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(54) Title: RAPID RELIEF OF MOTOR FLUCTUATIONS IN PARKINSON'S DISEASE

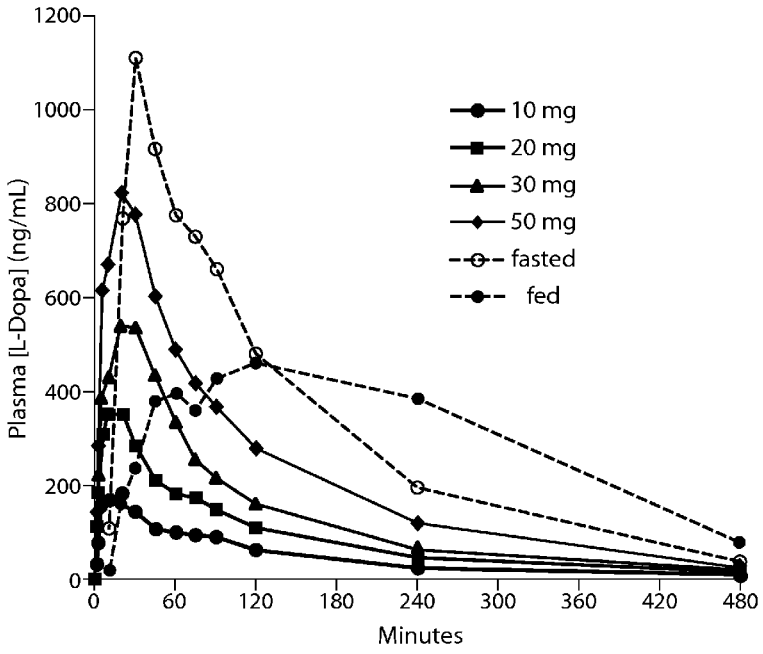

Fig. 1

(57) Abstract: The present invention provides methods for treating OFF episodes in a Parkinson's Disease patient comprising administering levodopa to the pulmonary system of a patient wherein after administration, the patient's Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 score is improved by, for example, at least about 5 points as compared to placebo control and/or as compared to the patient's UDPRS Part 3 score prior to administration. The invention also provides methods of reducing mean daily OFF time in a Parkinson's patient.

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RAPID RELIEF OF MOTOR FLUCTUATIONS IN PARKINSON'S DISEASE

BACKGROUND OF THE INVENTION

Parkinson's disease (also referred to herein as "PD") is characterized neuropathologically by degeneration of dopamine neurons in the basal ganglia and neurologically by debilitating tremors, slowness of movement and balance problems. It is estimated that over one million people suffer from Parkinson's disease. Nearly all patients receive the dopamine precursor levodopa or "L-Dopa", often in conjunction with the dopa-decarboxylase inhibitor, carbidopa. L-Dopa adequately controls symptoms of Parkinson's disease in the early stages of the disease. However, it tends to become less effective after a period which can vary from several months to several years in the course of the disease.

One example of L-Dopa's diminishing effectiveness is the development of motor fluctuations in a subject undergoing treatment. By "motor fluctuations" it is meant that a subject begins to show a variable response to dopamine replacement therapy such that for periods of time the therapeutic agents exhibit good efficacy and adequate control of Parkinson's disease symptoms (also referred to herein as "ON" time/episode" or "ON") whereas for other periods of time the agents appear to have little effect and there is a worsening of Parkinson's Disease symptoms also referred to herein as OFF time/episode" or "OFF". Motor fluctuations can manifest as a 'wearing-off' of efficacy, the efficacy of L-Dopa therapy does not last as long as initially observed, and an 'on-off' syndrome where the patient experiences disabling fluctuations in mobility ensues. Gradually, over a period of time, the efficacy of L-Dopa ("on-time") may be reduced to the extent that the usefulness of dopaminergic treatments becomes severely limited.

It is believed that the varying effects of L-Dopa in Parkinson's disease patients are related, at least in part, to the plasma half-life of L-Dopa which tends to be very short, in the range of 1 to 3 hours, even when co-administered with carbidopa. In the early stages of the disease, this factor is mitigated by the dopamine storage capacity of the targeted striatal neurons. L-Dopa is taken up and stored by the neurons and is released over time. However, as the disease progresses, dopaminergic neurons degenerate, resulting in decreased dopamine storage capacity.

Accordingly, the positive effects of L-Dopa become increasingly related to fluctuations of plasma levels of L-Dopa. In addition, patients tend to develop problems involving gastric emptying and poor intestinal uptake of L-Dopa. Erratic gastric emptying of levodopa contributes to random fluctuations in mobility. Patients exhibit increasingly marked swings in Parkinson's disease symptoms, ranging from a return to classic Parkinson' s disease symptoms, when plasma levels fall, to the so-called dyskinesis, when plasma levels temporarily rise too high following L-Dopa administration.

There remains a need to provide rapid relief of motor fluctuations and OFF episodes in a Parkinson's patient where that effect occurs in a clinically meaningful period of time and where the effect allows the patient sufficient duration of response.

SUMMARY OF THE INVENTION

The present invention provides methods for treating OFF episodes in a Parkinson's Disease patient comprising administering levodopa to the pulmonary system of a patient wherein after administration, the patient's Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 (also referred to herein as "UPDRS Part III" or "UDPRS III") score is improved by, for example, at least about 5 points as compared to placebo control and/or wherein after administration, the patient's Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 score is improved by, for example, at least about 5 points as compared to the patient's UDPRS Part 3 score prior to administration. In a preferred embodiment, the patient's UPDRS Part 3 score is improved, for example, within about 60 minutes of administration of levodopa. The invention also provides methods of reducing mean daily OFF time and methods of delivering levodopa to a patient. The invention is particularly useful in decreasing mean daily OFF time and the duration of OFF episodes in a Parkinson's patient.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Mean plasma levodopa concentration vs. time data following 90/8/2 inhalation and oral levodopa administration.

FIG. 2: Mean plasma levodopa concentration vs. time data following 90/8/2 inhalation compared to oral administration.

FIG. 3: Plasma levodopa concentrations in individual subjects following inhalation of 50 mg 90/8/2 or oral administration of 100 mg levodopa (CD/LD 25/100 mg) under fed and fasted conditions.

FIG. 4: Levodopa AUC $_{0-\infty}$ vs 90/8/2 fine particle dose.

FIG. 5: Levodopa C_{max} vs 90/8/2 fine particle dose.

FIG. 6: Pharmacokinetic modeling of mean plasma concentrations. Symbols represent observed mean concentrations and lines represent concentrations predicted by the model.

FIG. 7: Mean levodopa plasma concentrations with and without carbidopa (CD) pretreatment.

FIG. 8: Patients plasma levodopa concentrations are being compared to UPDRS scores.

FIG. 9: is a line graph showing the mean change in UPDRS Part 3 score versus time in minutes at Visit 6, the Primary Endpoint, between patients receiving Study Drug at Dose Level 2 which was 50 mg of 90/8/2 fine particle dose and patients receiving placebo.

FIG. 10: is a line graph showing the mean change in UPDRS Part 3 score versus time in minutes at Visit 4, the Primary Endpoint, between patients receiving Study Drug at Dose Level 1 which was 35 mg of 90/8/2 fine particle dose and patients receiving placebo.

FIG. 11: shows that there was no worsening in ON time with dyskinesia. Fig 11A shows the change in non-troublesome dyskenisia time (hours) over the time (weeks) between 90/8/2 as compared to placebo. Fig. 11B shows the change in troublesome dyskinesia time (hours) over a period of time (weeks) between 90/8/2 and placebo.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The half-life time ($T_{½}$) is the time for a concentration (C) of a drug in a body fluid or a tissue to reach the concentration C/2.

"$Cmax^{Pul}$" means the maximum observed plasma concentration (Cmax) as measured after pulmonary delivery. "$Cmax^{oral}$" means the maximum observed plasma concentration as measured after oral delivery.

The area under the curve, AUC, corresponds to the integral of the plasma concentration over a given time interval. The AUC is expressed in units of mass (mg, g) × liter−1×hour, and is a measure of the bioavailability of a drug.

"AUC^{Pul}" means the area under the plasma concentration versus time curve (AUC) as measured after pulmonary delivery. "AUC^{oral}" means the area under the plasma concentration versus time curve (AUC) as measured after oral delivery.

The term "coefficient of variation" (CV) which is expressed as %CV, is defined as the ratio of the standard deviation σ to the mean μ:

$$C_v = \sigma/\mu$$

As used herein, the phrase "nominal dose" or "nominal powder dose" means the percentage of levodopa which is present in the total mass of particles contained in the receptacle and represents the maximum amount of levodopa available for administration to the patient.

The fine particle fraction" or "FPF" corresponds to the percentage of particles in the mass of particles present in the receptacle that have an aerodynamic diameter of less than 5.6 μm.

The term "fine particle dose" as used herein is defined as the nominal dose multiplied by the FPF.

As used herein, a "reduction in the mean daily OFF time" in a patient refers to the mean reduction in the daily OFF time in a patient as recorded in a patient diary or as observed by a clinician.

The Unified Parkinson's Disease Rating Scale (UPDRS) as used herein is a well-established tool for measuring the signs and symptoms of Parkinson's disease. The total UPDRS consists of four (4) parts. Parts, 1, 2 and 3 contain 44 questions. Unless otherwise indicated, all items are rated from zero (normal) to four (severely affected) each item defined by a short sentence. The UPDRS includes both scoring by a clinician (motor examination) and a historical report of mental functioning and activities of daily living (ADL obtained by questioning the patient). Part 1 measures mentation, behavior and mood including intellectual impairment, thought disorder, motivation/initiative and depression. Part 2 measures activities of daily living (ADL) including speech, salivation, swallowing, handwriting, cutting food, dressing falling, freezing walking, tremor and sensory complaints. Part 3 is a motor examination and measures include speech, facial

expression, tremor at rest, action tremor, rigidity, finger taps, hand movements, hand pronation and supination, leg agility, arising from chair, posture, gait, postural stability, and body bradykinesia. Part 4 measures the complications of therapy including dyskinesia duration, disability pain, off periods and duration, sleep disturbance among others.

List of Abbreviations

A	y-axis intercept for distribution phase
α	Distribution phase rate constant
AUC	Area under the plasma concentration versus time curve
AUC_{0-t}	AUC from time 0 to last measureable plasma concentration
$AUC_{0-\infty}$	AUC from time 0 to infinity
AUC_{0-10m}	AUC from time 0 to 10 minutes
B	y-axis intercept for elimination phase
β	Elimination phase rate constant
BL	Baseline
BLQ	Below Level of Quantitation (of the assay)
C	y-axis intercept for absorption phase
CD/LD	Carbidopa/levodopa
CL/F	Clearance divided by fraction of drug absorbed
C_{max}	Maximum observed plasma drug concentration
$C_{max,10\ m}$	C_{max} observed in first 10 minutes
FPD	Fine particle dose
K01	Absorption rate constant
K10	Elimination rate constant, PK model
K12	Inter-compartmental rate constant, compartment 1->2
K21	Inter-compartmental rate constant, compartment 2->1
λ	Elimination rate constant
LD	Levodopa
L-Dopa	Levodopa
mg	Milligrams
min	Minutes
mL	Milliliters
NC	Not calculated
NCA	Non-compartmental PK analysis
ng	Nanograms
NS	No sample
Pbo	Placebo
PD	Parkinson's disease
SD	Standard deviation
SEM	Standard Error of the Mean
PK	Pharmacokinetic
$T_{1/2}$	Terminal half-life
$T_{1/2\alpha}$	Half-life of distribution phase
$T_{1/2\beta}$	Half-life of elimination phase
$T_{1/2k01}$	Absorption half-life
T_{lag}	Lag time

T_{max}	Time to maximum observed plasma drug concentration
T_{Cmax50}	Time to reach 50% of C_{max}
Vz/F	Volume of distribution divided by fraction of drug absorbed

The features and other details of the invention will now be more particularly described and pointed out in the claims. It will be understood that the particular embodiments of the invention are shown by way of illustration and not as limitations of the invention. The principle features of this invention may be employed in various embodiments without departing from the scope of the invention. As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise.

In accordance with the invention, a “dose of levodopa”, as that term is used herein means a formulation comprising an amount of levodopa in a dosage form suitable for delivery to a patient by inhalation. In one embodiment, a dose of levodopa in accordance with the invention comprises particles containing levodopa. Particles and methods for delivering levodopa to the respiratory system are described, for example, in U.S. Pat. No: 6,514,482 and U.S. Pat Reissue No. RE43711, the contents of both are incorporated herein by reference in their entirety. The particles are preferably in the form of a dry powder and are characterized by a fine particle fraction (FPF), geometric and aerodynamic dimensions and by other properties, as further described below.

Gravimetric analysis, using Cascade impactors, is a method of measuring the size distribution of airborne particles. The Andersen Cascade Impactor (ACI) is an eight-stage impactor that can separate aerosols into nine distinct fractions based on aerodynamic size. The size cutoffs of each stage are dependent upon the flow rate at which the ACI is operated. Preferably the ACI is calibrated at 60 L/min.

In one embodiment, a two-stage collapsed ACI is used for particle optimization. The two-stage collapsed ACI consists of stages 0, 2 and F of the eight-stage ACI and allows for the collection of two separate powder fractions. At each stage an aerosol stream passes through the nozzles and impinges upon the surface. Particles in the aerosol stream with a large enough inertia will impact upon the plate. Smaller particles that do not have enough inertia to impact on the plate will remain in the aerosol stream and be carried to the next stage.

The ACI is calibrated so that the fraction of powder that is collected on a first stage is referred to as fine particle fraction FPF (5.6). This FPF corresponds to the % of

particles that have an aerodynamic diameter of less than 5.6 μm. The fraction of powder that passed the first stage of the ACI and is deposited on the collection filter is referred to as FPF (3.4). This corresponds to the % of particles having an aerodynamic diameter of less than 3.4 μm.

The FPF (5.6) fraction has been demonstrated to correlate to the fraction of the powder that is deposited in the lungs of the patient, while the FPF(3.4) has been demonstrated to correlate to the fraction of the powder that reaches the deep lung of a patient.

The FPF of at least 50% of the particles of the invention is less than about 5.6 μm. For example, but not limited to, the FPF of at least 60%, or 70%, or 80%, or 90% of the particles is less than about 5.6 μm.

Another method for measuring the size distribution of airborne particles is the multi-stage liquid impinger (MSLI). The Multi-stage liquid Impinger (MSLI) operates on the same principles as the Anderson Cascade Impactor (ACI), but instead of eight stages there are five in the MSLI. Additionally, instead of each stage consisting of a solid plate, each MSLI stage consists of a methanol-wetted glass frit. The wetted stage is used to prevent bouncing and re-entrainment, which can occur using the ACI. The MSLI is used to provide an indication of the flow rate dependence of the powder. This can be accomplished by operating the MSLI at 30, 60, and 90 L/min and measuring the fraction of the powder collected on stage 1 and the collection filter. If the fractions on each stage remain relatively constant across the different flow rates then the powder is considered to be approaching flow rate independence.

The particles of the invention have a tap density of less than about 0.4 g/cm^3. Particles which have a tap density of less than about 0.4 g/cm^3 are referred to herein as "aerodynamically light particles". For example, the particles have a tap density less than about 0.3 g/cm^3, or a tap density less than about 0.2 g/cm^3, a tap density less than about 0.1 g/cm^3. Tap density can be measured by using instruments known to those skilled in the art such as the Dual Platform Microprocessor Controlled Tap Density Tester (Vankel, NC) or a GEOPYC™ instrument (Micrometrics Instrument Corp., Norcross, GA 30093). Tap density is a standard measure of the envelope mass density. Tap density can be determined using the method of USP Bulk Density and Tapped Density, United States Pharmacopia convention, Rockville, MD, 10th Supplement, 4950-4951, 1999. Features

which can contribute to low tap density include irregular surface texture and porous structure.

The envelope mass density of an isotropic particle is defined as the mass of the particle divided by the minimum sphere envelope volume within which it can be enclosed. In one embodiment of the invention, the particles have an envelope mass density of less than about 0.4 g/cm^3.

The particles of the invention have a preferred size, e.g., a volume median geometric diameter (VMGD) of at least about 1 micron (μm). In one embodiment, the VMGD is from about 1 μm to 30 μm, or any subrange encompassed by about 1 μm to 30 μm, for example, but not limited to, from about 5 μm to about 30 μm, or from about 10 μm to 30 μm. For example, the particles have a VMGD ranging from about 1 μm to 10 μm, or from about 3 μm to 7 μm, or from about 5 μm to 15 μm or from about 9 μm to about 30 μm. The particles have a median diameter, mass median diameter (MMD), a mass median envelope diameter (MMED) or a mass median geometric diameter (MMGD) of at least 1 μm, for example, 5 μm or near to or greater than about 10 μm. For example, the particles have a MMGD greater than about 1 μm and ranging to about 30 μm, or any subrange encompassed by about 1 μm to 30 μm, for example, but not limited to, from about 5 μm to 30 μm or from about 10 μm to about 30 μm.

The diameter of the spray-dried particles, for example, the VMGD, can be measured using a laser diffraction instrument (for example Helos, manufactured by Sympatec, Princeton, NJ). Other instruments for measuring particle diameter are well known in the art. The diameter of particles in a sample will range depending upon factors such as particle composition and methods of synthesis. The distribution of size of particles in a sample can be selected to permit optimal deposition to targeted sites within the respiratory tract.

Aerodynamically light particles preferably have "mass median aerodynamic diameter" (MMAD), also referred to herein as "aerodynamic diameter", between about 1 μm and about 5 μm or any subrange encompassed between about 1 μm and about 5 μm. For example, the MMAD is between about 1 μm and about 3 μm, or the MMAD is between about 3 μm and about 5 μm.

Experimentally, aerodynamic diameter can be determined by employing a gravitational settling method, whereby the time for an ensemble of particles to settle a certain distance is used to infer directly the aerodynamic diameter of the particles. An

indirect method for measuring the mass median aerodynamic diameter (MMAD) is the multi-stage liquid impinger (MSLI).

The aerodynamic diameter, d_{aer}, can be estimated from the equation:

$$d_{aer} = d_g\sqrt{\rho_{tap}}$$

where d_g is the geometric diameter, for example the MMGD, and ρ is the powder density.

Particles which have a tap density less than about 0.4 g/cm^3, median diameters of at least about 1 μm, for example, at least about 5 μm, and an aerodynamic diameter of between about 1 μm and about 5 μm, preferably between about 1 μm and about 3 μm, are more capable of escaping inertial and gravitational deposition in the oropharyngeal region, and are targeted to the airways, particularly the deep lung. The use of larger, more porous particles is advantageous since they are able to aerosolize more efficiently than smaller, denser aerosol particles such as those currently used for inhalation therapies.

In comparison to smaller, relatively denser particles the larger aerodynamically light particles, preferably having a median diameter of at least about 5 μm, also can potentially more successfully avoid phagocytic engulfment by alveolar macrophages and clearance from the lungs, due to size exclusion of the particles from the phagocytes' cytosolic space. Phagocytosis of particles by alveolar macrophages diminishes precipitously as particle diameter increases beyond about 3 μm. Kawaguchi, H., *et al.*, *Biomaterials*, 7: 61-66 (1986); Krenis, L.J. and Strauss, B., *Proc. Soc. Exp. Med.*, 107: 748-750 (1961); and Rudt, S. and Muller, R.H., *J. Contr. Rel.*, 22: 263-272 (1992). For particles of statistically isotropic shape, such as spheres with rough surfaces, the particle envelope volume is approximately equivalent to the volume of cytosolic space required within a macrophage for complete particle phagocytosis.

The particles may be fabricated with the appropriate material, surface roughness, diameter and tap density for localized delivery to selected regions of the respiratory tract such as the deep lung or upper or central airways. For example, higher density or larger particles may be used for upper airway delivery, or a mixture of varying sized particles in a sample, provided with the same or different therapeutic agent may be administered to target different regions of the lung in one administration. Particles having an aerodynamic diameter ranging from about 3 to about 5 μm are preferred for delivery to the central and upper airways. Particles having and aerodynamic diameter ranging from about 1 to about 3 μm are preferred for delivery to the deep lung.

Inertial impaction and gravitational settling of aerosols are predominant deposition mechanisms in the airways and acini of the lungs during normal breathing conditions. Edwards, D.A., *J. Aerosol Sci.*, 26: 293-317 (1995). The importance of both deposition mechanisms increases in proportion to the mass of aerosols and not to particle (or envelope) volume. Since the site of aerosol deposition in the lungs is determined by the mass of the aerosol (at least for particles of mean aerodynamic diameter greater than approximately 1 μm), diminishing the tap density by increasing particle surface irregularities and particle porosity permits the delivery of larger particle envelope volumes into the lungs, all other physical parameters being equal.

The low tap density particles have a small aerodynamic diameter in comparison to the actual envelope sphere diameter. The aerodynamic diameter, d_{aer}, is related to the envelope sphere diameter, d (Gonda, I., "Physico-chemical principles in aerosol delivery," in *Topics in Pharmaceutical Sciences 1991* (eds. D.J.A. Crommelin and K.K. Midha), pp. 95-117, Stuttgart: Medpharm Scientific Publishers, 1992)), by the simplified formula:

$$d_{aer} = d\sqrt{\rho}$$

where the envelope mass density is in units of g/cm^3.

Maximal deposition of monodispersed aerosol particles in the alveolar region of the human lung (~60%) occurs for an aerodynamic diameter of approximately d_{aer}=3μm. Heyder, J. *et al.*, *J. Aerosol Sci.*, *17*: 811-825 (1986). Due to their small envelope mass density, the actual diameter d of aerodynamically light particles comprising a monodisperse inhaled powder that will exhibit maximum deep-lung deposition is:

$$d = 3/\sqrt{\rho}\ \mu m \text{ (where } \rho\_ < 1 \text{ g/cm}^3\text{)};$$

where d is always greater than 3μm. For example, aerodynamically light particles that display an envelope mass density, $\mu = 0.1$ g/cm^3, will exhibit a maximum deposition for particles having envelope diameters as large as 9.5μm. The increased particle size diminishes interparticle adhesion forces. Visser, J., *Powder Technology*, *58*: 1-10. Thus, large particle size increases efficiency of aerosolization to the deep lung for particles of low envelope mass density, in addition to contributing to lower phagocytic losses.

The aerodynamic diameter can be calculated to provide for maximum deposition within the lungs. Previously this was achieved by the use of very small particles of less than about five microns in diameter, preferably between about one and about three microns, which are then subject to phagocytosis. Selection of particles which have a

larger diameter, but which are sufficiently light (hence the characterization "aerodynamically light"), results in an equivalent delivery to the lungs, but the larger size particles are not phagocytosed. Improved delivery can be obtained by using particles with a rough or uneven surface relative to those with a smooth surface.

In another embodiment of the invention, the particles have an envelope mass density, also referred to herein as "mass density" of less than about 0.4 g/cm^3. In some embodiments, the particle density is about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, less than 0.1, from 0.02 to 0.05, from 0.02 to 0.06 g/cm^3. Mass density and the relationship between mass density, mean diameter and aerodynamic diameter are discussed in U.S. Patent No. 6,254,854, issued on July 3, 2001, to Edwards, *et al.*, which is incorporated herein by reference in its entirety.

Particles that have compositions and aerodynamic properties described above may be produced by several methods including, but not limited to spray drying. Generally, spray-drying techniques are described, for example, by K. Masters in "Spray Drying Handbook", John Wiley & Sons, New York, 1984.

As used herein, the term "effective amount" or “therapeutically effective amount” means the amount needed to achieve the desired effect or efficacy. The actual effective amounts of drug can vary according to the specific drug or combination thereof being utilized, the particular composition formulated, the mode of administration, and the age, weight, condition of the patient, and severity of the episode being treated. In the case of a dopamine precursor, agonist or combination thereof it is an amount which reduces the Parkinson’s symptoms which require therapy. Dosages for a particular patient are described herein and can be determined by one of ordinary skill in the art using conventional considerations, (e.g. by means of an appropriate, conventional pharmacological protocol).

Administration of particles to the respiratory system can be by means such as known in the art. For example, particles are delivered from an inhalation device such as a dry powder inhaler (DPI). Metered-dose-inhalers (MDI), nebulizers or instillation techniques also can be employed.

In one embodiment delivery to the pulmonary system of particles is by the methods described in U.S. Patent 6,858,199 entitled, “High Efficient Delivery of a Large Therapeutic Mass Aerosol”, and U.S. Patent 7,556,798, entitled “Highly Efficient Delivery of a Large Therapeutic Mass Aerosol”. The entire contents of both these patents

are incorporated herein by reference. As disclosed therein, particles are held, contained, stored or enclosed in a receptacle. The receptacle, e.g. capsule or blister has a volume of at least about 0.37cm^3 and can have a design suitable for use in a dry powder inhaler. Larger receptacles having a volume of at least about 0.48 cm^3, 0.67 cm^3 or 0.95 cm^3 also can be employed. As used herein, the term "receptacle" includes but is not limited to, for example, a capsule, blister, film covered container well, chamber and other suitable means of storing particles, a powder or a respirable composition in an inhalation device known to those skilled in the art. In one embodiment, the receptacles are capsules, for example, capsules designated with a particular capsule size, such as 2, 1, 0, 00 or 000. Suitable capsules can be obtained, for example, from Shionogi (Rockville, MD). In one embodiment, the capsule shell may comprise hydroxypropyl methylcellulose (HPMC). In a further embodiment, the capsule shell may comprise hydroxypropyl methylcellulose (HPMC) and titanium dioxide. Blisters can be obtained, for example, from Hueck Foils, (Wall, NJ). Other receptacles and other volumes thereof suitable for use in the instant invention are known to those skilled in the art.

In one embodiment, the invention provides administering L-Dopa to the pulmonary system in a small number of steps, and preferably in a single, breath activated step. In one embodiment, at least 50% of the mass of the particles stored in the inhaler receptacle is delivered to a subject's respiratory system in a single, breath-activated step. In one embodiment at least 60%, preferably at least 70% and preferably at least 80% of the particles stored in the inhaler receptacle is delivered to a subject's respiratory system in a single, breath-activated step. In another embodiment, at least 1 to 80 milligrams of L-Dopa is delivered by administering, in a single breath, to a subject's respiratory tract particles enclosed in the receptacle. Preferably at least 10 15, 20, 25, 30, 35, 40, 50, 60, 75 and 80 milligrams can also preferably be delivered.

Delivery to the pulmonary system of particles in a single, breath-actuated step is enhanced by employing particles which are dispersed at relatively low energies, such as, for example, at energies typically supplied by a subject's inhalation. Such energies are referred to herein as "low." As used herein, "low energy administration" refers to administration wherein the energy applied to disperse and/or inhale the particles is in the range typically supplied by a subject during inhaling.

The invention also is related to methods for efficiently delivering powder particles to the pulmonary system. For example, but not limited to, at least about 60%, preferably

at least about 70% or preferably at least about 80% of the nominal powder dose is actually delivered.

In one embodiment, compositions used in this invention comprise particle such as dry powder particles suitable for pulmonary delivery comprising about 60-99% by weight (dry weight) of levodopa. Particularly preferred are particles that include about 75% by weight or more of levodopa and even more preferably comprise about 90% by weight or more of levodopa. Particles can consist entirely of L-Dopa or can further include one or more additional components. Examples of such suitable additional components include, but are not limited to, phospholipids, amino acids, sugars and salts. Specific examples of phospholipids include but are not limited to phosphatidylcholines dipalmitoyl phosphatidylcholine (DPPC), dipalmitoyl phosphatidylethanolamine (DPPE), distearoyl phosphatidylcholine (DSPC), dipalmitoyl phosphatidyl glycerol (DPPG) or any combination thereof. The amount of phospholipids, e.g., DPPC, present in the particles of the invention generally is less than 10 wt%.

Salts include a small amount of a strong electrolyte salt, such as, but not limited to, sodium chloride (NaCl). Other salts that can be employed include sodium citrate, sodium lactate, sodium phosphate, sodium fluoride, sodium sulfate and calcium carbonate. Generally, the amount of salt present in the particles is less than 10 wt %, for example, less than 5 wt%.

In one preferred embodiment, a formulation of levodopa suitable for pulmonary delivery to a patient by inhalation comprises, 90% by weight of levodopa, 8% by weight of dipalmitoyl phosphatidylcholine (DPPC) and 2% by weight sodium chloride and is referred to herein as "90/8/2".

In one embodiment, the present invention provides methods of treating OFF periods in Parkinson's disease patients comprising administering levodopa to the pulmonary system of a patient wherein after administration, the patient's Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 score improves, for example, by at least about 5 points as compared to placebo control. In one embodiment, the patients UPDRS III score improves, for example, at least about 8 points, preferably at least about 10 points and preferably at least about 12 points as compared to placebo control. In one embodiment the patient is administered between about 30 to about 60 mg fine particle dose (FPD) of levodopa preferably 90/8/2 FPD levodopa. In one preferred embodiment, the patient is administered 35 mg FPD of levodopa to the pulmonary system. In another

preferred embodiment the patient is administered 50 mg FPD of levodopa. In one embodiment, the patient does not experience increased dyskinesis as compared to the level of dyskinesis prior to pulmonary administration of levodopa. In one embodiment, the patient has about 3 to about 4 OFF episodes a day prior to administration of levodopa. In one embodiment, the patient has about 4 to about 8 hours of OFF episodes a day prior to administration of levodopa. In one embodiment, the FPD of levodopa is administered at the emergence of OFF symptoms.

In one embodiment, the present invention provides methods of treating OFF periods in Parkinson's disease patients comprising administering levodopa to the pulmonary system of a patient wherein after administration, the patient's Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 score improves, for example, by at least about 5 points as compared to the patient's UPDRS III score prior to pulmonary administration. In one embodiment, the patients UPDRS III score improves, for example, by at least about 8 points, preferably by at least about 10 points and preferably by at least about 12 points as compared to placebo control. In one embodiment the patient is administered between about 30 to about 60 mg fine particle dose (FPD) of levodopa preferably 90/8/2 FPD levodopa. In one embodiment, the patient is administered 35 mg FPD of levodopa to the pulmonary system. In another embodiment the patient is administered 50 mg FPD of levodopa. In one embodiment, the patient does not experience increased dyskinesis as compared to the level of dyskinesis prior to pulmonary administration of levodopa. In one embodiment, the patient has about 3 to about 4 OFF episodes a day prior to administration of levodopa. In one embodiment, the patient has about 4 to about 8 hours of OFF episodes a day prior to administration of levodopa. In one embodiment, the FPD of levodopa is administered at the emergence of OFF symptoms.

In one embodiment the invention provides a method for reducing the mean daily OFF time in a Parkinson's Disease patient comprising administering levodopa to the pulmonary system of a patient at least once a day and preferably at least twice a day, wherein after administration, the patient's mean daily OFF time is reduced by at least about one hour, preferably by at least about two hours, preferably by at least about three hours, preferably by at least about four hours preferably by at least about five hours or more. In one embodiment the patient is administered between about 30 to about 60 mg fine particle dose (FPD) of levodopa preferably 90/8/2 FPD levodopa. In one preferred

embodiment, the patient is administered 35 mg FPD of levodopa to the pulmonary system. In another preferred embodiment the patient is administered 50 mg FPD of levodopa. In one embodiment, the patient does not experience increased dyskinesis as compared to the level of dyskinesis prior to pulmonary administration of levodopa. In one embodiment, the patient has about 3 to about 4 OFF episodes a day prior to administration of levodopa. In one embodiment, the patient has about 4 to about 8 hours of OFF episodes a day prior to administration of levodopa. In one embodiment, the FPD of levodopa is administered at the emergence of OFF symptoms.

In one embodiment, the invention provides methods of delivering levodopa to a Parkinson's disease patient comprising administering levodopa to the pulmonary system of a patient wherein after administration, the patient has an improvement in the patient's Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 score of, for example, by at least about 5 to about 12 points as compared to the patient's UPDRS III score prior to pulmonary administration of said levodopa. In one embodiment the patient is administered between about 30 to about 60 mg fine particle dose (FPD) of levodopa preferably 90/8/2 FPD levodopa. In one preferred embodiment, the patient is administered 35 mg FPD of levodopa to the pulmonary system. In another preferred embodiment the patient is administered 50 mg FPD of levodopa. In one embodiment, the patient does not experience increased dyskinesis as compared to the level of dyskinesis prior to pulmonary administration of levodopa. In one embodiment, the patient has about 3 to about 4 OFF episodes a day prior to administration of levodopa. In one embodiment, the patient has about 4 to about 8 hours of OFF episodes a day prior to administration of levodopa. In one embodiment, the FPD of levodopa is administered at the emergence of OFF symptoms.

In one embodiment, after pulmonary administration of levodopa, the patient's UPDRS Part 3 score is improved by at least about 5 to about 15 points, preferably by at least about 5 to about 12 points, preferably by at least about 5 to about 10 points, preferably by at least about 5 to about 8 points, as compared to placebo control. In one embodiment, after pulmonary administration of levodopa, the patient's UPDRS Part 3 score is improved by at least about 2 to about 15 points, preferably by at least about 2 to about 12 points preferably by at least about 2 to about 10 points preferably by at least about 2 to about 8 points, preferably by at least about 2 to about 5 points, preferably by at least about 3 to about 15 points, preferably by at least about 3 to about 12 points

preferably by at least about 3 to about 10 points preferably by at least about 3 to about 8 points, preferably by at least about 3 to about 5 points, preferably by at least about 4 to about 15 points, preferably by at least about 4 to about 12 points preferably by at least about 4 to about 10 points and preferably by at least about 4 to about 8 points, as compared to placebo control.

In one embodiment, the patient's UPDRS Part 3 score is improved as compared to placebo control within about 60 minutes after pulmonary administration of levodopa, preferably within about 30 minutes after administration, preferably within about 20 minutes after administration, and preferably within about 10 minutes administration. In one embodiment the patient's UPDRS Part 3 score improves by at least about 2 points, preferably by at least about 5 points, and preferably by at least about 8 points, preferably by at least about 10 points, preferably by at least about 12 points and preferably by at least about 15 points within about 60 minutes, preferably within about 30 minutes, preferably within about 20 minutes and preferably within about 10 minutes, after administration of levodopa as compared to placebo control. In one embodiment, the patient does not experience increased dyskinesis as compared to the level of dyskinesis prior to pulmonary administration of levodopa. In one embodiment, the patient has about 3 to about 4 OFF episodes a day prior to administration of levodopa. In one embodiment, the patient has about 4 to about 8 hours of OFF episodes a day prior to administration of levodopa.

In one embodiment, the patient's UPDRS Part 3 score after administration is improved by at least 2 points, preferably by at least about 3 points, preferably by at least about 4 points preferably by at least about 5 points, preferably by at least about 6 points preferably by at least about 7 points, preferably by at least about 8 points, preferably by at last about 9 points, preferably by at least about 10 points, preferably by at least about 11 points preferably by at least about 12 points preferably by at least about 13 points, preferably by at least about 14 points preferably by at least about 15 points, as compared to the patients UPDRS Part 3 score prior to prior to pulmonary administration of levodopa.

In one embodiment the patient's UPDRS Part 3 score improves within about 60 minutes preferably within about 30 minutes, preferably within about 20 minutes and preferably within about 10 minutes after administration of levodopa as compared to the patient's UPDRS III score prior to pulmonary administration of said levodopa. In one embodiment the patient's UPDRS Part 3 score improves by at least about 2 points, preferably by at least about 5 points, preferably by at least about 8 points, preferably by at

least about 10 points, preferably by at least about 12 points and preferably by at least about 15 points, within about 60 minutes preferably within about 30 minutes, preferably within about 20 minutes and preferably within about 10 minutes after administration of levodopa as compared to the patient's UPDRS III score prior to pulmonary administration of levodopa. In one embodiment, the patient does not experience increased dyskinesis as compared to the level of dyskinesis prior to pulmonary administration of levodopa. In one embodiment, the patient has about 3 to about 4 OFF episodes a day prior to administration of levodopa. In one embodiment, the patient has about 4 to about 8 hours of OFF episodes a day prior to administration of levodopa. In one embodiment, the FPD of levodopa is administered at the emergence of OFF symptoms.

In one embodiment, the contents of at least one capsule containing said FPD of levodopa is administered to the patient via inhalation. In one embodiment, the contents of at least two capsules comprising said FPD of levodopa preferably 90/8/2 FPD levodopa is administered to the patient via inhalation. In one embodiment the fine particle dose of levodopa is delivered from at least one capsule to the pulmonary system by an inhalation device. In one embodiment, the inhalation device is a dry powder inhaler (DPI) or a metered-dose inhaler (MDI).

In one embodiment, the methods of the invention provide rapid relief of motor fluctuations in a Parkinson's disease patient. The methods of the invention are particularly useful for treatment of motor fluctuations which arise as a result of poorly controlled levodopa plasma levels in a patient.

In one embodiment, the methods of the invention comprise pulmonary administration of levodopa by inhalation at therapeutically effective concentrations such that the patient's plasma levodopa concentration increases by at least about 200 ng/ml within about 10 minutes or less post inhalation as compared to the concentration of levodopa in the patient's plasma prior to inhalation of the levodopa and wherein the patient's plasma concentration remains increased by at least about 200 ng/ml for a time period of at least about 15 minutes after inhalation.

In one embodiment, the patient's plasma levodopa concentration maintains an increase of at least about 200 ng/ml for a time period of at least about 20 minutes after administration. In one embodiment, the patient's plasma levodopa concentration maintains said increase of at least about 200 ng/ml for a time period of at least about 30 minutes after administration. In one embodiment, the patient's plasma levodopa

concentration maintains said increase of at least about 200 ng/ml for a time period of at least about 60 minutes after administration. In other embodiments, the increase is more than 200ng/ml, 200 to 500ng/ml, 300 to 400ng/ml or 250 to 450 ng/ml. In one embodiment, the patient's plasma levodopa concentration does not increase more than about 1000 ng/ml within 10 minutes.

In one embodiment, a method of the invention provides rapid relief of motor fluctuations in a Parkinson's disease patient comprising administering about 20 mg to about 75 mg of levodopa to a patient by inhalation, wherein said patient receives immediate relief of motor fluctuations within 10 minutes of said inhalation, and wherein said patient maintains said relief for a period of at least 30 minutes.

In accordance with any of the methods of the invention, the area under the curve (AUC) of levodopa in the patient's plasma at about 10 minutes after administration of a dose of levodopa by inhalation is increased by at least about 1000 ng-min/ml for every 4 mg of levodopa administered as compared to the patient's plasma levodopa concentration prior to administration of levodopa by inhalation. In one embodiment, the AUC of said levodopa in the plasma at about 10 minutes after administration of a dose of levodopa by inhalation is increased by at least about 1000-1500 ng-min/ml for every 4 mg of levodopa administered as compared to the patient's plasma levodopa concentration prior to administration of levodopa by inhalation.

In accordance with any methods of the invention, within about 10 minutes of administration of a dose of levodopa by inhalation, the patient's plasma levodopa concentration increases by at least about 175 ng/ml for every 10 mg of levodopa delivered as compared to the patient's plasma levodopa concentration prior to administration of levodopa by inhalation, wherein said patient's plasma levodopa concentration maintains said increase of at least about 175 ng/ml for a time period of at least about 15 minutes, preferably about 20 minutes, preferably about 25 minutes, preferably about 30 minutes, preferably about 45 minutes or preferably about 60 minutes after administration.

In one embodiment the invention provides a method of providing rapid relief of motor fluctuations in a Parkinson's disease patient comprising administering about 20 mg to about 75 mg of levodopa to a patient by inhalation wherein the $Cmax^{Pul}/AUC^{Pul}$ divided by $Cmax^{Oral}/AUC^{Oral}$ is greater than 1 wherein the dose of levodopa given orally is relatively the same as the dose given via pulmonary delivery.

In one embodiment, the invention provides a method of providing rapid relief of motor fluctuations in a Parkinson's disease patient comprising administering one or more doses of levodopa by inhalation wherein the ratio of $T^{1/2}$ / T^{max} is less than ½ and preferably less than 1/5.

In one embodiment, the dose used in any of the methods of the invention comprises about 10 mg to about 75 mg of levodopa delivered to the patient. In one embodiment, the dose comprises about 12 mg to about 35mg of levodopa. In one embodiment, the dose of levodopa comprises at least about 10 mg. levodopa, preferably at least about 25 mg levodopa, preferably at least about 35 mg levodopa, preferably at least about 50 mg levodopa and preferably at least about 75 mg levodopa.

In one embodiment, the amount of levodopa delivered to the pulmonary system is about 25 to about 60mg of levodopa after the inhalation of one or more capsules. In another embodiment, the amount of levodopa delivered to the pulmonary system is about 35 to 55mg, about 30 to 50mg, about 40 to 50mg, about 45 to 55mg after the inhalation of one or more capsules.

In one embodiment, the dose of levodopa used in any one of the methods of the invention comprise about 30 mg to about 60 mg FPD of levodopa. In one embodiment the dose used in any of the methods of the invention is about 35 mg FPD of levodopa. In one embodiment the dose used in any one of the methods of the invention is about 50 mg FPD of levodopa.

In some embodiments, the rapid motor relief or plasma increases of levodopa occur after in inhalation of the powder in one capsule of levodopa. In other embodiments, the rapid motor relief or plasma increases of levodopa occur after the inhalation of the powder in two, three, four or five capsules.

In one embodiment, the dose used in any of the methods of the invention contains a salt. In one embodiment, the dose contains a phospholipid.

In one embodiment, any of the methods of the invention further comprise co-administering a dopa decarboxylase inhibitor to the patient. In one embodiment, the dopa decarboxylase inhibitor is administered to the patient before administration of levodopa by inhalation, simultaneously with administration of levodopa by inhalation or after administration of levodopa by inhalation.

In one embodiment, any of the methods of the invention may further comprise administering an oral dosage of levodopa to said patient.

In one embodiment, any of the methods of the invention comprise maintaining relief of motor fluctuations for a period of at least 2 hours, preferably at least 3 hours, preferably at least 4 hours, preferably at least 5 hours and more preferably at least 6 hours or more.

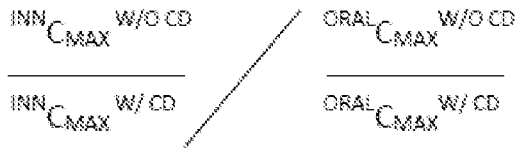
In one embodiment the Parkinson's disease patient treated in accordance with any of the methods the invention is a stage 2, 3 or stage 4 Parkinson's disease patients.

In accordance with any methods of the invention, the dosages of levodopa are not affected by a central nervous system food effect.

In one preferred embodiment the dose of levodopa used in any of the methods of the inventions comprises 90% by weight levodopa, 8% by weight dipalmitoylphosphatidylcholine (DPPC) and 2% by weight of sodium chloride.

The administration of more than one dopamine precursor, DOPA decarboxylase inhibitor or combinations thereof, including, but not limited to, L-Dopa, carbidopa, apomorphine and benserazide can be provided, either simultaneously or sequentially in time to administration of levodopa by inhalation in accordance with the invention. In one embodiment the administration of more than one dopamine precursor or DOPA decarboxylase inhibitor can be administered by intramuscular, subcutaneous, oral and other administration routes. In one embodiment, these other agents are also co-administered via the pulmonary system. These compounds or compositions can be administered before, after or at the same time as pulmonary administration of levodopa by inhalation and are deemed to be "co-administered" when used in conjunction with administration of levodopa via inhalation in accordance with the methods described herein.

In one embodiment, the patient does not require the co-administration of a DOPA decarboxylase inhibitor or allows for a lower or less frequent dose of a DOPA decarboxylase inhibitor. In another embodiment, the patient does not require the co-administration of carbidopa or allows for a lower or less frequent dose of carbidopa as compared to a patient receiving L-Dopa orally. In a further embodiment, the patient does not require the co-administration of benserazide or allows for a lower or less frequent dose of benserazide as compared to a patient receiving L-Dopa orally. In one embodiment, relationship between reliance on carbidopa between levodopa administered through the pulmonary route and levodopa administered through the oral route is:



where "w/o CD" means without carbidopa, "w/ CD" means with carbidopa, "INN" refers to the pulmonary route, and oral refers to the oral route of levodopa delivery to the patient.

In one embodiment, a precise dose of levodopa is needed to turn a patient on. For example, on one embodiment, a dose of levodopa must increase the patient's plasma levodopa concentration by between about 200 ng/ml and 500 ng/ml. Interestingly, this small increase in levodopa concentration applies to a wide range of patient dosing schedules. A patient who may need to have a plasma level of 1500-2000 ng/ml of levodopa to be "on" can be turned on by 200-500 ng/ml of levodopa in the plasma while a patient who may need to have a plasma level of 500-1000 ng/ml of levodopa to be "on" can be turned on by 200-500 ng/ml of levodopa in the plasma. More specifically, a patient can be turned on my increasing the patient plasma concentration by 200-400 ng/ml, 250-450 ng/ml 300-400 ng/ml or about 375-425 ng/ml.

Increasing the patient's plasma concentration by 200-500 ng/ml can be done by a in a variety of ways. The patient can be given levodopa orally, through the pulmonary route or parentally. If given by the pulmonary route, a patient could be provided a dose of 25-50 mg of levodopa to the patient's pulmonary system. In one embodiment, the dose provided to the patient's pulmonary system could be 25-35 mg, 27-32 mg, 28-32 mg, 29-31 mg, or about 30 mg. Providing the dose to the patient's pulmonary system can be done in a variety of ways. In one embodiment a capsule is contains 35-40 mg of levodopa powder, said capsule provides 40-60% of the powder in the capsule to the patient's pulmonary system, and said powder comprises 75-98% levodopa.

The following Examples are intended to illustrate the invention but cannot be construed as limiting the scope thereof.

EXAMPLE 1

Summary

A 90/8/2 dry powder levodopa formulation was provided to evaluate the safety, tolerability and levodopa pharmacokinetics (PK) following administration of 90/8/2

pulmonary levodopa powder compared with oral levodopa in adult healthy volunteers. The pulmonary levodopa powder described in these examples is comprised of particles of 90% levodopa, 8% dipalmitoylphosphatidylcholine and 2% sodium chloride, all by dry weight and is referred to herein as 90/8/2. This data provides a description of the PK of levodopa following single inhaled doses of 90/8/2 and a comparison to orally administered levodopa (LD) in the fasted or fed conditions as well as a comparison of the PK with and without pretreatment with carbidopa (CD). This was a two-part study in healthy adult male and female subjects as follows: Part A- Dose Escalation Segment with comparison to oral levodopa; and Part B-90/8/2 plus or minus a Carbidopa Pre-treatment Segment.

Part A was an open-label, 3-period crossover, single-ascending dose study. Each subject received a single oral dose of CD/LD (25/100 mg) in a fed or fasted state in one session, and two different doses of inhaled 90/8/2 (10 and 30 mg or 20 and 50 mg levodopa fine particle dose (FPD), in single ascending doses, in two different treatment sessions. Two groups of nine subjects each were enrolled.

Part B was an open-label, randomized, two-period, period balanced crossover study. Eight subjects underwent an evaluation of the safety, tolerability and levodopa PK following administration of a single inhaled 90/8/2 dose (40 mg levodopa FPD) with and without pre-treatment with CD.

Blood samples were collected over 24 hours and plasma levodopa concentrations were determined by Simbec Research Limited (UK) using a validated liquid chromatography - tandem mass spectrometry (LC-MS-MS) assay with a lower limit of quantitation of 9.84 ng/mL. Pharmacokinetic analysis was performed using non-compartmental methods followed by PK modeling using a two-compartment model with a lag time. 90/8/2 administered by inhalation at doses of 10 to 50 mg levodopa FPD produced rapidly increasing, dose-proportional plasma levodopa concentrations, achieving potentially therapeutically relevant levels within 5 to 10 minutes after fine particle doses of 20 to 50 mg in healthy adults.

Levodopa plasma concentrations following 90/8/2 inhalation increased faster than those following oral administration in the fasted condition and much faster than those under fed conditions. Exposure over the first ten minutes following drug administration expressed as the partial area under the plasma concentration versus time curve, AUC from 0 to 10 minutes ($AUC_{0\text{-}10m}$) and as the maximum plasma concentration observed over the

first ten minutes post-dose ($C_{max,10m}$) indicated much earlier systemic exposure following 90/8/2 inhalation compared to oral administration.

Subject to subject variability in plasma concentrations was greatly reduced with inhalation compared to oral administration and what would have been expected with pulmonary administration. The analysis also indicated that oral administration in the fasted state lead to more rapid absorption compared to the fed state but still much slower than following inhalation. Pharmacokinetic modeling indicated a lag time of approximately 9 to 10 minutes following oral administration in the fed or fasted state compared to a lag time of less than 0.5 minute following 90/8/2 inhalation. Furthermore, the absorption half-life was shorter following inhalation compared to oral administration.

Following 90/8/2 inhalation, systemic levodopa exposure was proportional to the 90/8/2 dose administered. Dose-normalized C_{max} and AUC were very similar across the 90/8/2 doses administered. Dose-normalized (based on estimated fine particle dose) exposure following inhalation was 1.3 to 1.6 times greater based on AUC and 1.6 to 2.9 times greater based on C_{max} compared to oral administration. As has been described in the literature, following oral administration, considerable reduction in C_{max} and prolongation in T_{max} was observed in fed subjects; however, AUC was similar between fed and fasted subjects.

Plasma concentrations from Part B of the study in which a 40 mg fine particle dose of 90/8/2 was inhaled with or without carbidopa pretreatment in a cross-over design demonstrated rapid absorption with plasma concentration achieving potentially therapeutic levels. Plasma levodopa clearance was approximately four-fold faster without CD pretreatment. Correspondingly, C_{max} and AUC were lower and T_{max} and $T_{1/2}$ were somewhat shorter without CD pretreatment. The main findings of this study were:

- Inhaled 90/8/2 resulted in rapid increases in plasma levodopa concentrations;
- Systemic exposure to levodopa based on C_{max} and AUC was much greater over the first 10 minutes after dosing with 90/8/2 inhalation compared to oral drug administration;
- Potentially therapeutically relevant levodopa plasma concentrations were achieved within 5 to 10 minutes after inhalation of fine particle doses of 20 to 50 mg in healthy adults;

- Subject to subject variability in plasma levodopa concentrations was considerably less following inhalation compared to oral administration and what would have been expected with pulmonary administration;
- Systemic levodopa exposure was proportional to levodopa fine particle dose administered;
- Pharmacokinetic modeling indicated that inhaled 90/8/2 had much shorter lag times and faster absorption rates than oral administration;
- Dose-normalized (based on estimated fine particle dose) exposure following inhalation was 1.3 to 1.6 times greater based on AUC and 1.6 to 2.9 times greater based on C_{max} compared to oral administration;
- Plasma levodopa clearance was approximately four-fold greater and levodopa exposure was reduced in the absence of carbidopa pre-treatment.

Introduction

In this example, 90/8/2 has been tested as an episodic treatment of motor fluctuations ("off episodes") in patients with Parkinson's disease who experience intermittent inadequate response to their standard oral medications. 90/8/2 may be used as an adjunct to the patient's existing dopadecarboxylase inhibitor (i.e., carbidopa or benserazide)-inclusive Parkinson's disease medication regimen. This study was the first study in humans with 90/8/2 and is designed to evaluate the safety, tolerability and levodopa pharmacokinetics (PK) following administration of 90/8/2 compared with oral levodopa in adult healthy volunteers.

Safety and tolerability results have been tested in clinical trials. This PK data analysis provides a description of the PK of levodopa following single inhaled doses of 90/8/2 and a comparison to orally administered levodopa (LD; L-Dopa) in the fasted or fed conditions as well as a comparison of the PK of levodopa with and without pretreatment with carbidopa (CD). Oral levodopa was administered as a routinely prescribed combined carbidopa/levodopa preparation.

Study Design and Objectives

This was a two-part study in healthy adult male and female subjects as follows:

- Part A: Dose Escalation Segment with comparison to oral levodopa.
- Part B: 90/8/2 ± Carbidopa Pre-treatment Segment.

The primary pharmacokinetic objective of Part A of the study was to investigate the pharmacokinetics of levodopa following administration of single, inhaled doses of 90/8/2 in healthy adults. Secondary objectives were to explore the dose proportionality of levodopa following single inhaled dose administration and to compare the PK of 90/8/2 to oral levodopa administered in the fasted state or fed state. The objective of Part B was to compare the tolerability and pharmacokinetics of 90/8/2 with and without pretreatment with carbidopa.

Part A was an open-label, 3-period crossover, single-ascending dose study. All subjects were treated with oral carbidopa one day prior to and on the day of study drug treatment. Each subject received a single oral dose of CD/LD (25/100 mg) in a fed or fasted state in one session, and two different inhaled doses of 90/8/2, in single ascending doses, in two different sessions. Two groups of nine subjects each were enrolled. The study design for Part A is outlined in Table 1 below:

Table 1: Part A Study Design.

Group	N	Dose Group	Levodopa Dose* (mg)
1	9	Oral CD/LD Fed or Fasted	100
		90/8/2 Dose Level 1	10
		90/8/2 Dose Level 3	30
2	9	Oral CD/LD Fed or Fasted	100
		90/8/2 Dose Level 2	20
		90/8/2 Dose Level 4	50

* Levodopa dose for 90/8/2 administration indicates estimated fine particle dose (FPD; i.e., 'lung-delivered' dose); oral CD/LD (25 mg/100mg).

Part B was an open-label, two-period, period balanced crossover study. Following preliminary review of safety and PK data from Part A, eight subjects underwent an evaluation of the safety, tolerability and levodopa PK following administration of a single inhaled 90/8/2 dose (40 mg levodopa FPD) with and without pre-treatment with CD in a randomized, balanced fashion so that equal numbers of subjects received one of the two dosing sequences A->B or B->A, defined as follows:

Regimen A: 90/8/2 with CD pre-treatment

Regimen B: 90/8/2 without CD pre-treatment

Carbidopa treatments in Parts A and B of the study were standardized according to the schedule in Table 2.

In Part A, blood samples were collected pre-dose and following oral CD/LD administration at 10, 20, 30, 45, 60, 75, 90, 120 min, 4, 8, 16 and 24h. During 90/8/2 inhalation treatment sessions in Parts A and B, samples were collected at the same times plus additional samples at 1, 2, and 5 minutes. Plasma levodopa concentrations were determined by Simbec Research Limited using a validated liquid chromatography - tandem mass spectrometry (LC-MS-MS) assay with a lower limit of quantitation of 9.84 ng/mL (2, 3).

Table 2: Carbidopa Treatment Schedule.

	Carbidopa (LODOSYN®) Dose and Timing	
Treatment Session	**Day -1**	**Day 1***
Oral CD/LD: Part A	50 mg every 8 h prior to Day 1 dosing (0, 8 and 16 h, ≥1 h from the nearest meal)**	25 mg*** 1 h pre-dose 50 mg 7 and 15 h post-dose
90/8/2: Part A & Part B (+ CD)	50 mg every 8 h prior to Day 1 dosing (0, 8 and 16 h, ≥1 h from the nearest meal)	50 mg 1 h pre-dose, 7 and 15 h post-dose
90/8/2: Part B (– CD)	---	50 mg 7 and 15 h post-dose

* When an oral and inhaled dosing session were scheduled to occur over two consecutive days, the CD dosing regimen administered for the first dosing session adequately covered the CD pre-treatment required for the second dosing session. Subjects in Part A and Part B (+ CD) received 3 doses of CD during the day before receipt of study medication.
** Does not apply to subjects randomized to fed state.
***Note: 25 mg carbidopa also administered at T0 as part of oral CD/LD administration

Pharmacokinetic Analysis Methods

Non-compartmental Analysis

Data analysis was performed on plasma concentrations and time for each subject and each treatment. Non-compartmental analysis was performed with WINNONLIN® professional version 5.3. The area under the curve from time zero to the last measureable time point (AUC_{0-t}) was estimated using the linear trapezoid method. Linear regression

over the last three or more time points was used to estimate the elimination rate constant (λ) which was used to estimate terminal half-life ($T_{1/2}$) and AUC from zero to infinity ($AUC_{0-\infty}$) from the following equations:

$$T_{1/2} = \ln(2)/\lambda$$

$$AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda$$

where C_t is the last measureable concentration predicted by the regression line. Serum clearance divided by bioavailability (CL/F) and the apparent volume of distribution in the terminal phase divided by the bioavailability (Vz/F) were estimated from the equations below:

$$CL/F = Dose/AUC_{0-\infty}$$

$$Vz/F = Dose/(\lambda * AUC_{0-\infty})$$

the maximum concentration (C_{max}) and the time it was observed (T_{max}) were determined directly from the data.

The partial AUC over the first 10 minutes after drug administration (AUC_{0-10m}) was calculated by the trapezoid method. The maximum plasma concentration observed over the first 10 minutes ($C_{max, 10m}$) was determined as the highest plasma concentration observed from dosing up to an including the 10 minute sampling time. Inhalation-to-oral exposure ratios were calculated for each subject by dividing the dose-normalized C_{max} or AUC following 90/8/2 inhalation by the dose-normalized parameter following oral administration. The exposure ratio based on AUC is the relative bioavailability of inhaled to oral drug.

An additional parameter, time to achieve half of the maximum observed plasma concentration, (T_{Cmax50}) was calculated (Microsoft Excel) by linear interpolation between the two time points with the plasma concentrations bracketing the plasma concentration calculated from C_{max} divided by two.

Pharmacokinetic Modeling

Pharmacokinetic modeling was performed using WINNONLIN®, professional version 5.3. A number of different models were evaluated including one- and two-compartment models with and without lag times. All evaluated models had first order input. Models were evaluated based on a number of diagnostic criteria including the Aikaike Information Criterion, the sum of squared residuals, the relative values of the estimated parameters and their respective standard error estimates, the correlation of

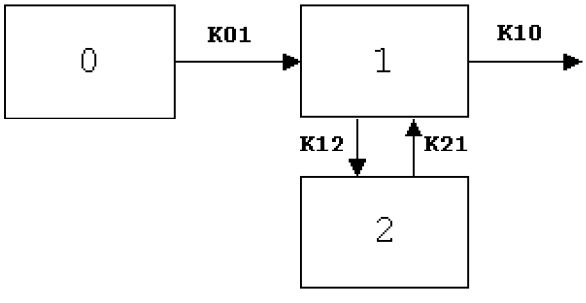
observed and predicted concentrations, and general trends in variation between predicted and observed concentrations.

The model that best described most of the plasma concentration versus time curves was a two-compartment model with a lag time (WINNONLIN® model 12). Most of the data sets from subjects receiving inhaled 90/8/2 were also well described by a model without a lag time because the estimated lag times from these subjects were very short, less than one minute in most cases. However for comparison to data sets from oral administrations the lag time model was used for all subjects and all treatments. Most data sets were described better by a two-compartment model than a one-compartment model. In some cases a one-compartment model could not be fit. For cases in which a one-compartment model was better, based on the statistical diagnostic criteria, the difference between the two models was very small. Therefore, the results of modeling using a two-compartment model are presented herein. The model, of two-compartment model scheme 1, generates estimates for the volume of distribution divided by the fraction of dose absorbed (V/F), the lag time (T_{lag}), the rate constants associated with absorption and elimination, k01 and k10, respectively, and the inter-compartmental rate constants, k12 and k21.The rate constants associated with the distribution and elimination phases of the curve, α and β, are calculated from k12, k21, and k10. Other secondary parameters calculated from the primary parameters include AUC, C_{max}, T_{max}, CL/F, and the half-lives associated with the absorption, distribution and elimination phases of the curve ($T_{1/2k01}$, $T_{1/2\alpha}$, $T_{1/2\beta}$). The model is represented by the equation:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-k01t}$$

C_t is the plasma levodopa concentration at time t after administration, A, B and C are the y-axis intercepts of the distribution, elimination and absorption phases of the curve and are calculated from the dose, volume and rate constants.

Scheme 1



Uniform weighting was used in all analyses and plasma concentrations reported as below the level of quantitation of the assay (BLQ, <9.84 ng/mL) were treated as missing values. No data points were excluded from the analyses.

Results and Discussion

90/8/2 administered by inhalation at doses of 10 to 50 mg levodopa FPD produced rapidly increasing, dose-proportional plasma levodopa concentrations, achieving potentially therapeutically relevant levels (400 to 500 ng/mL) within 5 to 10 minutes after fine particle doses of 20 to 50 mg levodopa in healthy adults.

FIG. 1 presents the mean levodopa plasma levodopa concentrations following 90/8/2 inhalation and following a 100 mg oral dose under fed and fasted conditions. Individual values and concentration versus time plots were calculated for each inhaled dosage of 10mg, 20 mg, 30 mg and 50 mg levodopa, respectively as well as 100 mg levodopa orally under fed and fasted conditions and with and without carbidopa pretreatment.

Plasma levodopa concentrations following 90/8/2 inhalation increased faster than those following oral administration in the fasted condition and much faster than those under fed conditions. Potentially therapeutically relevant plasma concentrations were achieved by approximately five minutes following 90/8/2 inhalation. Within five minutes of inhalation of 90/8/2, 20 to 50 mg FPD, plasma concentrations were 400 to 500 ng/mL or greater, a range that has been observed to be of potential therapeutic relevance (4). Plasma concentrations achieved following 90/8/2, 40 and 50 mg FPD were in the same range as those observed following oral CD/LD (25/100 mg) dosing (FIG. 3).

FIG. 2 shows the mean plasma concentrations over the first ten minutes compared to those following oral administration. Exposure over the first ten minutes following drug administration is expressed both as the AUC from 0 to 10 minutes ($AUC_{0\text{-}10m}$) and as the maximum plasma concentration observed over the first ten minutes ($C_{max,10m}$) in Table 3. In some individuals the $C_{max,10m}$ was observed in less than 10 minutes.

Oral administration in the fasted state lead to more rapid absorption compared to the fed state but still much slower than following inhalation. As has been described in the literature (5), following oral administration, considerable reduction in C_{max} and prolongation in T_{max} was observed in fed subjects; however, AUC (Table 5) was similar between fed and fasted subjects.

Table 3: Levodopa Exposure after 90/8/2 Inhalation or Oral Levodopa Administration.

Dose (mg)	Mean ± SD $C_{max, 10m}$ (ng/mL)	Mean ± SD AUC_{0-10m} (ng-min/mL)	Median T_{Cmax50} min	Median T_{max} min
90/8/2				
10	187 ± 58	1240 ± 391	3.08	10
20	368 ± 148	2590 ± 1283	2.64	10
30	456 ± 59	3176 ± 769	2.90	30
50	729 ± 265	4824 ± 1896	4.10	20
Oral				
100 Oral fasted	109 ± 99	561 ± 477	18.32	45
100 Oral fed	18 ± 21	124 ± 95	39.84	120

Between-subject variability in plasma concentrations following treatment was much less following 90/8/2 inhalation than following oral administration. As seen in FIG. 3, following inhalation (filled symbols), plasma concentrations in most subjects receiving 50 mg 90/8/2 were above 400 ng/mL at 10 minutes after dosing, some were above 400 ng/mL at 5 minutes, and all by 20 minutes. Following oral administration (open symbols), the response was much slower with no subjects approaching 400 ng/mL within 10 minutes of dosing. Individual plasma concentration and variability data for other dose groups, indicate that at levodopa FPD doses of 20 mg and above plasma concentrations above 400 ng/mL were achieved in some subjects within 5 to 10 minutes of dosing and the responses were much less variable than following oral administration. The extent of variability expressed as the %CV in plasma concentrations within a treatment group at a given sampling time, shown in Table 4, demonstrates that within the first 30 minutes of dosing the variability in the 90/8/2 treated subjects was less than half that seen in the fasted oral group and approximately five-fold less than all oral subjects (fed and fasted combined).

Table 4: Variability in Plasma Levodopa Concentrations (%CV).

	Minutes after Dosing							
	10	**20**	**30**	**45**	**60**	**75**	**90**	**120**
90/8/2*								
10 mg	31	43	42	29	28	25	26	20
20 mg	43	39	35	26	27	31	35	24
30 mg	18	19	21	18	24	15	12	10
50 mg	30	32	27	23	24	18	30	23
Oral**								
Oral (fasted)	91	86	64	34	22	20	32	22
Oral (all)	132	117	101	62	48	47	42	27

*Refers to estimated levodopa fine particle dose
** Oral levodopa dose 100 mg

A summary of the pharmacokinetic parameters estimated by non-compartmental analysis is shown in Table 5. Parameter estimates for individuals were determined from the non-compartmental PK analyses for each inhaled dosage of 10 mg, 20 mg, 30 mg and 50 mg as well as 100 mg oral dosage under fasted and fed conditions and with and without CD pretreatment. The results indicate that levodopa exposure was proportional to the 90/8/2 dose administered. Dose-normalized C_{max} and AUC are very similar for all 90/8/2 doses. Dose proportionality is further illustrated in FIG. 4 and FIG. 5. $T_{1/2}$ is similar for all doses.

Table 5: Levodopa Pharmacokinetic Parameters (Mean ± SD) Estimated by Non-compartmental Analysis.

Dose mg*	**C_{max} ng/mL**	**C_{max}/Dose ng/mL/mg**	**AUC ng-min/mL**	**AUC/Dose ng-min/mL/mg**	**$T_{1/2}$*** min**
90/8/2**					
10	196 ± 60	19.60 ± 5.99	23,374 ± 4,656	2,337 ± 466	120
20	393 ± 137	19.67 ± 6.83	44,150 ± 8,504	2,208 ± 425	122
30	576 ± 95	19.19 ± 3.17	66,914 ± 6,185	2,230 ± 206	108
50	884 ± 249	17.69 ± 4.99	106,011 ± 21,234	2,120 ± 427	101
Oral					
100(fasted)	1,317±558	13.17±5.58	156,598±26,921	1,566±269	101
100(fed)	637±144	6.37±1.44	159,042±30,544	1,590±305	114

*Dose: levodopa dose
**Refers to estimated fine particle dose
*** Median value

Bioavailability of inhaled 90/8/2 relative to oral levodopa was calculated for individual subjects from the ratios of the dose-normalized $AUC_{0-\infty}$. Since each subject in Part A of the study received one oral and two inhaled doses, two bioavailability estimates were determined for each subject, one for each inhaled dose. Relative exposure calculations were also performed on the dose-normalized C_{max} values. Calculations were performed separately for oral doses administered under fed and fasted conditions. The means and standard deviations for the relative bioavailability calculations are presented in Table 6. Individual values were calculated as relative levodopa exposures following inhalation of 90/8/2 (10-50 mg levodopa fine particle dose) compared to carbidopa/levodopa 25/100 mg) oral administration calculated from the dose-normalized Cmax. There does not appear to be a major difference between fed and fasted subjects or among dose groups. Dose-normalized (based on estimated fine particle dose) exposure following inhalation was approximately 1.3 to 1.6 times greater based on AUC and 1.6 to 2.9 times greater based on C_{max} compared to oral administration.

Table 6: Exposure Ratios (Mean ± SD) of Inhaled 90/8/2 Relative to Oral Levodopa

90/8/2 FPD mg	AUC		C_{max}	
	Oral Fasted	**Oral Fed**	**Oral Fasted**	**Oral Fed**
10	1.61±0.27	1.31±0.37	1.72 ± 0.72	2.95 ± 1.47
20	1.50±0.12	1.41±0.23	1.96 ± 0.60	2.81 ± 1.04
30	1.47±0.11	1.34±0.34	1.65 ± 0.63	2.89 ± 0.29
50	1.35±0.14	1.41±0.24	1.57 ± 0.54	2.83 ± 1.02
All	1.49±0.19	1.37±0.27	1.72 ± 0.59	2.86 ± 0.95

Plasma concentration versus time profiles were best described by a two-compartment model with first order input and a lag time. Modeling was performed on individual data sets and observed and predicted concentration versus time plots were prepared using WINNONLIN® model 12. In some cases estimates of the terminal half-life ($T_{1/2\beta}$) were very large due to a few points in the terminal phase of the curve having concentrations that were similar or fluctuating, resulting in a flat slope. In many of these cases the large $T_{1/2\beta}$ produced a very large estimate for AUC. Other variations in parameter estimates from the model caused a few aberrant values in some parameter estimates. These values were not excluded from the data analysis or treated statistically as outliers. Instead, data are summarized by the median value rather than the mean. Thus the unusually high or low values remain in the data presented but do not exert undue influence on the group summary statistics.

Pharmacokinetic modeling results shown in Table 7 indicate that there was a lag time of approximately nine minutes following oral administration. By comparison, the lag time associated with inhaled 90/8/2 was negligible, less than 0.5minutes. Furthermore, the absorption rate of inhaled 90/8/2 was faster (shorter $T_{1/2k01}$) than that following oral administration in the fasted state and approximately ten-fold faster than absorption in the fed state. The much shorter lag time and faster absorption rate following 90/8/2 inhalation account for the greater systemic exposure observed within the first 5 to 10 minutes after dosing compared to oral administration. The calculated parameter, time to reach 50% of C_{max} (T_{Cmax50}) also indicates that 90/8/2 inhalation produced earlier levodopa systemic exposure than oral administration. With the exception of oral administration in the fed state, absorption was much faster than elimination.

The combined effects of the lag time and absorption rates on plasma concentrations in the first few minutes following administration is illustrated in FIG. 6 which presents pharmacokinetic modeling of mean plasma concentration data. This plot shows concentrations predicted by the pharmacokinetic model for 90/8/2 inhalation and oral levodopa administration over the first sixty minutes following dosing. The symbols represent observed mean concentrations and the lines represent concentrations predicted by the pharmacokinetic model. The good correlation of predicted and observed values indicates that the model describes the data very well. The figure also illustrates the other observations from the study that 90/8/2 inhalation results in rapid increases in plasma levodopa concentrations, potentially clinically relevant plasma concentrations can be achieved within 5 to 10 minutes of dosing, and exposure is dose-proportional.

Table 7: Pharmacokinetic Parameters (Median Values) Estimated by Pharmacokinetic Modeling

Dose (mg)	T_{lag}(min)	$T_{1/2k01}$(min)	$T_{1/2\alpha}$(min)	$T_{1/2\beta}$(min)
90/8/2*				
10	0.21	4.31	8.18	180.33
20	<0.01	3.53	11.54	135.04
30	<0.01	5.47	33.38	167.66
50	0.29	7.37	26.12	142.46
Oral				
100(fasted)	9.41	9.96	9.64	132.40
100 (fed)	9.78	65.39	7.49	98.21

*Refers to estimated fine particle dose

PART B

Plasma concentrations from Part B of the study in which 90/8/2, 40 mg levodopa FPD was inhaled with or without carbidopa pretreatment in a cross-over design are shown in FIG. 7. Peak plasma concentrations and exposure were higher with carbidopa pretreatment. Plasma levodopa clearance was approximately four-fold faster without CD pretreatment. Correspondingly, C_{max} and AUC were lower and T_{max} and $T_{1/2}$ were somewhat shorter without CD pretreatment (Table 8).

Table 8: Levodopa Pharmacokinetic Parameters (Mean ± SD) Estimated by Non-compartmental Analysis Following Inhalation of 40 mg 90/8/2 with and without Carbidopa Pretreatment.

Treatment	**C_{max} ng/mL**	**T_{max}* min**	**$AUC_{0-\infty}$ ng-min/mL**	**CL/F mL/min**	**$T_{1/2}$* min**
40mg with Carbidopa	895 ± 276	20	95,058 ± 15,979	429 ± 59	113
40mg without Carbidopa	423 ± 126	8	27,005 ± 8,756	1,619 ± 504	85

*Median value

Conclusions

The main findings of this study were: (i) that inhaled 90/8/2 resulted in rapid increases in plasma levodopa concentrations; (ii) Systemic exposure to levodopa based on C_{max} and AUC was much greater over the first 10 minutes after dosing with 90/8/2 inhalation compared to oral drug administration; (iii) Potentially therapeutically relevant plasma levodopa concentrations were achieved within 5 to 10 minutes after 90/8/2 doses of 20 to 50 mg levodopa fine particle dose in healthy adults; (iv) Subject to subject variability in plasma levodopa concentrations was considerably less following inhalation compared to oral administration; (v) Systemic levodopa exposure was proportional to levodopa fine particle dose administered; (vi) Pharmacokinetic modeling indicated that inhaled 90/8/2 had much shorter lag times and faster absorption rates than oral administration; vii) Dose-normalized (based on estimated fine particle dose) exposure following inhalation was 1.3 to 1.6 times greater based on AUC and 1.6 to 2.9 times greater based on C_{max} compared to oral administration; and viii) Plasma levodopa clearance was approximately four-fold greater and levodopa exposure was reduced in the absence of carbidopa pre-treatment.

EXAMPLE 2

A Phase 2 study testing two doses of pulmonary levodopa (25 mg and 50 mg of study drug) was a multicenter, randomized, double blind, placebo-controlled, single dose, cross-over design with three arms (placebo, 25 mg and 50 mg) and included an "open label" oral Sinemet arm. The twenty four PD (24) patients treated in this study underwent serial evaluations of L-dopa plasma levels, motor response, and safety at each visit. The patients were administered the study drug in the OFF state with the serial evaluations starting prior to dosing and continuing for up to 180 minutes post-dose. Motor function was measured using a tapping test, the Unified Parkinson's Disease Rating Scale Part III (UPDRS III), and subjective evaluation of "meaningful" ON and OFF. Safety parameters monitored included pulmonary function, clinical laboratory data, EGCs, and vital signs (blood pressure, heart rate, and orthostatic blood pressure). This study was designed to measure the time, magnitude, and durability of pulmonary levodopa's effect on motor function, to evaluate the safety and tolerability of pulmonary levodopa in Parkinson's disease patients.

In a comparison of pharmacokinetic parameters to pharmacodynamic parameters, the inventors discovered a surprisingly steep curve between patient's being in the off state and patients being in the on state. In FIG. 8, patient's plasma levodopa concentrations are being compared to UPDRS scores. UPDRS is a standard test for Parkinson's disease patients to test their response to drug treatment and their disease progression. As can be seen from FIG. 8, there is a very small levodopa plasma concentration difference between a patient being on and a patient being off. As little as 200-400ng/ml of levodopa plasma concentration makes the difference between being in the off state and being in the on state. What is really striking is that of the four different patients shown here, they all have significantly different baseline plasma concentrations of levodopa. The different baseline levels of levodopa plasma relate to the fact that each patient has a different effective dose or effective concentration for the levodopa to have an effect on each patient. Despite the different effective doses or effective concentrations among a patient population, the increase in plasma concentration needed to go from off to on is very small.

EXAMPLE 3

Phase 2(b) Randomized, Double-Blind Placebo Controlled Study

Phase 2b Study Design and Methods with 90/8/2

This study was a randomized, double-blind, placebo-controlled, multicenter study of inhaled (inhaled levodopa [LD] powder) or placebo for the treatment of up to 3 OFF episodes per day in Parkinson's disease (PD) subjects experiencing motor fluctuations (OFF episodes). Subjects were randomly assigned in a 1:1 ratio to receive inhaled 90/8/2 (also referred herein as the "Study Drug") or placebo; randomization was stratified by the subject's Hoehn and Yahr stage (<2.5 versus ≥2.5) to balance for disease severity in each group.

90/8/2 LD FPD is comprised of homogeneous particles composed of 90% LD, 8% dipalmitoyl phosphatidylcholine (DPPC), and 2% sodium chloride (NaCl). 90/8/2 was delivered using an inhaler device for the inhalation of powders as is described in U.S. Pat. No. 8,496,002, incorporated herein by reference. 90/8/2 was provided in size 00 hypromellose (hydroxypropyl methylcellulose [HPMC]) capsules, each at a nominal fill weight of 32 mg (27.6 mg LD per capsule), designed to deliver an approximate respirable dose of LD 17 mg FPD to the lung.

The two selected 90/8/2 dose levels (approximately 34 mg FPD and 50 mg FPD) were based on safety and pharmacokinetic (PK) data from the study in healthy adult volunteers and safety of Example 1 herein, PK, from the study conducted in Example 1 on healthy adult volunteers and safety, PK and pharmacokinetics data from the study conducted in PD patients as described in Example 2. In order to maintain the blind, all patients were given identical-looking study drug kits and instructed to inhale an identical number of capsules for each dose (2 capsules during Weeks 1 and 2, and 3 capsules during Weeks 3 and 4). Patients were allowed to sip water in between capsule inhalations, if needed.

Placebo inhalation powder was e supplied in size 00 HPMC capsules, each at a nominal fill weight of 10 mg. Placebo inhalation powder is inhalation-grade lactose monohydrate, NF. The particle size of the lactose was selected to provide comparable head deposition of inhalation powder and to mimic the sensation of inhalation.

Two 90/8/2 dose levels were examined during the study: Dose Level 1 (DL1), approximately 35 mg LD fine particle dose (FPD) and Dose Level 2 (DL2) approximately

50 mg LD FPD per treated episode. The first dose of blinded inhaled study drug, DL1, was given in the clinic at Visit 3 (i.e., 2 capsule inhalations of either 90/8/2 or placebo); each 90/8/2 capsule delivers approximately 17.5 mg LD FPD. The first dose of blinded study drug at DL2 was administered in the clinic at Visit 5 (i.e., 3 capsule inhalations of either 90/8/2 or placebo).

The study had 3 periods: screening, treatment, and follow-up, with a total of 7 visits (2 screening visits, 4 treatment visits, and 1 follow-up visit). For each subject, the treatment period was approximately 4 weeks, and the study duration ranged from approximately 8 to 10 weeks. Each patient will self-administered up to 3 doses of inhaled study drug per day for 4 weeks. No change in the dose or dosing schedule of a subject's usual PD medications was permitted from screening until the final study visit.

Subject Eligibility

Male and female subjects between the ages of 30 and 80 years were eligible for participation in this study if they had idiopathic PD diagnosed after the age of 30 years; had met Steps 1 and 2 of the UK Brain Bank criteria; were classified as modified Hoehn and Yahr Stage 1-3 in an ON state; had experienced motor fluctuations for a minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) by self-report and confirmed by the PD diary; and showed acceptable LD responsiveness. Subjects must have been on a stable oral LD-containing therapy dose/regimen at least 2 weeks prior to Screening Visit 1; the LD/dopamine decarboxylase inhibitor (DDI)-containing regimen must have included a dose schedule administration at least 4 times during the waking day. Subjects should have been stable on other PD medications for at least 4 weeks prior to Screening Visit 1. Subjects must have had a $\geq$ 25% difference between UPDRS Part 3 scores recorded in their OFF and ON states at screening. Subjects must have understood (with or without caregiver assistance) and not changed their daily medication doses during the study. Subjects must have had normal cognition as confirmed by a score of $\geq$ 25 on the Mini-Mental State Examination (MMSE). Subjects must have had a screening FEV1 > 60% of predicted, and a FEV1/FVC ratio $\geq$ 75% of predicted by spirometry in the ON state at screening and no history of lung disease.

Evaluation Criteria and Endpoints

Study objectives and variables are described in Table 9.

Table 9 Study Objectives and Variables

Objective		Variable	Measurement
Priority	**Type**		
Primary	Efficacy	Mean change from predose in the average UPDRS Part 3 score at 10 to 60 minutes postdose at Visit 6	UPDRS Part 3
Secondary	In-Clinic Efficacy	Mean change from predose in the average UPDRS Part 3 score at 10 to 60 minutes postdose at Visit 4 (end of 1 week of treatment at DL1) and Visit 5 (first dose of DL2)	UPDRS Part 3
		Change and percent change from predose baseline in UPDRS Part 3 score at specified time points postdose	UPDRS Part 3
		Best change and best percent change from predose in the average UPDRS Part 3 motor score at 10 to 60 minutes postdose at all study visits	UPDRS Part 3
		Number and proportion of subjects achieving an 'objective motor response,' defined as a $\geq$ 20%, $\geq$ 30%, $\geq$ 6 point and $\geq$ 11 point reduction from predose in the UPDRS Part 3 motor score	UPDRS Part 3
		Examiner-rated time to resolution of an OFF episode to an ON state following observed treatment of subjects experiencing an OFF episode	Examiner observation and time elapsed from administration of study medication to ON state
		Occurrence and severity of dyskinesia following study medication administration	Examiner observation
	Out-Patient Efficacy	Mean daily OFF time, ON time without dyskinesia, and ON time with dyskinesia (troublesome and non-troublesome)	PD Diary

Objective		Variable	Measurement
Priority	**Type**		
		Patient reported mean time to resolution of a treated OFF episode to an ON state during the 2-week at-home period	Screening ON/OFF Episodes and Medication Log; Inhaled Medication Treatment Log
		Patient reported number and proportion of subjects achieving an objective motor response at specified time points postdose	Screening ON/OFF Episodes and Medication Log; Inhaled Medication Treatment Log
		Patient reported proportion of treated OFF episodes that resolve to an ON state overall and at prespecified categorical time points postdose	Screening ON/OFF Episodes and Medication Log; Inhaled Medication Treatment Log
Safety		Change from baseline in safety parameters over time and at Visit 3 and Visit 5 Potentially clinically significant change from baseline in safety parameters	Physical examination Vital signs (blood pressure, respiratory rate, and heart rate) Clinical laboratory values (hematology, biochemistry, and urinalysis) Electrocardiograms
		Change in pulmonary function from predose to postdose over time and at Visit 3 and Visit 5	Spirometry
		Adverse events	Adverse event monitoring at each visit
		Suicidality Daytime sleepiness Impulsive/compulsive disorders	C-SSRS Epworth Sleepiness Scale QUIP
Exploratory	Efficacy	Differences in motor responses between the 2 dose levels in the 90/8/2 treatment arm	UPDRS Part 3
		Change in PDQ-39 from baseline to Visits 5 and 6	PDQ-39
		PGI-C ratings measured at predose at Visits 5 and 6	PGI-C

Abbreviations: C-SSRS = Columbia Suicidal Severity Rating Scale; PD = Parkinson's disease; PDQ-39 = 39-Item Parkinson's Disease Questionnaire; PGI-C = Patient Global Impression of Change; QUIP = Questionnaire for Impulsive/Compulsive Disorders in Parkinson's; UPDRS = Unified Parkinson's Disease Rating Scale.

Efficacy was evaluated from both in-clinic and at-home (outpatient) assessments, as outlined by the following criteria:

In-clinic Criteria: UPDRS Part 3 motor score; time to resolution of an OFF episode to an ON state after study drug was administered in the clinic (per examiner assessment); occurrence, duration, and severity of dyskinesia following study medication administration.

At-home Criteria: Subject-reported time to resolution of an OFF episode to an ON state after study drug was administered (from Inhaled Medication Treatment Log), PD diary information on daily ON time without dyskinesia, ON time with dyskinesia (troublesome and non-troublesome), and OFF time.

Exploratory evaluations of the following were performed: PGI-C, PDQ-39, efficacy criteria as noted above (for evaluating potential differences between the 2 dose levels in the 90/8/2 treatment arm).

Safety was assessed from physical examination, adverse event (AE) reporting, standard and orthostatic vital signs (blood pressure, and heart rate), respiratory rate, clinical laboratory values (hematology, biochemistry, and), electrocardiograms (ECGs), and spirometry for evaluation of pulmonary function. In addition, evaluations for assessing suicidality, somnolence, and impulse control behaviors were performed at baseline and follow-up visits.

Baseline Characteristics

Eighty-six patients (86) were enrolled in the study. During the 3 consecutive days prior to Visit 2, patients completed a screening PD diary, recording their waking ON/OFF status (time OFF, time ON without dyskinesia, time ON with non-troublesome dyskinesia, time ON with troublesome dyskinesia) and time asleep. In addition, patients will complete a screening ON/OFF Episodes and Medication Log for the 7 days prior to Visit 2, recording the following information for each OFF episode experienced during the waking day: the time of start of the OFF episode, the time of start of the next ON, and how they used their standard LD medication.

Despite patients taking their current levodopa treatment regimen approximately every three hours; these patients reported being OFF approximately 1/3 to ½ of their waking hours (see Tables 10 and 11).

Table 10

	ALL (n = 86)
Age (yr)	**62.4 (8.7)**
Time since PD Dx (yr)	**9.4 (3.9)**
Duration of LD Tx (yr)	**7.8 (3.9)**
Time since emergence of fluctuations (yr)	**4.3 (3.6)**
Average OFF time per day (hr)	**3.5 (1.5) – Self 5.7 (1.8) – PDD***
Ave. # OFF episodes per day	**3.6 (1.1)**

***~1h early morning OFF (15-20% of total daily OFF time)**

Table 11

Mean (range)	**ALL (n = 86)**
Scheduled daily L-dopa doses	**5.9 (1.9)**
Inter-dose Interval (hr)	**~2.7**

Daily oral L-dopa dose	**770 (306) [250-1800]**
Other oral agents	**DAs ~65%** **COMT-Is ~40%** **MAO-Bs ~40%** **Amantadine ~33%**

Therefore, it is clear that management of OFF periods remains a significant unmet need for PD patients as indicated in Tables 12 and 13. Table 12 provides the average dosing regimen for each patient prior to receiving the study drug or a placebo.

Table 12

Phase 2b Study	**ALL (n = 86)**
Scheduled daily L-dopa doses	5.9 (1.9)
Inter-dose Interval (hr)	~2.7
Daily oral L-dopa dose	770 (306) [250-1800]
Other oral agents	DAs ~65% MAO-Bs ~40% COMT-Is ~40% Amantadine ~33%

Table 13 provides the average daily OFF and ON times as reported by patients in the diaries prior to receiving the study drug or placebo.

Table 13

PD diary	**ALL (n = 86)**
Total OFF time/day* (hr) (~1/3 of waking day)	**5.7 (1.8)** **(est. ~1h = early am OFF)**
N (%) with Daily OFF time **<4.5h/d** **≥4.5h/d**	25 (29.1) 61 (70.9)
ON Time (hr): **Without dyskinesia** **With non-troublesome dyskinesia** **With troublesome dyskinesia**	 8.0 (3.2) 1.8 (2.5) 0.4 (1.1)
Dyskinesia before V3*	50 (58.1)

* ≥1 hr/day of any dyskinesia on at least 2 days on PD diary

Baseline UPDRS Part 3 Scores were measured during the screening phase of the Phase 2b study and prior to either group receiving either study drug or placebo. The data is shown in Table 14.

TABLE 14

Mean(SD) **[Median; Range]**	**90/8/2** **N = 43**	**Placebo** **N = 43**	**ALL** **N = 86**
**********	**********	*******	********
UPDRS, Part 3 Score			
OFF	**35.0 (12.4)**	**36.2 (12.1)**	**35.6 (12.2)**
ON	**16.2 (8.1)**	**18.9 (9.7)**	**17.5 (9.0)**
OFF – ON Difference	18.8 (9.0)	17.3 (7.6)	**18.1 (8.3)**

OFF – ON % Difference	53.4 (15.8)	48.9 (15.9)	**51.1 (15.9)**
OFF – ON Difference (categorical)			
≥ 30% reduction	38 (88.4)	38 (88.4)	76 (88.4)
≥ 20% reduction	42 (97.7)	43 (100)	85 (98.8)
≥ 6 pt reduction	42 (97.7)	43 (100)	85 (98.8)
≥ 11 pt reduction	35 (81.4)	33 (76.7)	68 (79.1)

The total documented study days of exposure to either the study drug or placebo was about 6.5 patient years (2,369 patient days). The total number of treated OFF periods is equal to the total doses administered and was about 4,484 with placebo being administered 2314 doses and the Study Drug being administered 2369 doses. The total capsules of placebo or Study Drug used for the entire study was 11,115. One patient experienced a dose reduction for troublesome dyskinesia but that patient was on placebo. One patient on the Study Drug was given a dose reduction because of nausea. Based on the patients' own documentation, the average uses of the Study Drug per day were 2.1 uses per day which excludes the early morning "OFF" time.

Results

The primary endpoint of the Phase 2b study was to evaluate the difference between the Study Drug versus the placebo in the mean change from the pre-dose average UPDRS Part 3 score (10-60 minutes post dose) at Visit 6 (DL2). The same difference at Visit 4 using DL1 and Visit 5 (first dose of DL2) were used as secondary endpoints. In keeping with the UPDRS, a clinically important difference (CID) on the UPDRS motor score are 2.5 points for miminal, 5.2 points for moderate, and 10.8 points for large CIDs (Shulman et al., *Arch Neurol* , Vol. 67 (Jan 2010)).

90/8/2 met the primary endpoint of statistically significant reduction in mean UPDRS Part 3 motor score from placebo (over the time period of 10-60 minutes after dosing) at Visit 6 at the 50mg dose. 87% of patients achieved a clinically meaningful reduction in UPDRS III at the 60 minute time point. Further, 90/8/2 demonstrated clinically relevant and statistically significant reductions at all time-points (i.e., 10, 20, 30

& 60 minutes) evaluated for both tested doses (35mg and 50mg) at Visits 4, 5 and 6. Clinically relevant UPDRS III improvements were evident as early as 10 minutes post-dose. At Visit 6, following treatment with 90/8/2 (50 mg dose), clinically significant responses were sustained until at least 60 minutes post-dose. Differences between 90/8/2 and placebo were statistically significant at each post-dose time point.

Table 15 provides a comparison of UPDRS predose scores between the Study Drug group and the Placebo group at the prescreening and visit 4 (V4), visit 5 (v5) and visit 6 (v6). Dose level 1(DL1) was delivered at Visit 4, while Dose level 2 (DL2) was delivered at Visits 5 and 6.

Table 15

Mean (SD) [median]	90/8/2	Placebo
SCREENING	35.0 (12.4)	36.2 (12.1)
V4 (DL1)	33.0 (12.8)	34.2 (11.7)
V5 (DL2)	33.2 (10.9)	32.4 (13.3)
V6 (DL2)	33.0 (10.1)	33.7 (12.3)

As shown in FIGs. 9 and 10, there was a statistical difference between the Study drug administered at 50 mg FPD (Fig. 9) and 35 mg (Fig. 10) at every time point.

Table 16 provides the Average Best UPDRS Part 3 change for each of Visits 4-6.

	Pbo	90/8/2
Visit 4*	-7.9 (1.2)	-13.0 (1.5)
Visit 5*	-5.8 (1.2)	-14.3 (1.7)
Visit 6*	-5.8 (1.4)	-13.9 (1.5)

Mean (SEM)

* Statistically significant difference at all visits

Table 17 shows the average best percent (%) UPDRS Part 3 change for each of Visits 4-6.

	Pbo	90/8/2
Visit 4*	-25.1 (3.7)	-38.0 (4.5)
Visit 5*	-16.0 (3.8)	-42.2 (4.2)
Visit 6*	-16.2 (4.0)	-42.5 (4.1)

Mean (SEM)

* Statistically significant difference at all visits

Summary

As per the data provided herein, the Phase 2b Study achieved its primary endpoint showing a statistically significant mean change from predose in the average UPDRS Part 3 score at 10 to 60 minutes postdose at Visit 6 as compared to placebo. The data also showed that the shape of the UPDRS time curves indicated both rapid and durable responses with the 35 mg dose (DL1) having a similar amplitude to the 50 mg dose (DL2) but potentially with a slightly shorter duration of effect. The Best Change and Best Percent Change in UDPRS Part 3 scores were also statistically significant across all visits and the doses with significant separation even at V4 (DL1) before attenuation of the placebo response.

Together the data showed a robust clinically meaningful and statistically significant improvement in daily OFF time without increase in ON time with dyskinesia as shown in FIG. 11. FIG. 11 shows data reporting troublesome and non-troublesome

dyskinesia in patients (as self-reported in their respective PD diaries) tested in the Study Drug group as compared to the placebo group. The Studies of Example 1 and 2 and the present Example also show that the drug is safe ant well tolerated at all dose levels tested in all Phase 1, 2a and 2b studies.

The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims. It should also be understood that the embodiments described herein are not mutually exclusive and that features from the various embodiments may be combined in whole or in part in accordance with the invention.

CLAIMS

What is claimed is:

1. A method for treating OFF episodes in a Parkinson's Disease (PD) patient comprising administering levodopa to the pulmonary system of a patient wherein after administration, the patient's Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 score is improved by at least 10 points as compared to placebo control within 60 minutes following administration of said FPD of levodopa, wherein the patient is administered 30 mg to about 60 mg fine particle dose (FPD) of levodopa to the pulmonary system, wherein the patient does not experience increased dyskinesis as compared to the level of dyskinesis prior to pulmonary administration of said levodopa, wherein the patient has about 4 to about 8 hours of OFF episodes a day.

2. The method of claim 1, wherein the patient has about 3 to about 4 OFF episodes a day.

3. The method of claim 1, wherein the contents of at least one capsule containing said FPD of levodopa is administered to the patient via inhalation.

4. The method of claim 3, wherein the contents of at least two capsules comprising said FPD of levodopa is administered to the patient via inhalation.

5. The method of claim 3, wherein the fine particle dose of levodopa is delivered from said at least one capsule to the pulmonary system by an inhalation device.

6. The method of claim 5, wherein the inhalation device is a dry powder inhaler (DPI) or a metered-dose inhaler (MDI).

7. The method of claim 1, wherein said administration occurs at the emergence of OFF symptoms.

8. A method for reducing the mean daily OFF time in a Parkinson's Disease patient comprising administering levodopa to the pulmonary system of a patient at least twice a day wherein the patient's mean daily OFF time is reduced by at least one hour wherein the patient is administered about 30 mg to about 60 mg fine particle dose (FPD) of levodopa to the pulmonary system, wherein the patient does not experience increased dyskinesis as compared to the level of dyskinesis prior to pulmonary administration of said levodopa.

9. The method of claim 8, wherein the patient's mean daily OFF time is reduced by at least 3 hours.

10. The method of claim 8, wherein the patient has about 3 to about 4 OFF episodes a day.

11. The method of claim 8, wherein the patient has about 4 to about 8 hours of OFF episodes a day.

12. A method for delivering levodopa to a Parkinson's Disease patient comprising administering levodopa to the pulmonary system of a patient, wherein the patient's Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 score is improved by at least 8 points as compared to the patient's UPDRS score prior to administration within 60 minutes following administration of said FPD of levodopa, wherein the patient is administered about 30 mg to about 60 mg FPD of levodopa to the pulmonary system.

13. A method for delivering levodopa to a Parkinson's Disease patient comprising administering levodopa to the pulmonary system of a patient wherein after administration, the patient's Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 score is improved by at least 5 points as compared to placebo control within 60 minutes following administration of said FPD of levodopa, wherein the patient is administered about 30 mg to about 60 mg FPD of levodopa to the pulmonary system, wherein the patient does not experience increased dyskinesis as compared to the level of dyskinesis

prior to pulmonary administration of said levodopa, wherein said administration occurs at the emergence of OFF symptoms.

14. The method of claim 13, wherein the contents of at least one capsule containing said FPD of levodopa is administered to the patient via inhalation.

15. The method of claim 14, wherein the contents of at least two capsules comprising said FPD of levodopa are administered to the patient via inhalation.

16. The method of claim 14, wherein the fine particle dose of levodopa is delivered from said at least one capsule to the pulmonary system by an inhalation device.

17. The method of claim 14, wherein the inhalation device is a dry powder inhaler (DPI) or a metered-dose inhaler (MDI).

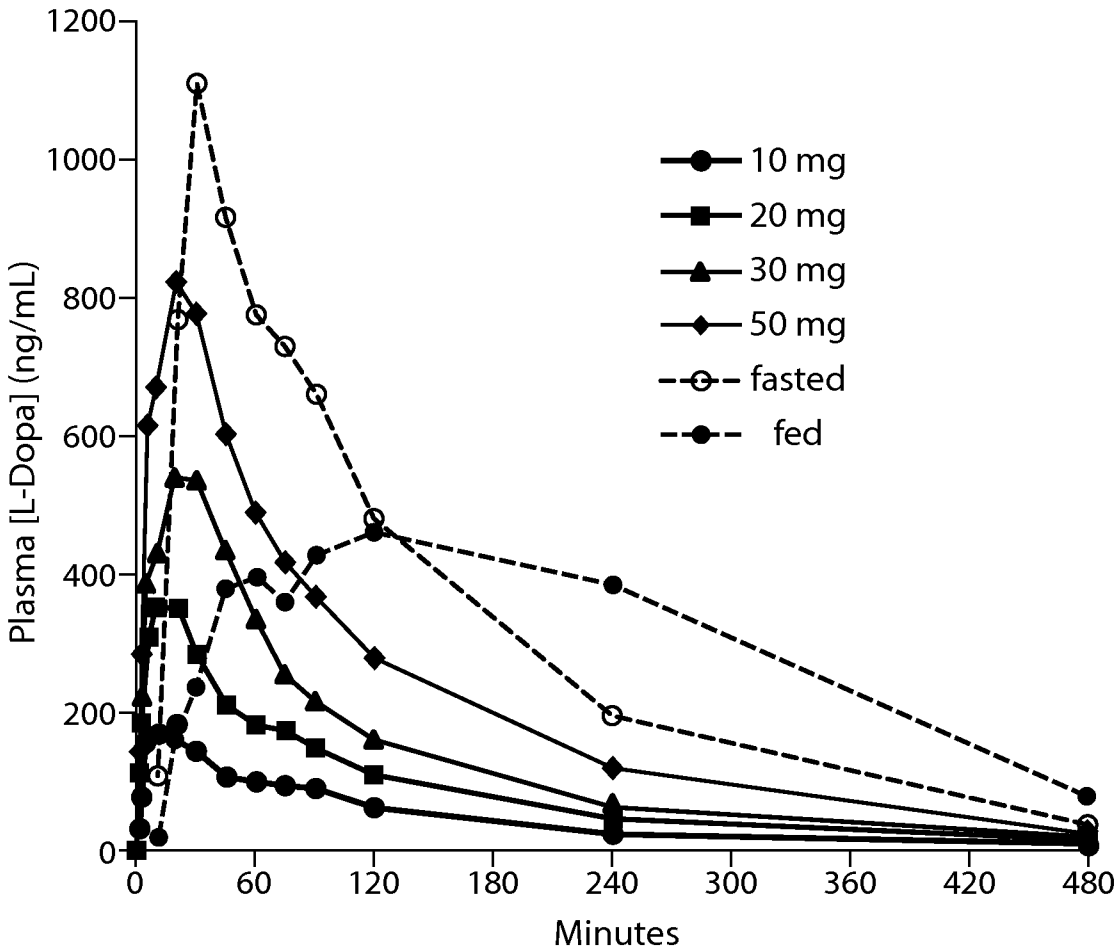

1200
1000
800
600
400
200
0
Plasma [L-Dopa] (ng/mL)
0
60
120
180
240
300
360
420
480
Minutes
10 mg
20 mg
30 mg
50 mg
fasted
fed

Fig. 1

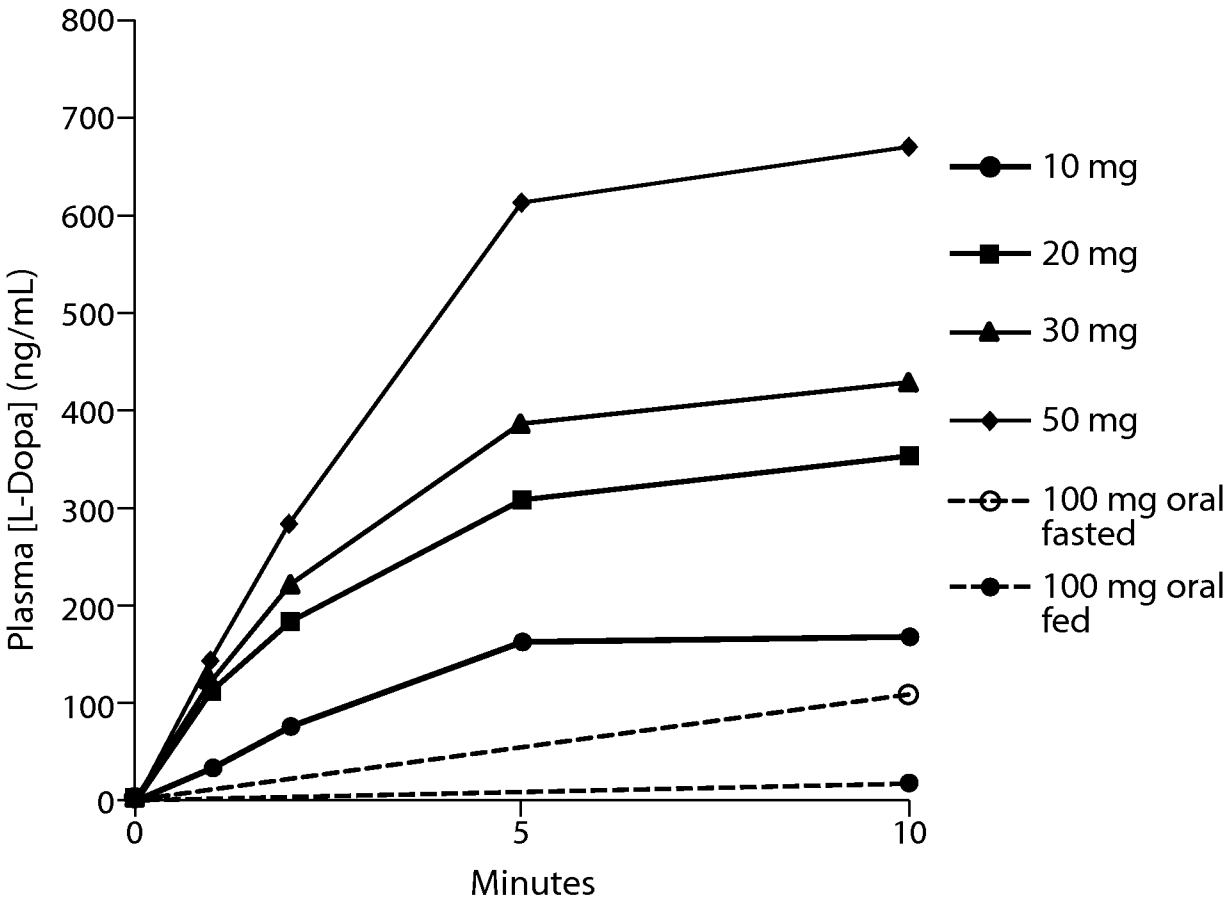

800
700
600
500
400
300
200
100
0
Plasma [L-Dopa] (ng/mL)
0
5
10
Minutes
10 mg
20 mg
30 mg
50 mg
100 mg oral fasted
100 mg oral fed

Fig. 2

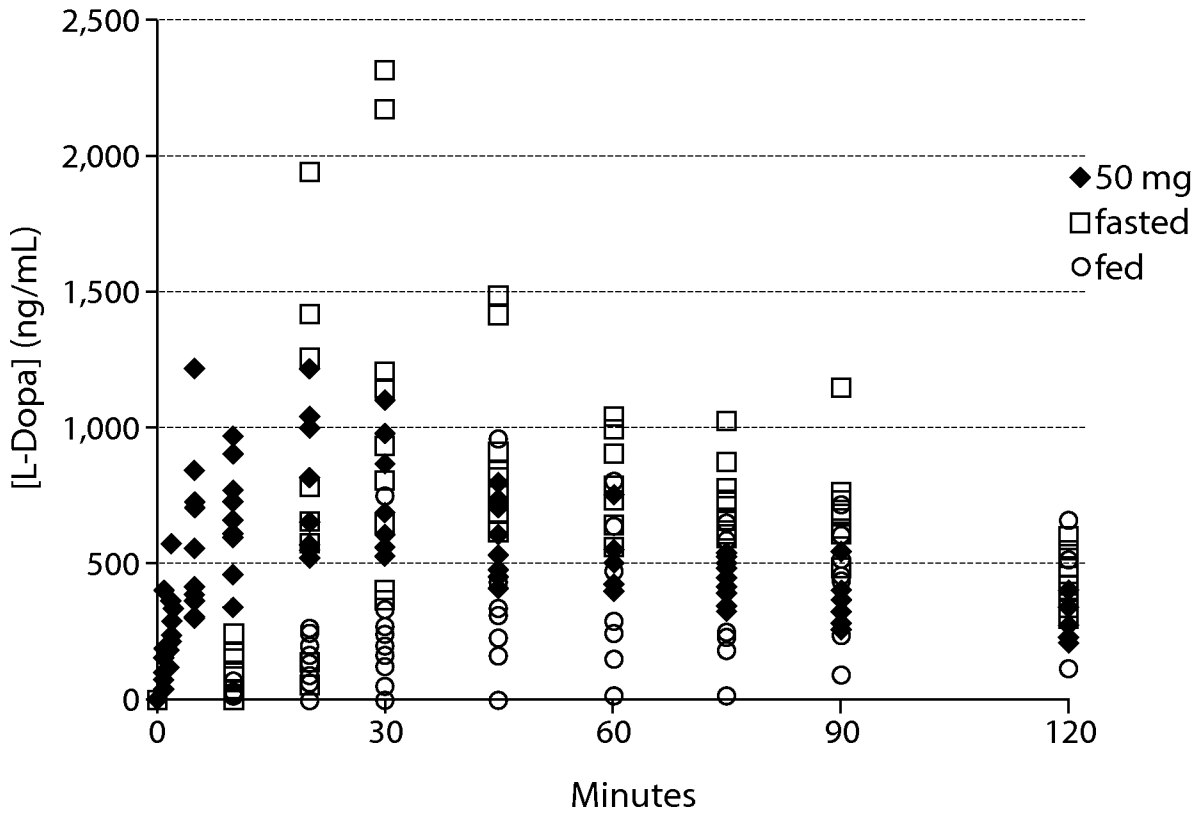

2,500
2,000
1,500
1,000
500
0
[L-Dopa] (ng/mL)
0
30
60
90
120
Minutes
50 mg
fasted
fed

Fig. 3

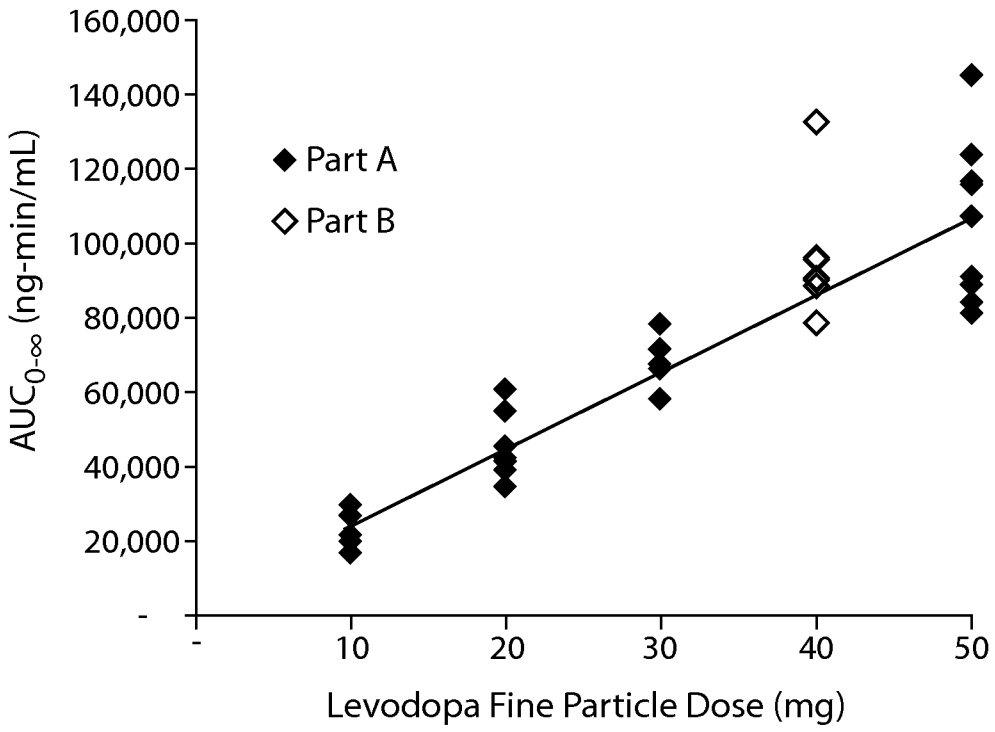

160,000
140,000
120,000
100,000
80,000
60,000
40,000
20,000
-
AUC0-∞ (ng-min/mL)
Part A
Part B
-
10
20
30
40
50
Levodopa Fine Particle Dose (mg)

Fig. 4

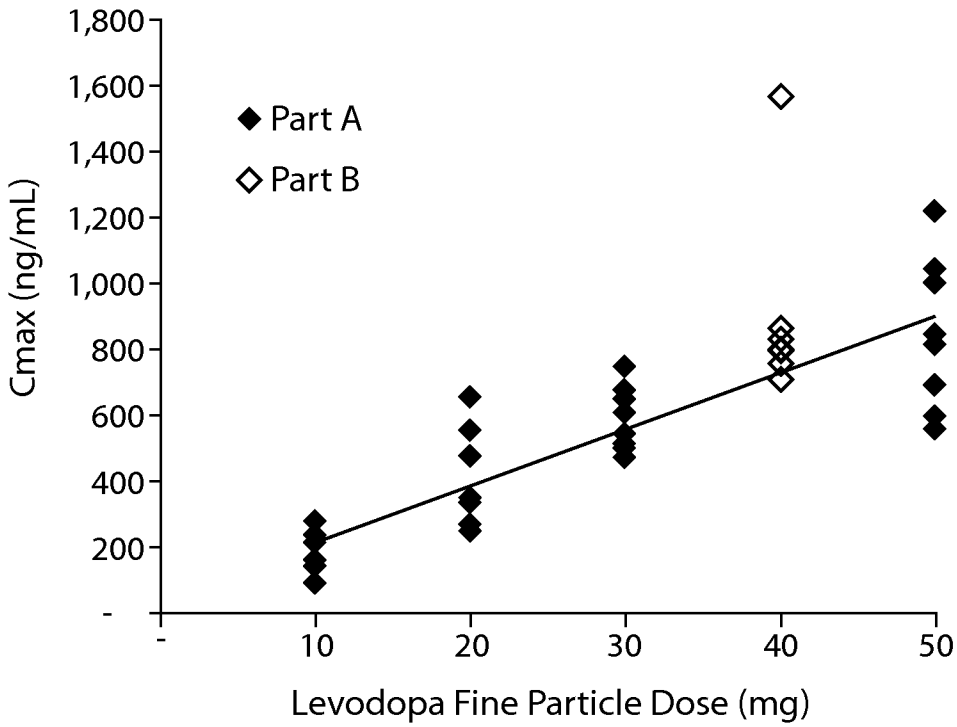

1,800
1,600
1,400
1,200
1,000
800
600
400
200
-
Cmax (ng/mL)
Part A
Part B
-
10
20
30
40
50
Levodopa Fine Particle Dose (mg)

Fig. 5

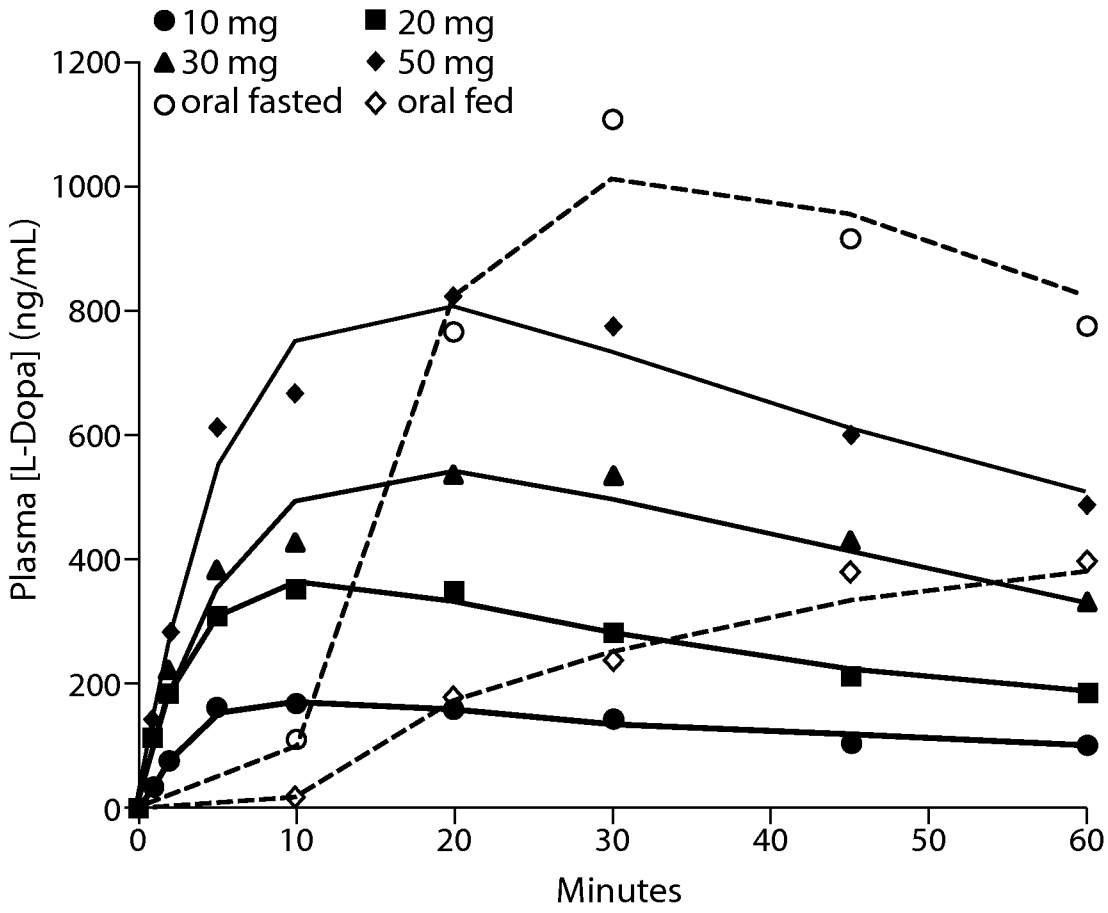

10 mg
20 mg
30 mg
50 mg
oral fasted
oral fed
Plasma [L-Dopa] (ng/mL)
1200
1000
800
600
400
200
0
0
10
20
30
40
50
60
Minutes

Fig. 6

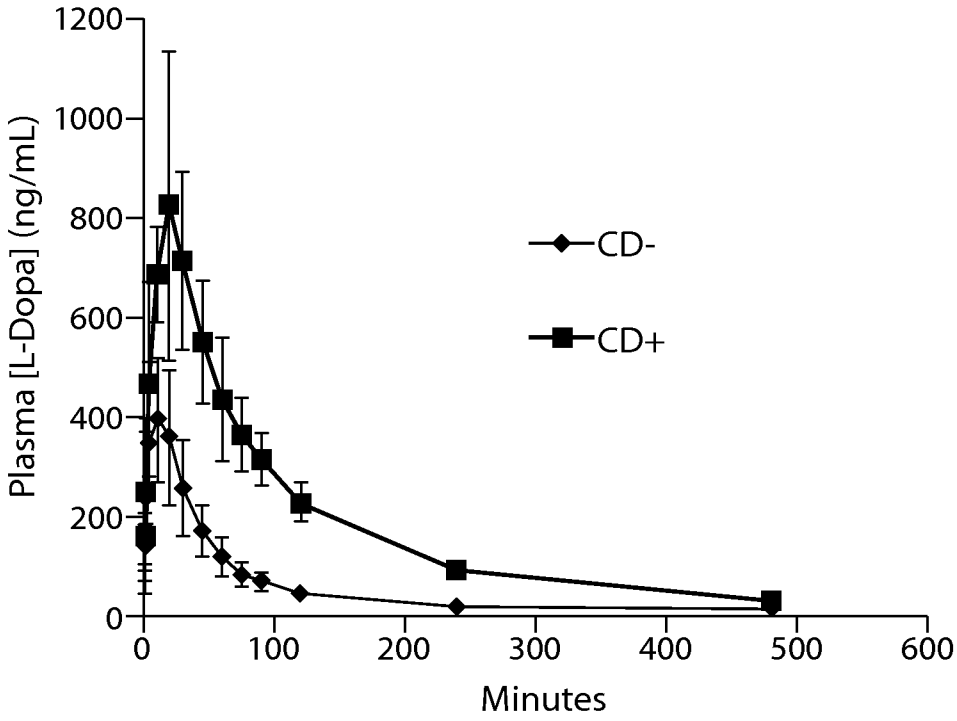

1200
1000
800
600
400
200
0
Plasma [L-Dopa] (ng/mL)
0
100
200
300
400
500
600
Minutes
CD-
CD+

Fig. 7

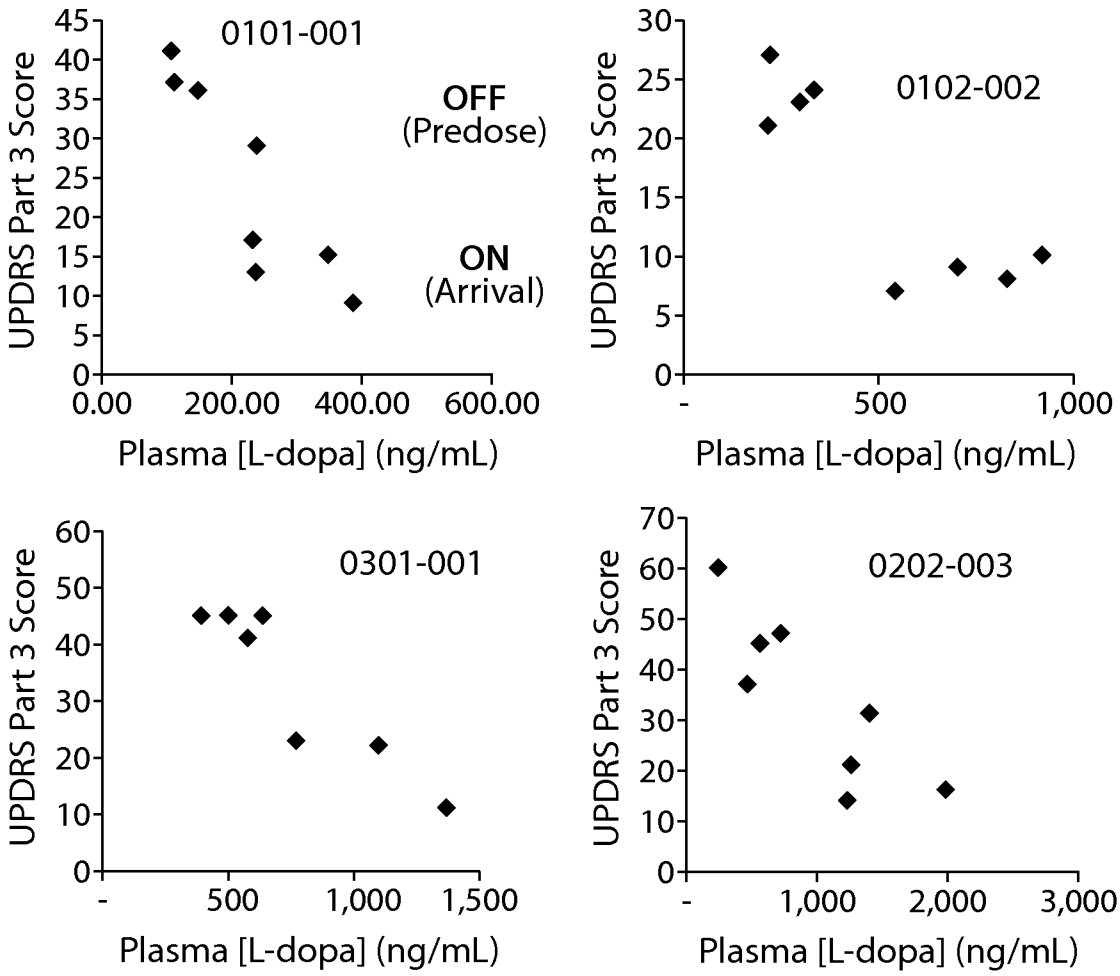

0101-001
OFF
(Predose)
ON
(Arrival)
UPDRS Part 3 Score
Plasma [L-dopa] (ng/mL)
0102-002
0301-001
0202-003

Fig. 8

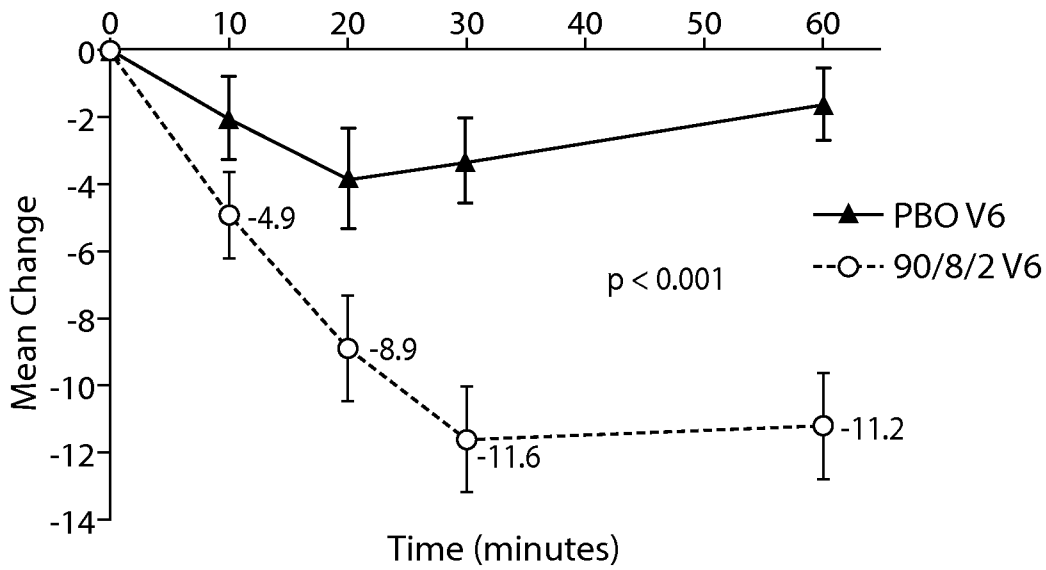

0
10
20
30
40
50
60
0
-2
-4
-6
-8
-10
-12
-14
Mean Change
-4.9
-8.9
-11.6
-11.2
p < 0.001
PBO V6
90/8/2 V6
Time (minutes)

Fig. 9

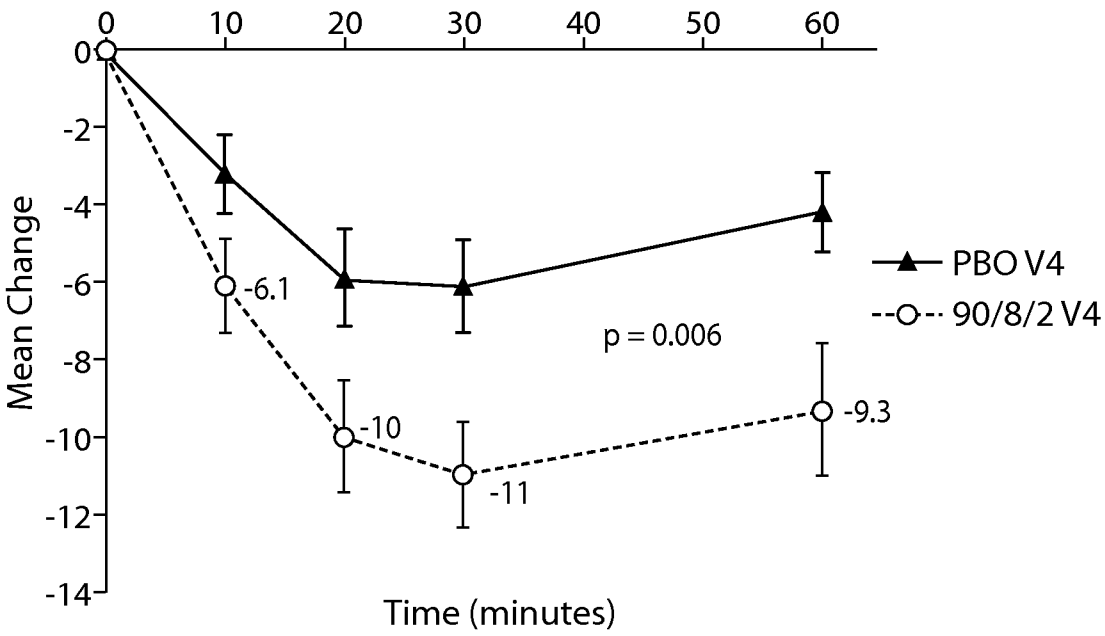

0
10
20
30
40
50
60
0
-2
-4
-6
-8
-10
-12
-14
Mean Change
-6.1
-10
-11
-9.3
p = 0.006
PBO V4
90/8/2 V4
Time (minutes)

Fig. 10

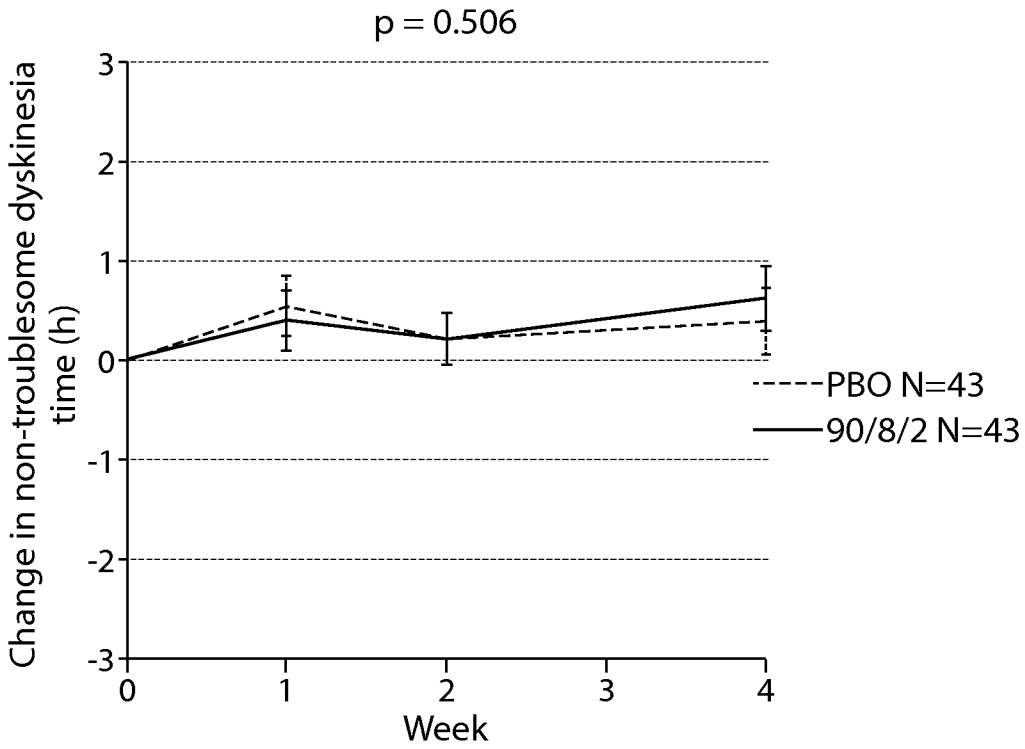


Fig. 11A

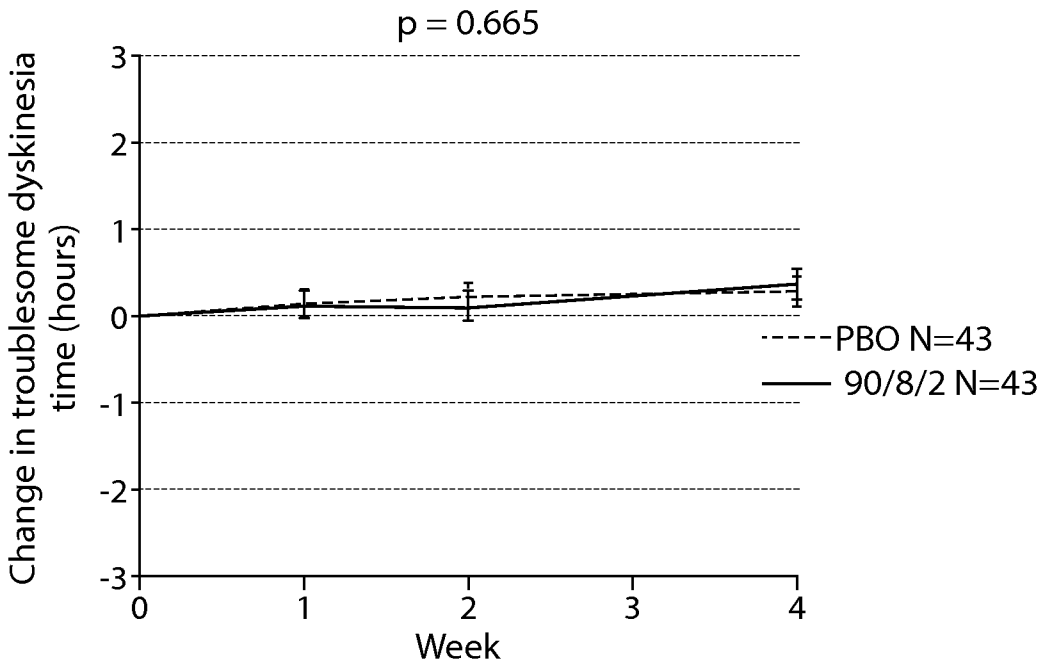


Fig. 11B