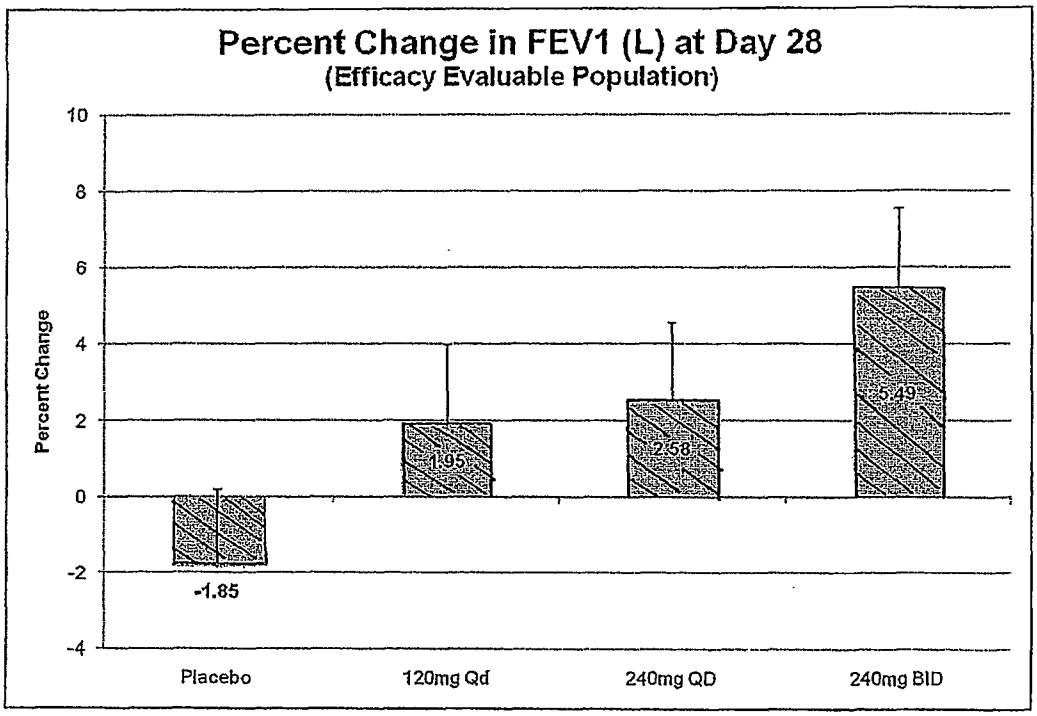
Percent Change in FEV1 (L) at Day 28
(Efficacy Evaluable Population)
Percent Change
10
8
6
4
2
0
-2
-4
-1.85
1.95
2.58
5.49
Placebo
120mg Qd
240mg QD
240mg BID

FIGURE 7

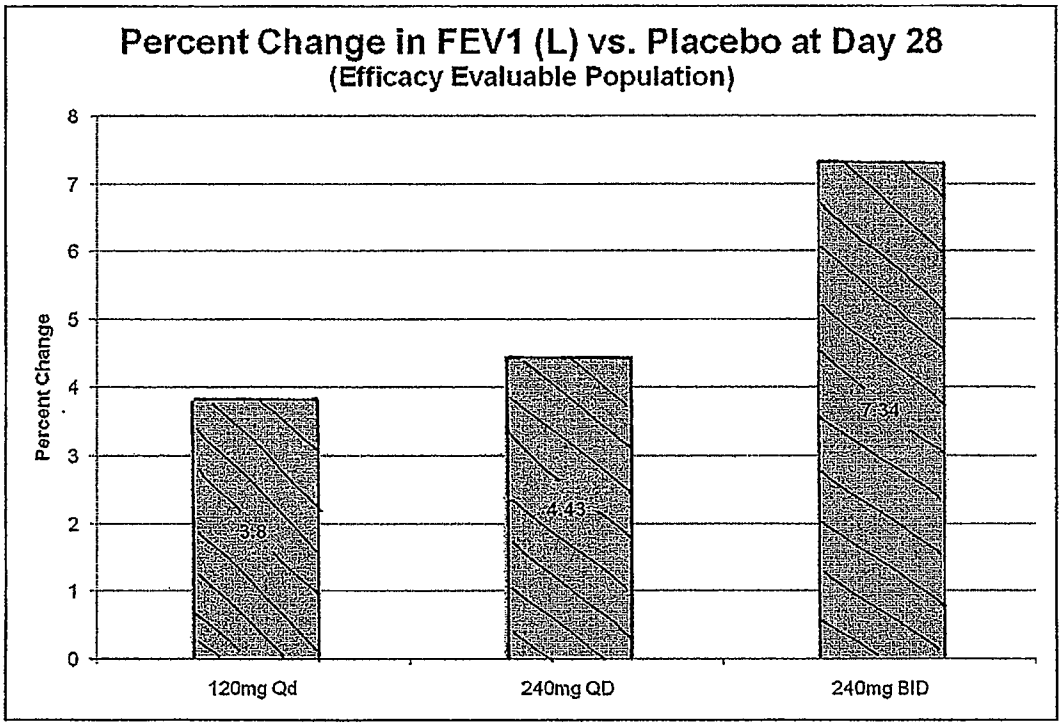
Percent Change in FEV1 (L) vs. Placebo at Day 28
(Efficacy Evaluable Population)
Percent Change
8
7
6
5
4
3
2
1
0
3.8
4.43
7.34
120mg Qd
240mg QD
240mg BID

FIGURE 8

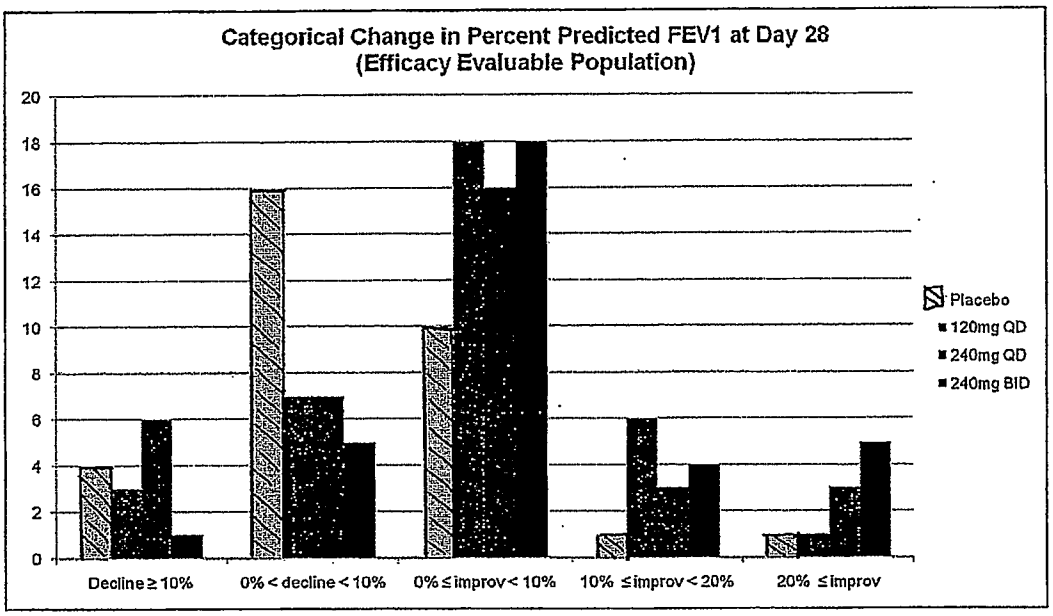
Categorical Change in Percent Predicted FEV1 at Day 28
(Efficacy Evaluable Population)
20
18
16
14
12
10
8
6
4
2
0
Decline ≥ 10%
0% < decline < 10%
0% ≤ improv < 10%
10% ≤ improv < 20%
20% ≤ improv
Placebo
120mg QD
240mg QD
240mg BID

FIGURE 9

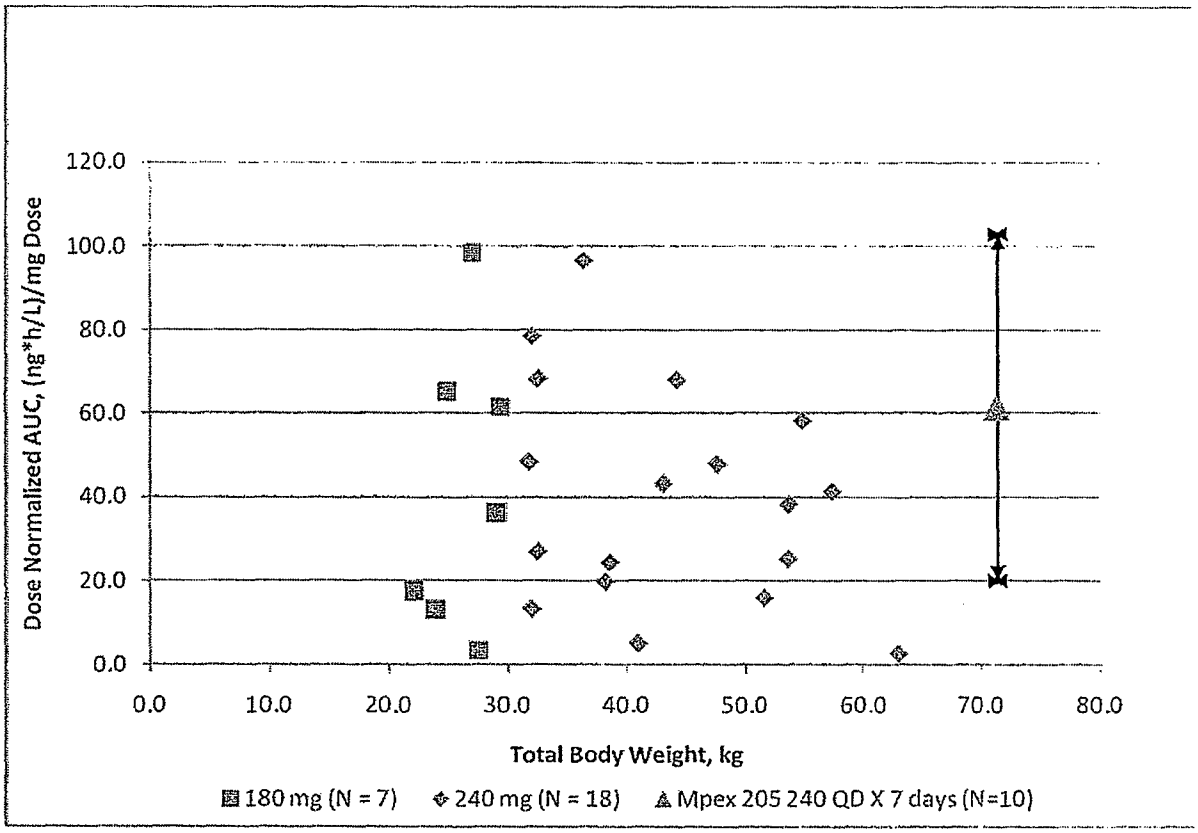
Dose Normalized AUC, (ng*h/L)/mg Dose
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
Total Body Weight, kg
180 mg (N = 7)
240 mg (N = 18)
Mpex 205 240 QD X 7 days (N=10)

FIGURE 10

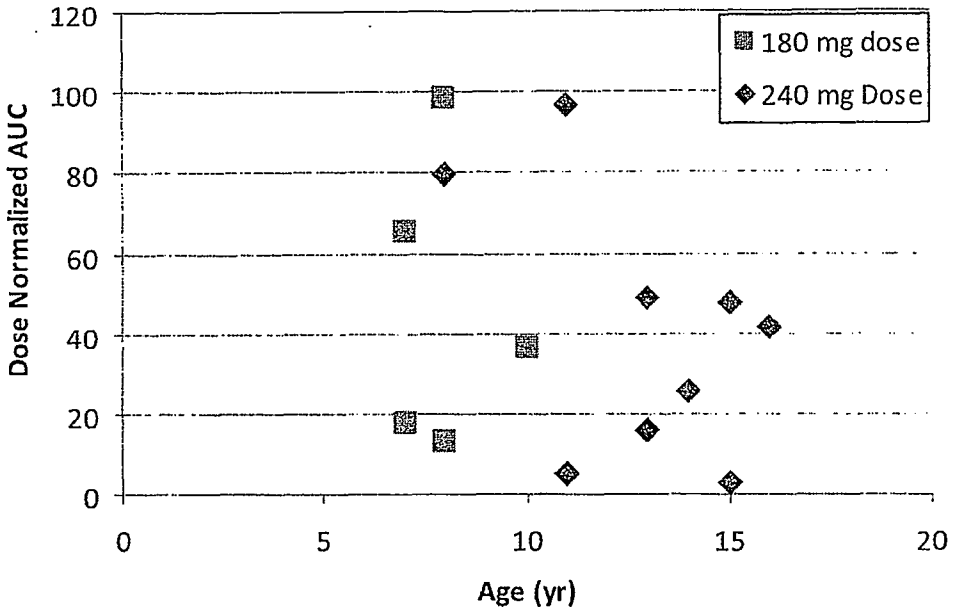

FIGURE 11A

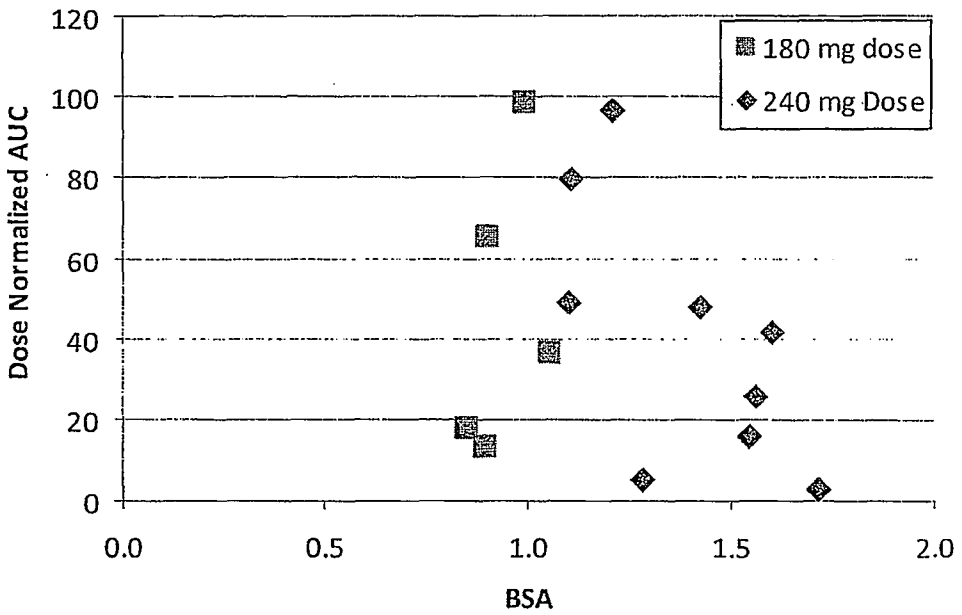

FIGURE 11B

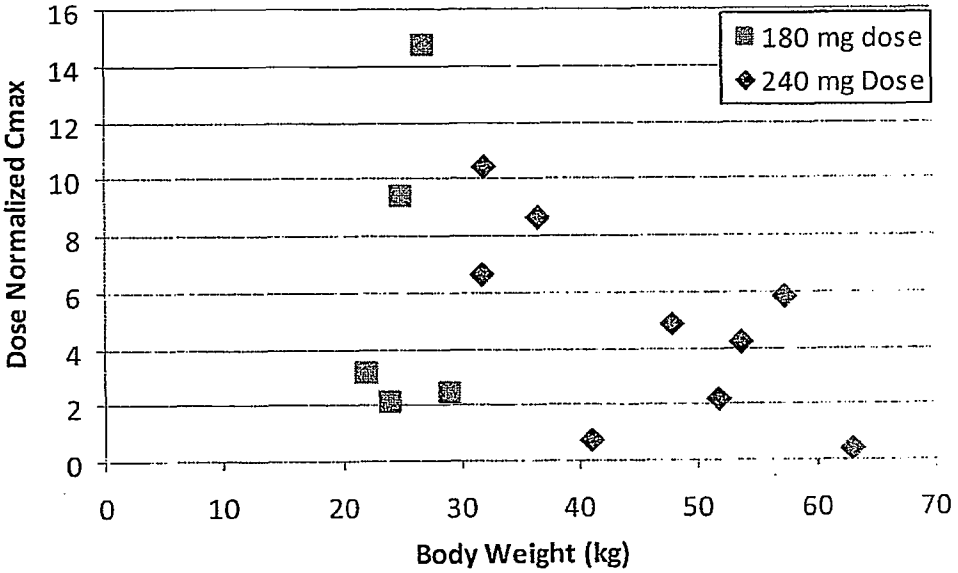

FIGURE 11C

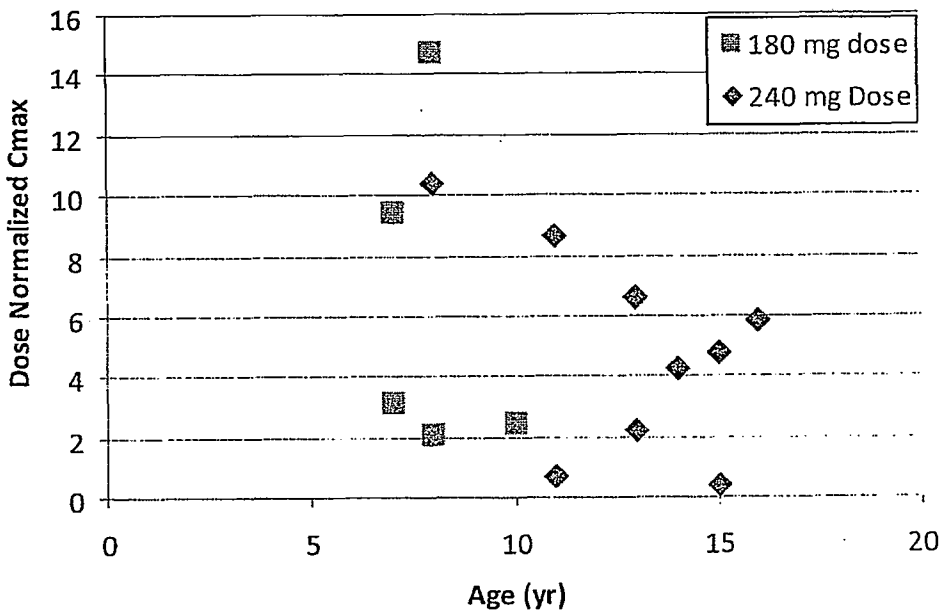

FIGURE 11D

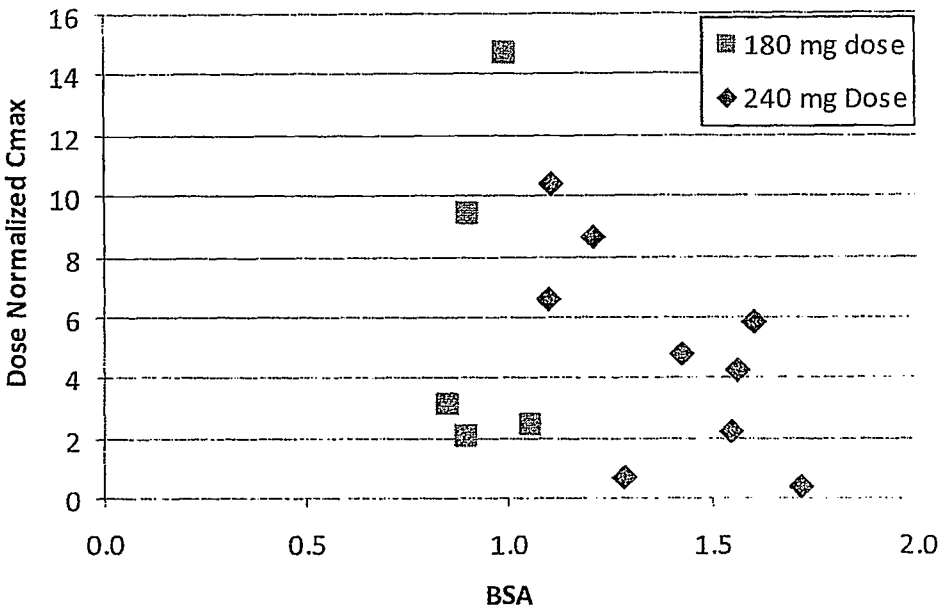
16
14
12
10
8
6
4
2
0
Dose Normalized Cmax
0.0
0.5
1.0
1.5
2.0
BSA
180 mg dose
240 mg Dose

FIGURE 11E

REFERENCES CITED IN THE DESCRIPTION

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