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Title Page

Title:

Pharmacokinetic/Pharmacodynamic Correlation Analysis of Amantadine for Levodopa-Induced Dyskinesia

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Running Title Page

Running Title: PK/PD Analysis of Amantadine for Levodopa-Induced Dyskinesia

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Number of text pages: 15

Number of tables: 1

Number of figures: 4

Number of references: 35

Number of words in the Abstract (≤ 250): 242

Number of words in the Introduction (≤ 750): 750

Number of words in the Discussion (≤ 1500): 760

List of Nonstandard Abbreviations

6-OHDA, 6-hydroxydopamine

AE, adverse event

AIMS, abnormal involuntary movements

ALO, axial, limb, and orolingual

AUC_{inf}, area under plasma concentration-time curve at infinity

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CI, confidence interval

C_{max}, maximal plasma concentrations

CNS, central nervous system

CRL, Charles River Laboratories

EC_{50}, 50% effective plasma concentrations

E_{max}, maximum possible effect

IP, intraperitoneal

IR, immediate-release

IV, intravenous

LID, levodopa-induced dyskinesia

MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

NHP, nonhuman primate

NMDA, N-methyl-d-aspartate

PK/PD, pharmacokinetic/pharmacodynamic

PK, pharmacokinetics

SC, subcutaneous

UDysRS, Unified Dyskinesia Rating Scale

Recommended section assignment: Behavioral Pharmacology

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ABSTRACT

Dyskinesia is a common motor complication associated with the use of levodopa to treat Parkinson's disease. Numerous animal studies in mice, rats, and non-human primates have demonstrated that the NMDA antagonist, amantadine, dose dependently reduces levodopa-induced dyskinesia (LID). However, none of these studies characterized the amantadine plasma concentrations required for a therapeutic effect. This study evaluates the pharmacokinetic-pharmacodynamic (PK/PD) relationship between amantadine plasma concentrations and antidyskinetic efficacy across multiple species to define optimal therapeutic dosing. The pharmacokinetic profile of amantadine was determined in mice, rats, and macaques. Efficacy data from the 6-OHDA-rat and MPTP-macaque model of LID, along with previously published antidyskinetic efficacy data, were used to establish species-specific PK/PD relationships using a direct effect E_{max} model. Results from the PK/PD model were compared with amantadine plasma concentrations and antidyskinetic effect in a phase 2 study in patients with Parkinson's disease treated with ADS-5102, an extended release amantadine capsule formulation. Outcomes from each of the species evaluated indicate that the 50% effective plasma concentrations (EC_{50}) of amantadine for reducing dyskinesia range from 1025 to 1633 ng/mL (1367 ng/mL for an all-species model). These data are consistent with the mean amantadine plasma concentrations observed in patients with Parkinson's disease (~1500 ng/mL) treated with ADS-5102 at doses that demonstrated a statistically significant reduction in dyskinesia. These results demonstrate that the EC_{50} of amantadine for reducing dyskinesia is consistent across multiple species and provides a plasma concentration target of ~1400 ng/mL to achieve therapeutic efficacy.

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Introduction

Dopamine replacement therapy with the dopamine precursor, L-3,4-dihydroxyphenylalanine (levodopa), remains the most effective symptomatic treatment for Parkinson's disease. However, long-term treatment with levodopa often leads to the development of motor complications including dyskinesia, which is characterized by involuntary movements that are nonrhythmic, purposeless, and may be unpredictable in onset and severity.. In patients treated with levodopa, dyskinesia can develop early, affects nearly 90% of such patients within approximately 10 years of treatment (Ahlskog and Muenter, 2001), and has a substantial adverse effect on quality of life (Suh et al., 2012).

Although the progressive loss of dopaminergic neurons is the hallmark of Parkinson's disease, the dysregulation of glutamatergic signalling pathways is a major contributor to the development and expression of dyskinesia (Sgambato-Faure and Cenci, 2012). Adaptations to fluctuating levels of dopamine and loss of dopamine modulation has been associated with increased concentrations of extracellular glutamate in animal models (Jonkers et al, 2002; Robelet et al, 2004; Dupre et al, 2011), and increased expression and/or increased activity of the N-methyl-d-aspartate (NMDA)-type glutamate receptor in animal models and humans (Calon et al., 2002). The role of glutamate dysregulation in the development and expression of dyskinesia is supported by the antidyskinetic activity of diverse NMDA receptor antagonists in animal models of Parkinson's disease and in humans. For example, a competitive NMDA receptor antagonist (LY235959) significantly decreased dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned parkinsonian nonhuman primates (NHPs) treated with levodopa (Papa and Chase, 1996). Treatment with the high-

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affinity, uncompetitive NMDA receptor antagonist, MK-801, in rodent and NHP models of levodopa-induced dyskinesia (LID) resulted in reduced dyskinesia (Bibbiani et al., 2005), and treatment with dextromethorphan, also an uncompetitive NMDA receptor antagonist, reduced dyskinesia in humans with Parkinson's disease (Verhagen Metman et al., 1998a).

Amantadine is a low-affinity, uncompetitive NMDA receptor antagonist (Parsons et al., 1995). Numerous studies in mice, rats, and NHPs have demonstrated that amantadine reduces dyskinesia in models of LID in a dose-dependent manner. In mouse and rat, effective doses of amantadine ranged from 10–60 mg/kg (subcutaneous [SC] or intraperitoneal [IP] administration) in the 6-hydroxydopamine (6-OHDA) model. Amantadine had a consistent benefit at ≥40 mg/kg, whereas lower doses had variable effects (Dekundy et al., 2007; Bido et al., 2011; Kobylecki et al., 2011; Paquette et al., 2012; Papathanou et al., 2014; Bortolanza et al., 2016; Sebastianutto et al., 2016). In NHPs (cynomolgus macaques and marmosets) administered MPTP to induce parkinsonian disability, chronic treatment with levodopa produces dyskinesia similar to humans. Acute treatment (oral or SC) with amantadine at 0.3–30 mg/kg resulted in significant reduction of dyskinesia (Blanchet et al., 1998; Hill et al., 2004; Bibbiani et al., 2005; Kobylecki et al., 2011; Bezard et al., 2013; Gregoire et al., 2013; Ko et al., 2014). Results from multiple small clinical studies indicate an immediate-release (IR) form of amantadine provides antidyskinetic benefits in patients with Parkinson's disease, with efficacy increasing at higher plasma concentrations (Verhagen Metman et al, 1998b).

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Despite a half-life of approximately 17 hours, the total daily dose of amantadine IR is typically split to two- or three-times daily administration due to dose-limiting central nervous system (CNS) adverse events (AEs) associated with once-daily dosing (Parkes et al., 1970; Hayden et al., 1983). Higher doses that may produce a greater antidyskinetic effect are associated with increased frequency of CNS AEs, such as dizziness, hallucinations, and sleep disturbances (Parkes et al., 1970). ADS-5102 (amantadine) extended release capsule (GOCOVRI™, Adamas Pharmaceuticals, Inc., Emeryville, California) is the first and only US Food and Drug Administration-approved medicine for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications. The recommended dose of ADS-5102 for the treatment of dyskinesia is 274 mg once daily at bedtime (equivalent to daily 340-mg amantadine HCl). Bedtime administration of ADS-5102 provides high amantadine plasma concentrations in the morning, which are sustained throughout the day when dyskinesias occur (Hauser RA, Pahwa R, Wargin W, et al. Pharmacokinetics of ADS-5102 [amantadine] extended release capsules administered once-daily at bedtime for the treatment of dyskinesia. [Submitted]). Multiple randomized, placebo-controlled trials demonstrated that ADS-5102 significantly reduced dyskinesia in patients with Parkinson's disease treated with levodopa, with a secondary benefit of reduced OFF-time associated with motor complications (Pahwa et al., 2015; Oertel et al., 2017; Pahwa et al., 2017).

To date, none of the reported animal studies included a determination of amantadine plasma concentrations required to obtain a therapeutic effect. The objective of the current analysis was to determine the amantadine plasma concentrations required to reduce dyskinesia in

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multiple species and any correlations across species. The pharmacokinetic (PK) profile of amantadine was determined in mice, rats, and cynomolgus macaques, and the efficacy of amantadine in reducing LID was assessed in Parkinson's disease models (6-OHDA-rat and MPTP-macaque). The PK data were used to build species-specific PK-models that were applied to new efficacy data reported herein and previously published efficacy data in mice, rats, and macaques. A pharmacokinetic/pharmacodynamic (PK/PD) relationship was established to determine the 50% effective plasma concentrations (EC_{50}) of amantadine required for the reduction of dyskinesia in these LID animal models. In a recent clinical study, amantadine plasma concentrations associated with antidyskinetic efficacy of ADS-5102 were reported in patients with Parkinson's disease (Pahwa et al., 2015); these concentrations were compared with the results of the model. These results provide the rationale for target therapeutic plasma amantadine concentrations, with the goal of maximizing antidyskinetic efficacy, in patients with Parkinson's disease treated with levodopa as well as supporting the validity of these animal models for testing novel antidyskinetic drugs.

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Methods

The PK time-course of amantadine plasma levels was determined in mice (8 per group), rats (6 per group), and macaques (8 per group), and efficacy was evaluated in rat and macaque models of Parkinson's disease with established LID (n = 6 per group for rats and 8 per group for macaques). All studies were performed with local Institutional Animal Care and Use Committee approval as well as in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the National Health Institute Committee on Care and Use

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of Laboratory Animals (1996). The mouse PK study was conducted at Charles River Laboratories (CRL; Wilmington, Massachusetts) in normal C57BL/6J mice (The Jackson Laboratory, Sacramento, California), the rat PK study was conducted at CRL (Wilmington, Massachusetts) in normal Sprague Dawley rats (CRL, Raleigh, North Carolina), and the NHP PK and LID efficacy study was conducted at Atuka (Suzhou, People's Republic of China) in levodopa-treated MPTP macaques (*Macaca fascicularis*, Suzhou Xishan Zhongke Laboratory Animal Company, People's Republic of China).

Blood samples (0.1-0.15mL) were collected at the time points specified for each species below and collected plasma was stored frozen (–70°C to –80°C) until processed and analyzed by liquid chromatography-tandem mass spectrometry as described in the bioanalysis section of the Supplemental Materials. A rat LID efficacy study was conducted at Atuka (Toronto, Ontario, Canada) in levodopa-treated 6-OHDA-lesioned Sprague Dawley rats (CRL, Senneville, Quebec, Canada). Plasma concentrations were reported in this experiment. Additional pharmacodynamic data were included from a selection of publications that reported antidyskinetic efficacy in mouse, rat, or cynomolgus macaque to support the PK/PD model. In addition, amantadine plasma concentrations and antidyskinetic efficacy data from a phase 2 study in Parkinson's disease patients treated with ADS-5102, an extended release amantadine capsule formulation (Pahwa et al., 2015), were compared with the model. Greater detail for all rodent, macaque, and human studies is provided in Supplemental Materials.

PK Studies and PK Modelling. Normal male and female C57BL/6J mice were administered a single IP dose of 10, 30, or 60 mg/kg amantadine HCl (MOEHS Catalana, S.L., Barcelona,

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Spain), and sparse blood samples were collected from the submandibular vein at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours after dosing. Each mouse contributed 2 samples to the analysis, and each time point represented samples from 4 animals per sex.

Normal male and female Sprague Dawley rats were administered a single IP dose of 15, 45, or 90 mg/kg amantadine HCl (Sigma-Aldrich, St. Louis, Missouri), and blood samples were obtained via jugular vein cannula at predose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after dosing. Plasma also was collected in levodopa-treated 6-OHDA-lesioned rats infused SC continuously for 12 days with amantadine via ALZET pump (see below).

Four oral doses of amantadine (1, 3, 10, and 30 mg/kg) were given to each of 8 MPTP-lesioned macaques in an ascending, nonrandomized treatment design after an overnight fast. Blood samples were collected from the saphenous vein at predose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours postdose. A 1-week washout occurred between each treatment.

Time-course PK data for each species were fit to an appropriate model and curve using Phoenix WinNonlin version 6.3 (Build 6.3.0.395; Certara, Princeton, New Jersey). For each species, the critical constants for the exposure-time curve for each dose level were averaged to produce a dose-independent exposure-time curve that could be used to simulate exposure-time curves for dose levels used in the literature for which no experimentally determined PK data were available.

Behavioral Assessment of Effects of Amantadine on Dyskinesia and Abnormal

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Involuntary Movements (AIMs). Overview. Results from a 6-OHDA rat study and a MPTP macaque study described below along with the previously published studies identified in Supplemental Table 1 were used as the data source for the effect of amantadine on NHP dyskinesia or the rodent correlate (AIMs). Published mouse and rat studies in which amantadine was administered IP and reported a time-course of reduction of AIMs after levodopa treatment, and published NHP studies in which macaques received oral amantadine, were included in the analyses. Variations in the key study design components are also presented in Supplemental Table 1.

Continuous Amantadine Administration in 6-OHDA–Lesioned Rats. Female Sprague Dawley rats (6 per group) received unilateral nigrostriatal dopaminergic lesions of the median forebrain bundle using standard stereotaxic techniques (Paxinos and Watson, 1986). Only animals demonstrating ≥85% asymmetry score in the forelimb asymmetry cylinder test were included in the study. These animals were treated with 10 mg/kg levodopa methyl ester HCl in combination with 15 mg/kg benserazide HCl once daily IP in a dose volume of 1 mL/kg for 58 days to induce stable AIMs.

Three subtypes of AIMs (axial, limb, and orolingual [ALO]) were assessed (Supplemental Materials). Animals were observed for 1 minute before levodopa treatment and 1 minute every 20 minutes for 3 hours after levodopa treatment. Animals obtaining a score of 3 (marked) or 4 (severe) for AIMs during at least 1 assessment point were included in the study. Animals were assigned to treatment groups so that the baseline AIMS scores (via blinded assessment) were not different between each group. ALZET osmotic pumps (model

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2ML2, 5 μL/h, 14-day pump; Cupertino, California) containing either vehicle (25 mM sodium acetate buffer, pH 5.0) or amantadine HCl delivering 22.5, 45, or 83 mg/kg per day SC were used. During the amantadine treatment period, all animals received once-daily IP levodopa (10 mg/kg levodopa/15 mg/kg benserazide), and the effects of treatments on AIMs were assessed on treatment day 12 as described in the Supplemental Materials. Cumulative AIMs (20–120 min) resulting from the levodopa challenge on amantadine treatment day 12 was compared with cumulative AIMs scored at baseline, before pump implantation.

Referenced AIMs Data From Published Rodent Studies. In addition to the de novo efficacy data generated and reported herein, efficacy data from mouse and rats studies were collected from literature reports (Bido et al., 2011; Papathanou et al., 2014; Bortolanza et al., 2016; Sebastianutto et al., 2016), in which amantadine was administered as a single IP dose; ALO AIMs in these reported studies were assessed as described in the Supplemental Materials and Supplemental Table 1. Where not explicitly provided, AIMs data were extracted using WebPlotDigitizer (version 3.6).

Oral Administration of Amantadine in MPTP Macaques. For the NHP, both de novo efficacy data reported here as well as data obtained from literature reports were utilized to build the PK/PD model (Bezard et al., 2013; Gregoire et al., 2013; Ko et al., 2014). For our study, the development of the MPTP-macaque LID model is described in the Supplemental Materials.

For efficacy assessments, in an acute-challenge randomized design, each of 8 macaques was

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administered (via oral gavage) vehicle (water) or 4 doses of amantadine (1, 3, 10, or 30 mg/kg) after an overnight fast. Amantadine or vehicle was administered 1 hour before levodopa, and dyskinesia was assessed over a 6-hour period of observation (Supplemental Materials). A 72-hour washout period occurred between treatments. Data derived from assessment of NHP measures of dyskinesia were graphed as median scores (time-course).

For the efficacy data from the literature (Bezard et al., 2013; Gregoire et al., 2013; Ko et al., 2014) included in the NHP PK/PD analysis, the severity of dyskinesia was rated using dyskinesia scales described in the original publication and summarized in Supplemental Table 1. Where not explicitly provided, dyskinesia data were extracted using WebPlotDigitizer (version 3.6).

PK/PD Analysis. A similar methodology was used for all species. Simulated PK exposure-time curves were used to provide plasma levels of amantadine at the time points post amantadine treatment that correlated with the AIMs or dyskinesia observations time points described below. Peak dyskinesia or AIMs generally occur beginning approximately 20 minutes after administration of levodopa and are sustained through 120 minutes post levodopa administration. Amantadine plasma concentrations were used to assess the exposure-response relationship for reduction of dyskinesia at time points in which moderate dyskinesia was measured in the vehicle group (Supplemental Fig. 1). Values less than zero were assigned a value of zero. For the PK/PD relationship, a sigmoidal maximum possible effect (E_{max}) model using Prism version 3.6 (GraphPad Software, La Jolla, California) was fit to the data assuming an E_{max} of 100%. Details of doses and time points from previously

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published rodent and macaque studies are provided in Supplemental Materials and Supplemental Table 1.

Results

Amantadine PK/PD Analysis in Mice. The mean amantadine plasma concentration-time profiles after IP administration of a single dose of amantadine (10, 30, or 60 mg/kg) in mice are displayed in Fig. 1A. Amantadine exposures increase proportionally with dose over this range, with mean maximal plasma concentrations (C_{max}) ranging from 1268−8826 ng/mL and mean area under plasma concentration-time curve at infinity (AUC_{inf}) ranging from 1781−13,877 ng·h/mL (Table 1). The composite profile of each dose was modelled using a 1-compartment model with an intravenous (IV) bolus to optimize the fit to C_{max}, and the average parameters (Table 1) were used to simulate a 40-mg/kg dose (Fig. 1B). Bido et al. (2011) and Sebastianutto et al. (2016) demonstrated that 40 mg/kg amantadine IP decreased AIMs as a function of time after a levodopa challenge, achieving a maximum reduction of 76% and 42%, respectively, compared with vehicle.

Percent reduction in AIMs was plotted as a function of simulated amantadine plasma concentrations (Fig. 1C). A sigmoidal E_{max} model provided a good fit for the data with an amantadine EC_{50} of 1145 ng/mL (95% confidence interval [CI], 756–1735 ng/mL) for the reduction of AIMs (Supplemental Table 2).

Amantadine PK/PD Analysis in Rats. The mean amantadine concentration-time profile for single IP dose administration in rats is displayed in Fig. 1D. Plasma concentrations were dose

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proportional between 15 and 45 mg/kg, which was most appropriate for the range used in the LID efficacy studies. The mean C_{max} for 15 and 45 mg/kg doses were 2769 and 6982 ng/mL, respectively, and the mean AUC_{inf} estimates were 4199 and 14,114 ng·h/mL, respectively (Table 1). A 2-compartment IV bolus model using the full time-course of available data (12 hours) was fit to the 15- and 45-mg/kg dose data (Table 1), and the average parameters were used to simulate PK profiles for 10-, 20-, and 40-mg/kg doses (Fig. 1E).

Two previous publications, Papathanou et al. (2014) and Bortolanza et al. (2016) demonstrated a dose-dependent reduction of AIMs after a single IP dose of 10, 20, or 40 mg/kg amantadine in the 6-OHDA rat model with a maximum reduction of AIMs >75%. In another publication, Bido et al. (2011) demonstrated that 40 mg/kg amantadine IP decreased AIMs, achieving a maximum reduction of 63% compared with vehicle.

Percent reduction in AIMs was plotted as a function of the simulated amantadine plasma concentrations (Fig. 1F). A sigmoidal E_{max} model provided a good fit for the data with an amantadine EC_{50} of 1633 ng/mL (95% CI, 1419–1879 ng/mL) for the reduction of AIMs (Supplemental Table 2).

Amantadine PK/PD Analysis in Cynomolgus Macaques

Dose proportionality was observed over the dose range of 1 to 30 mg/kg amantadine (Fig. 2A), with mean C_{max} ranging from 161–4633 ng/mL and mean AUC_{inf} ranging from 2287–65,372 ng·h/mL (Table 1). A 1-compartment model with constrained input rate equivalent to output was fit to the data, and the average parameters (Table 1) were used to simulate PK

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profiles for doses of 0.3, 1, 5, 10, 20, and 30 mg/kg (Fig. 2B) that were used in the 3 referenced studies (Bezard et al., 2013; Gregoire et al., 2013; Ko et al., 2014). In our efficacy study, single oral doses of amantadine resulted in a dose-dependent decrease in dyskinesia in MPTP macaques, with up to a 78% reduction in median levels of LID occurring at 30 mg/kg amantadine (Fig. 2C).

Percent reduction in dyskinesia was plotted as a function of the simulated amantadine plasma concentrations (Fig. 2D). A sigmoidal E_{max} model provided a good fit for the data with an amantadine EC_{50} of 1025 ng/mL (95% CI, 716–1467 ng/mL) for the reduction of dyskinesia (Supplemental Table 2).

PK/PD Relationships Across Species. The exposure-response relationships for mouse, rat, and macaque data each fit the sigmoidal E_{max} model fairly well, with R^2 values ranging from 0.407 to 0.682. The relationships for each species also showed close agreement with regard to the EC_{50}, which ranged from 1025 to 1633 ng/mL. Combining data from all species for model fitting resulted in similar estimates as obtained individually, with an R^2 of 0.429 and EC_{50} of 1367 ng/mL (95% CI, 1139–1639 ng/mL; Supplemental Table 2 and Fig. 3).

A study was conducted in dyskinetic 6-OHDA–lesioned rats using ALZET pumps to ensure constant amantadine plasma levels that bracketed the EC_{50} (1367 ng/mL). Subcutaneous infusion for 12 days of 83 mg/kg/day amantadine resulted in plasma concentrations of 2922 ng/mL (Fig. 4A), and a significant reduction from baseline in cumulative AIMs was observed at this dose compared with vehicle (37.2% vs 0.1% reduction, respectively; $P = .008$; Fig.

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4B). Conversely, sustained plasma concentrations below 900 ng/mL, achieved with SC infusion for 12 days of 22.5 or 45 mg/kg per day amantadine, did not significantly impact AIMs. These data are included in the rat and all species E_{max} models presented in Fig. 1F and Fig. 3, respectively.

In a previously reported clinical study (Pahwa et al., 2015), steady-state amantadine plasma concentrations were measured in patients with Parkinson's disease administered 210, 274, or 338 mg ADS-5102 (amantadine) extended release capsules once daily at bedtime (equivalent to 260, 340, or 420 mg amantadine HCl, respectively). Mean (standard deviation) steady-state amantadine plasma concentrations were 1383 (354), 1431 (707), and 1677 (512) ng/mL for the respective doses (Fig. 4C). The least-square mean change from baseline at week 8 in the Unified Dyskinesia Rating Scale (UDysRS) total score was –6.7, –12.3, –17.9, and –16.7 for the placebo, 210-mg, 274-mg, and 338-mg groups, respectively (Fig. 4D). Reductions in the UDysRS total score for the 274-mg and 338-mg groups (corresponding to 43% and 41% reduction, respectively) were significant compared with placebo, and are consistent with the nonclinical PK/PD relationship described above.

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Discussion

Amantadine has been shown to be effective in reducing dyskinesia in animal models of LID as well as in patients with Parkinson's disease treated with levodopa, but the plasma concentrations associated with efficacy have not been well characterized. The analyses described herein are the first to correlate amantadine plasma concentrations with efficacy endpoints for reducing dyskinesia in different species and models of LID. Using an approach

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that correlates simulated amantadine plasma concentrations from mouse, rat, and macaque PK studies with the previously published and new efficacy data for reducing dyskinesia in LID models, these results define exposure-response relationships that fit sigmoidal E_{max} models and predict EC_{50} between 1025 and 1633 ng/mL when assessed individually or combining data from all species. Differences in plasma protein binding, blood-brain partitioning, NMDA receptor affinity, or models of Parkinson's disease might have been anticipated to affect amantadine's efficacy in reducing LID across the species. However, these results show that without correcting for any differences, an EC_{50} of approximately 1400 ng/mL appears to be a commonality across the species examined and provides a target therapeutic plasma amantadine concentration for reducing dyskinesia in patients with Parkinson's disease.

Further support for the efficacy of this range of concentrations is provided by the study in the rat 6-OHDA model dosed with a constant SC infusion of amantadine, which showed significant percent reductions from baseline in cumulative AIMs assessments compared with vehicle for average plasma concentrations of 2922 ng/mL, while no significant effect on AIMs was observed in the dose groups resulting in average amantadine plasma concentrations below 900 ng/mL. Additionally, clinical data from patients with Parkinson's disease treated with the recommended dose of 274 mg ADS-5102, showed a statistically significant reduction in dyskinesia and mean steady-state amantadine plasma concentration of ~1500 ng/mL, which approximates the EC_{50} described for the nonclinical species (Pahwa et al., 2015). In Pahwa, et. al., the median amantadine plasma concentration in patients who discontinued due to CNS-related AEs was approximately 2100 ng/mL (Pahwa et al., 2015).

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Verhagen Metman et al. (1998b) reported that amantadine IR reduced dyskinesia in patients with Parkinson's disease treated with levodopa, with plasma concentrations that are consistent with the PK/PD model presented herein (average plasma concentration ~1600 ng/mL), despite differences in study design elements and endpoint measures. Although limited, the PK/PD data in patients with Parkinson's disease provide support that the animal models are predictive of a relationship between amantadine plasma concentration and reduction in dyskinesia in humans.

Improvements in continuous delivery of amantadine would provide a smooth PK profile achieving high concentrations and better coverage throughout the day compared to the peaks and troughs associated with bolus dosing. As reported in Hauser et al. (2017), ADS-5102 can be dosed once daily at bedtime to achieve high morning and sustained daytime amantadine plasma concentrations when symptoms of dyskinesia occur. Pharmacokinetic modelling suggested the recommended daily ADS-5102 dosage (274 mg once daily at bedtime) provided maximum steady-state concentrations of ~1500 ng/mL in PD patients, which is ~2-fold higher than that achieved with amantadine IR dosing (81 mg, equivalent to amantadine HCl 100 mg, administered at 8 AM and 4 PM, based on prescription data, which indicated that ~85% of Parkinson's disease patients treated with amantadine IR were prescribed 161 mg a day or less) (Navarro et al., 2017). Therefore, target amantadine plasma concentrations required to reduce dyskinesia based on the current model can be achieved throughout the day with the recommended once-daily dose of ADS-5102 but not with the commonly used dosing paradigm for amantadine IR.

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Collectively, these data show good correlation across species between amantadine plasma concentrations and reduction in LID, highlighting an EC_{50} of approximately 1400 ng/mL (~9 μM) as an efficacious target plasma concentration. While the mechanism of amantadine for the reduction in dyskinesia and OFF remains to be fully elucidated, these results also correlate well with the range of 50% inhibitory drug concentration values reported for amantadine for the NMDA receptor (10-90 μM) (Kornhuber et al., 1991; Bresink et al., 1995; Parsons et al., 1995; Parsons et al., 1996). In particular, the IC_{50} of amantadine for inhibition of striatal NMDA receptors was reported to be 12 μM (Parsons et al., 1996), or 1800 ng/mL, and support the involvement of the NMDA receptor and the glutamatergic pathway in mediating the expression of dyskinesia and motor complications in Parkinson's disease.

In summary, the correlation between the effective concentrations in animals (rodents and NHPs, ~1400 ng/mL) and efficacious plasma concentrations in humans (1500 ng/mL) demonstrate that animal models of LID are predictive of efficacy in humans. These results provide a benchmark amantadine plasma concentration of ~1400 ng/mL for the reduction of dyskinesia, and provide evidence that the recommended dose of ADS-5102 (274 mg) can provide plasma concentrations in patients with Parkinson's disease that achieve that benchmark, further supporting the use of ADS-5102 for the treatment of dyskinesia in patients with Parkinson's disease.

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Acknowledgments

Editorial support was provided by The Curry Rockefeller Group, LLC and Nuventra Pharma Sciences. This support was funded by Adamas Pharmaceuticals.

Authorship Contributions

Participated in research design: Brigham, Johnston, Holt, Nguyen

Conducted experiments: Brigham, Johnston, Brown, Fox, Brotchie

Contributed new reagents or analytic tools: Not applicable

Performed data analysis: Brigham, Johnston, Brown

Wrote or contributed to the writing of the manuscript: Brigham, Johnston, Brown, Holt, Fox, Hill, Howson, Brotchie, Nguyen

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Footnotes

a) Unnumbered footnote providing the source of financial support.

This study was supported by funding from Adamas Pharmaceuticals, Inc.

b) Unnumbered footnote providing thesis information, citation of meeting abstracts where the work was previously presented, etc.

Brigham EF, Johnston TH, Brown C, Holt JDS, Fox SH, Hill MP, Howson PA, Brotchie JM and Nguyen JT. PK-PD analysis identifies similar high amantadine plasma concentrations needed to reduce L-DOPA induced dyskinesia across multiple species. Poster presented at: The Society for Neuroscience Annual Meeting; November 11-15, 2017; Washington, DC

c) The name and full address and e-mail address of person to receive reprint requests.

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Full financial disclosure for the previous 12 months

T.H.J. has received consultancy payments from and holds an equity stake in Atuka Inc.

S.H.F. has received consultancy and research funding from Avanir, Biotie, Britannia, C2N, Cynapsus, Kyowa, Orion, and Zambon; honoraria from the International Parkinson and Movement Disorder Society, CHDI, and American Academy of Neurology; research funding from the Michael J. Fox Foundation for Parkinson's Research, NIH, Parkinson Society

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Canada, and Toronto Western Foundation; and a salary from UHN Department of Medicine Practice Plan.

M.P.H. has received consultancy payments from and holds an equity stake in Atuka Inc.

P.A.H. has received consultancy from Atuka Inc.

J.M.B has received consultancy payments from Atuka Inc. and Adamas Pharmaceuticals, Inc. and holds an equity stake in Atuka Inc.

E.F.B., J.D.S.H., C.B., and J.T.N. are employees of and have received compensation and stock options from Adamas Pharmaceuticals, Inc.

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Figure legends

Fig. 1. Amantadine plasma concentration-time profiles after a single intraperitoneal (IP) injection dose in mice for (A) observed plasma concentrations (mean ± standard deviation [SD]; LOQ, limit of quantitation) and (B) simulated plasma concentrations (the pharmacokinetic [PK] model). (C) Determination of pharmacokinetic/pharmacodynamic (PK/PD) relationship and the 50% effective plasma concentration (EC_{50}) in mouse. Percent reduction from vehicle in abnormal involuntary movements (AIMs) is plotted as a function of the log(amantadine plasma concentration) in mouse. EC_{50} = 1145 ng/mL. Shaded area represents 95% confidence interval. Amantadine plasma concentration-time profiles after a single IP injection dose in rat for (D) observed plasma concentrations (mean ± SD) and (E) simulated plasma concentrations (the PK model). The simulated model was fit optimized to maximum plasma concentration, 2-compartment intravenous bolus model. (F) Determination of PK/PD relationship and EC_{50} in rat. Percent reduction from vehicle in AIMs is plotted as a function of the log(amantadine plasma concentration) in rat. EC_{50} = 1633 ng/mL. Shaded area represents 95% confidence interval.

Fig. 2. Amantadine (AMT) plasma concentration-time profiles and dyskinesia score after a single oral dose in dyskinetic cynomolgus macaque for (A) observed plasma concentrations (mean ± standard deviation), (B) simulated plasma concentrations (the pharmacokinetic [PK] model), and (C) dyskinesia score by treatment (median). The PK model was fit optimized to maximum plasma concentration, 1-compartment model with constrained input rate equivalent to output. (D) Determination of PK/pharmacodynamic relationship and the 50% effective plasma concentration (EC_{50}) in macaque. Percent reduction from vehicle in

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dyskinesia is plotted as a function of the log(amantadine plasma concentration) in macaque. EC_{50} = 1025 ng/mL. Shaded area represents 95% confidence interval.

Fig. 3. Determination of pharmacokinetic/pharmacodynamic relationship and the 50% effective plasma concentrations across species. Percent reduction from vehicle in abnormal involuntary movements (mouse and rat) or dyskinesia (macaque) is plotted as a function of the log (amantadine plasma concentration) in mouse, rat, and macaque. EC_{50} = 1367 ng/mL. Shaded area represents 95% confidence interval.

Fig. 4. Comparison of amantadine plasma concentrations (mean ± standard deviation [SD]) (A) and associated cumulative abnormal involuntary movements (AIMs; % reduction from baseline, mean ± standard error of mean) (B) in a rat 6-hydroxydopamine levodopa-induced dyskinesia model dosed with a constant subcutaneous infusion of amantadine for 12 days. The percent reduction of AIMs was statistically significant (P = .008) for the 83 mg/kg per day amantadine dose, designated by the asterisk (B). (C) Mean (± SD) steady-state amantadine plasma concentrations and (D) observed change in Unified Dyskinesia Rating Scale (UDysRS) total score (least-square mean ± standard error) from baseline to week 8 (a decrease indicates improvement). Doses are represented as freebase. These plasma concentrations are predicted to represent high, sustained amantadine exposure throughout the waking hours based on steady-state PK in healthy subjects (Hauser RA, Pahwa R, Wargin W, et al. Pharmacokinetics of ADS-5102 [amantadine] extended release capsules administered once-daily at bedtime for the treatment of dyskinesia. [Submitted]) Source: Pahwa R, et al. Mov Disord 2015; 30: 788-795 (Pahwa et al., 2015) Reprinted with permission.

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Table

TABLE 1. Amantadine PK parameters by species

Mouse, sexes combined				
NCA parameter	**10 mg/kg**	**30 mg/kg**	**60 mg/kg**	**Mean[a]**
C_{max} (ng/mL)	1268	3733	8826	–
C_{max}/dose (ng/mL)/(mg/kg)	127	124	147	–
T_{max} (h)	0.25	0.5	0.25	–
AUC_{inf} (ng·h/mL)	1781	5522	13,877	–
AUC_{inf}/dose (ng·h/mL)/(mg/kg)	178	184	231	–
$t_{1/2}$ (h)	1.1	1.0	1.5	–
Modeled parameters (using C(T) = D/V·exp(–K10·T)				
V (mL/kg)	6378	6459	5436	6091
K10 (1/h)	0.8424	0.7811	0.8075	0.810

Rat, sexes combined				
NCA parameter	**15 mg/kg**	**45 mg/kg**	**90 mg/kg**	**Mean[b]**
C_{max} (ng/mL)	2769	6982	24,899	–
C_{max}/dose (ng/mL)/(mg/kg)	185	155	277	–
T_{max} (h)	0.25	0.25	0.25	–
AUC_{inf} (ng·h/mL)	4199	14114	52563	–
AUC_{inf}/dose (ng·h/mL)/(mg/kg)	280	314	578	–
$t_{1/2}$ (h)	1.18	1.95	1.91	–
Modeled parameters (using C(T) = A·exp(–alpha·T)+B·exp(–beta·T))				
V1 (mL/kg)	3816	3862	1518	3839
K10 (1/h)	0.87	0.77	1.09	0.82
K12 (1/h)	0.61	1.63	3.49	1.12
K21 (1/h)	1.14	1.68	2.31	1.41

Cynomolgus macaque, sexes combined					
NCA parameter	**1 mg/kg**	**3 mg/kg**	**10 mg/kg**	**30 mg/kg**	**Mean[c]**
C_{max} (ng/mL)	161	539	1599	4633	–
C_{max}/dose (ng/mL)/(mg/kg)	161	180	160	154	–
T_{max} (h)	4.0	3.5	3.75	5.75	–
AUC_{inf} (ng·h/mL)	2287	5710	21,746	65,372	–
AUC_{inf}/dose (ng·h/mL)/(mg/kg)	2287	1903	2175	2179	–
$t_{1/2}$ (h)	11.5	6.49	6.95	6.27	–
Modeled parameters (using C(T) = K·(D/V)·T·exp(–K·T))					
V_F (mL/kg)	2466	2171	2324	2663	2406
K (1/h)	0.3	0.32	0.26	0.22	0.274
T_{lag} (h)[d]	0.39	0.45	0.41	0.52	0.440

[a]Mean of 10-, 30-, and 60-mg/kg doses used to simulate 40-mg/kg PK profile.

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[b]Mean of 15- and 45-mg/kg doses used to simulate 10, 20 and 40-mg/kg PK profile.

[c]Mean of 1-, 3-, 10-, and 30-mg/kg doses used to simulate PK profiles.

[d]T_{lag} max = 1.73 h.

PK, pharmacokinetics; NCA, noncompartmental analysis; C_{max}, maximum plasma concentration; T_{max}, T, time; time to C_{max}; AUC_{inf}, area under plasma concentration-time curve at infinity; $t_{1/2}$, half-life; V, volume; V_F, apparent volume; V1, volume of central compartment; T_{lag}, time lag: D, dose administered; K and K01 and K10 and K21, rate constant; A and B, coefficients; alpha, alpha phase elimination rate constant; beta, beta phase elimination rate constant.

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Figures

Fig. 1.

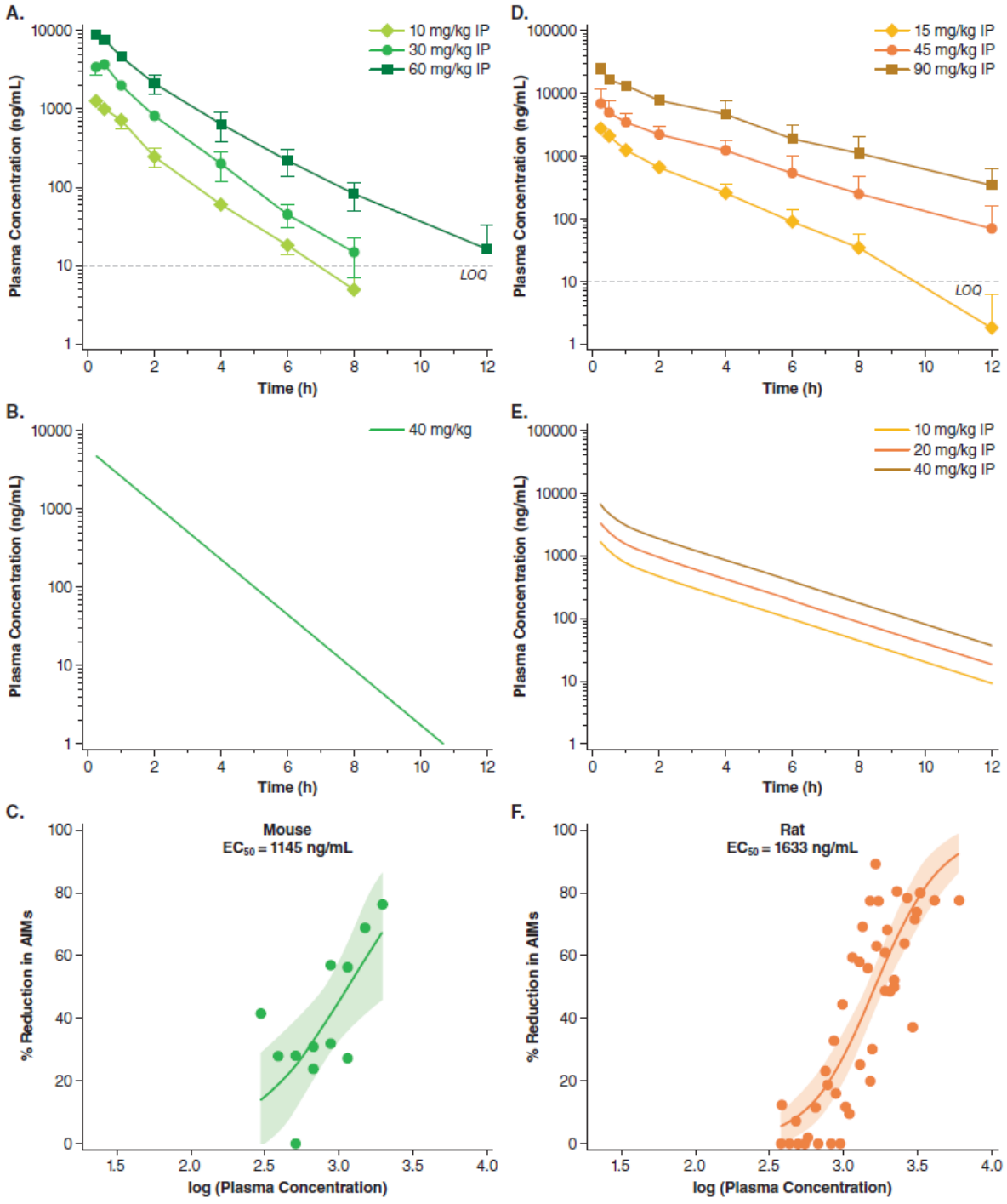

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Fig. 2

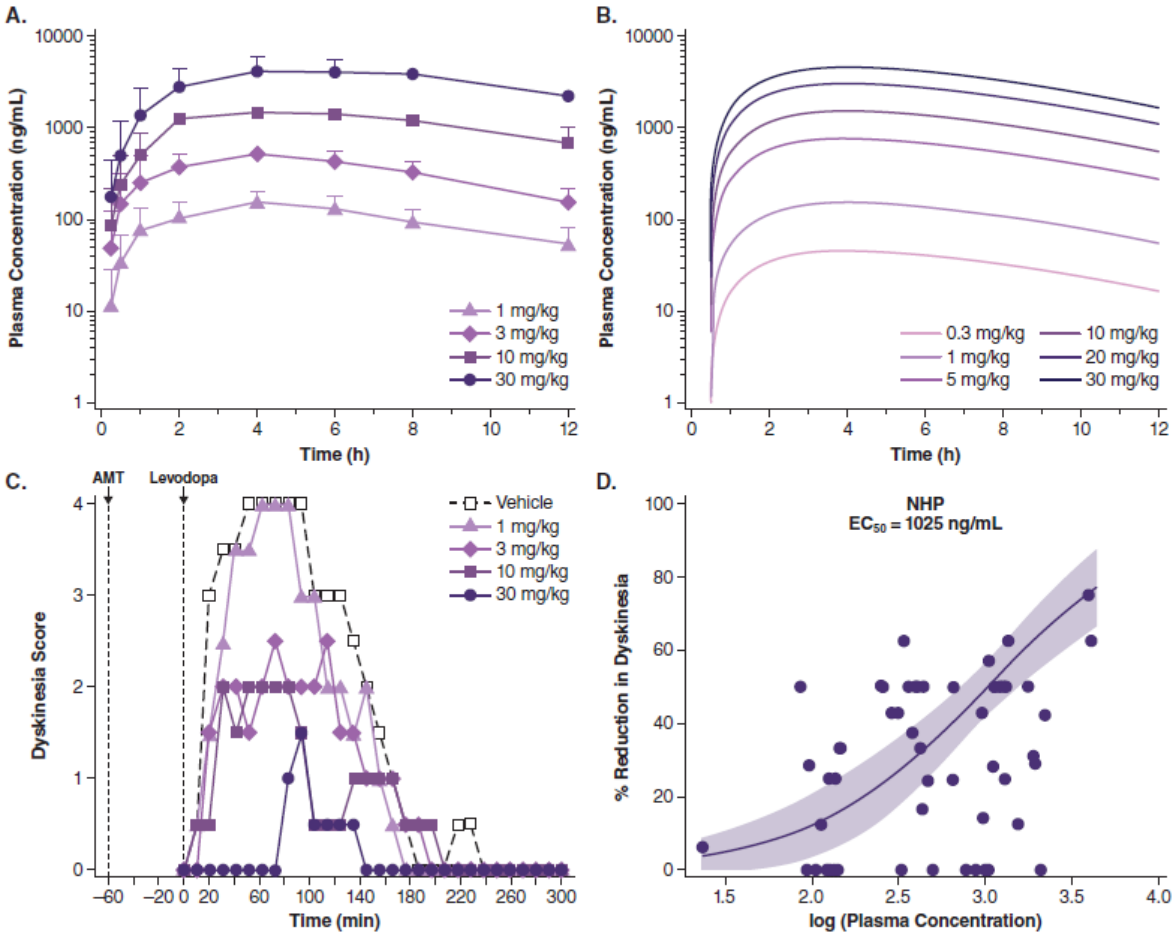

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Fig. 3

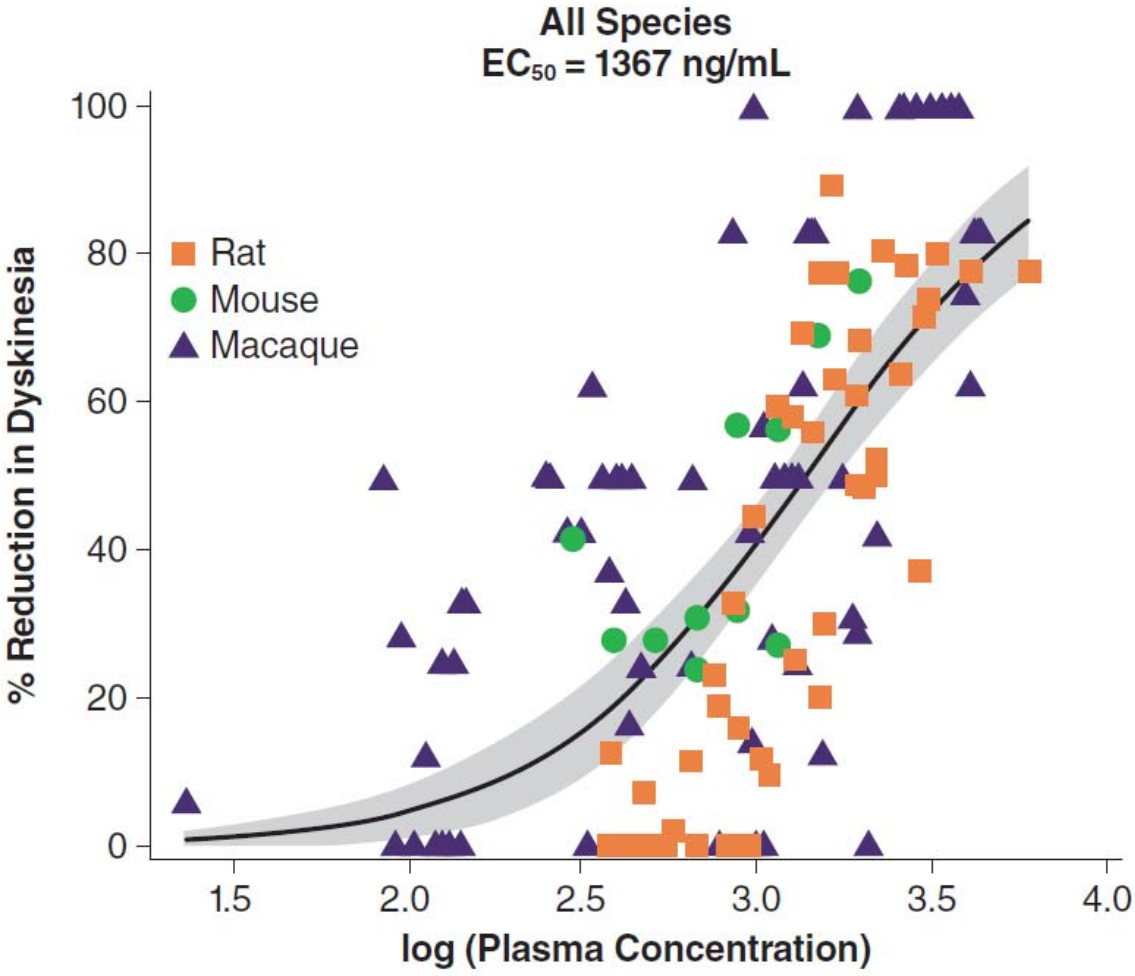

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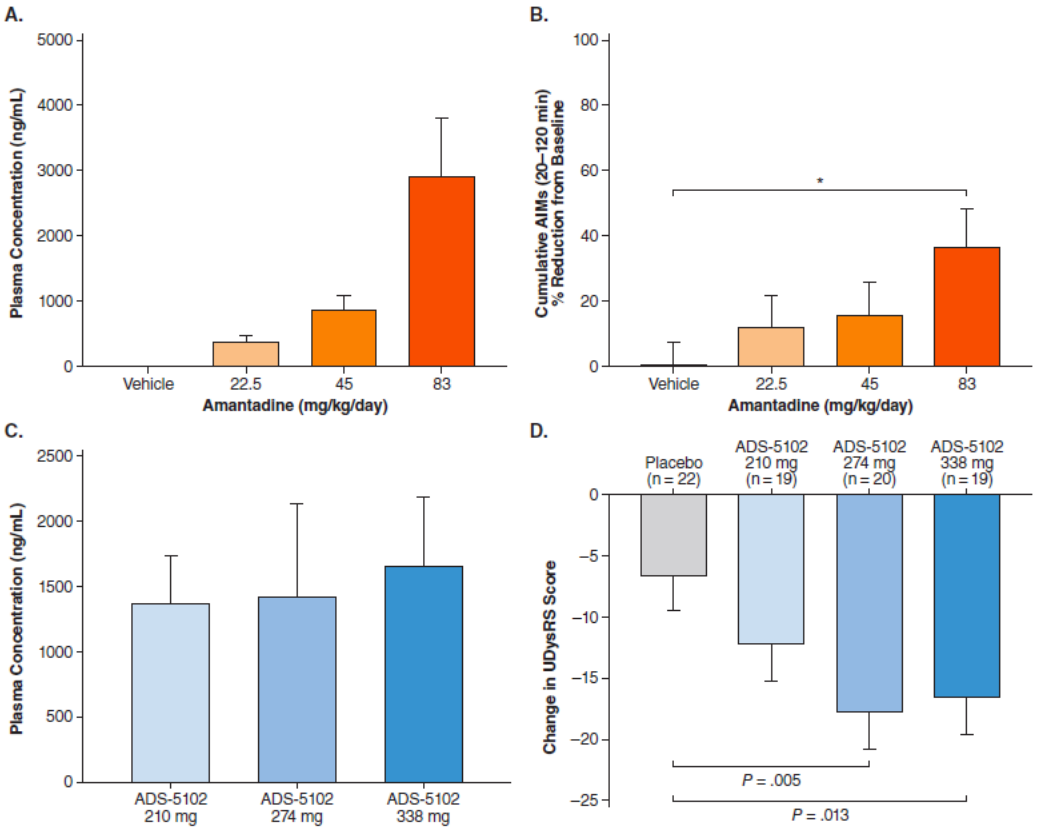
Fig. 4



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