
Investigator's Brochure

Drug Product	MEDI1341
Project Code	D6340000000
Edition Number and Edition Date	Version 3, 26 June 2019
Data Cut-off Date	09 May 2019

Investigator's Brochure

MEDI1341

D6340000000

Parkinson's Disease

Edition superseded: Version 2; 15 November 2017

C O N F I D E N T I A L

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Special Term	Explanation
AI	Accumulation index
ANOVA	Analysis of variance
AUC _{inf}	Area under curve extrapolated to infinity
AUC _{0-∞}	Area under curve from time zero to infinity
AUC _{last}	Area under concentration time curve from zero to last time point
AZ	AstraZeneca
CD	Cluster of differentiation
CL	Clearance
CL _{ss}	Steady state clearance
C _{last}	Last measurable concentration
C _{max}	Maximum observed concentration
CNS	Central nervous system
CSF	Cerebrospinal fluid
C _{trough}	Last measurable time point
DELFA	Dissociation enhanced lanthanide fluorescence immunoassay
DLB	Dementia with Lewy Bodies
ECG	Echocardiogram
ELISA	Enzyme-linked immunosorbent assay
Fc	Fragment crystallizable
FDA	United States Food and Drug Administration
FTIH	First-time-in-human
GLP	Good Laboratory Practice
HTRF	Homogeneous time-resolved fluorescence
IBA-1	Ionized calcium-binding adapter molecule 1
IC ₅₀	Half-maximal inhibitory concentration
IgG	Immunoglobulin G
IHC	Immunohistochemical
ip	Intraperitoneal

Abbreviation or Special Term	Explanation
ISF	Interstitial fluid
iv	Intravenous
ivIg	Intravenous immunoglobulin
K _D	Equilibrium dissociation constant
LLOQ	Lower limit of quantification
LV	Lentiviral vector
mAb	Monoclonal antibody
MSA	Multiple system atrophy
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PCR	Polymerase chain reaction
PD	Parkinson's Disease
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
SAE	Serious adverse event
SD	Standard deviation
SEM	Standard error of mean
SUSAR	Suspected unexpected serious adverse reaction
t _{1/2}	Half-life
t _{1/2λz}	Apparent terminal elimination half-life
tg	Transgenic
TM	Triple mutation
t _{max}	Time of C _{max}
TEAE	Treatment-emergent adverse event
ULOQ	Upper limit of quantification
US	United States
V _{ss}	Steady state volume of distribution
V _z	Terminal volume of distribution

1. SUMMARY

[REDACTED]

[REDACTED] MEDI1341 is being developed as a therapeutic antibody for the treatment of patients with Parkinson's disease (PD).

[REDACTED]

MEDI1341 recognizes both the monomeric and aggregated forms of human α -synuclein. MEDI1341 cross reacts with both cynomolgus monkey and rat α -synuclein with a relative affinity within [REDACTED]-fold by epitope competition assay. MEDI1341 is a high affinity antibody [REDACTED] to human α -synuclein and is highly selective for α -synuclein, with no significant binding to β -synuclein or γ -synuclein.

In a mouse in vivo model, passive immunization with the anti- α -synuclein antibody, Aslo0452 ngl-3 (a mouse version of MEDI1341 with retained effector function), significantly reduced the ipsilateral to contralateral trans-axonal spreading of α -synuclein aggregates observed when compared with an isotype control antibody, NIP228 in non-transgenic (tg) wild type mice or α -synuclein tg mice that had both been injected with a lentiviral vector to drive expression of human α -synuclein on one side of the hippocampus. Importantly, an effector null D265A mutant version of Aslo0452 ngl-3 was equally effective as Aslo0452 ngl-3 at reducing α -synuclein spreading in the model, which strongly indicates that anti- α -synuclein antibody-mediated prevention of α -synuclein spreading does not require Fc-associated effector functions as a key mechanism of action.

Intravenous administration of MEDI1341 elevates total α -synuclein concentrations compared to vehicle in rat and cynomolgus monkey plasma. MEDI1341 also lowers free α -synuclein levels in the cerebrospinal fluid (CSF) and interstitial fluid (ISF) of rats and in the CSF of cynomolgus monkeys, thus demonstrating central nervous system (CNS) target engagement.

Following administration of a single intravenous (iv) dose of 3 mg/kg to rats, total MEDI1341 exhibited a mean clearance (CL) of 6.53 mL/day/kg and a mean terminal volume of distribution (V_z) of 44.2 mL/kg that resulted in a half-life ($t_{1/2}$) of 4.79 days. Maximum observed concentration (C_{max}) increased in a dose proportional manner. Area under concentration time curve from zero to last time point (AUC_{last}) increased in a dose proportional manner between 3 and 30 mg/kg and increased in a slightly less than dose proportional manner between 30 and 100 mg/kg.

Following administration of a single iv dose of [REDACTED] mg/kg to monkeys, total MEDI1341 exhibited a mean CL of [REDACTED] mL/day/kg and a mean V_z of [REDACTED] mL/kg, resulting in a mean $t_{1/2}$

of [REDACTED] days. Following single iv dose administration, free MEDI1341 plasma exposure [REDACTED] across the dose groups. In comparison, after single iv dose administration, total MEDI1341 plasma exposure increased [REDACTED] than dose proportionally over the [REDACTED] to 30 mg/kg dose range. Following repeat 10 mg/kg/week iv dose administration the accumulation index (AI) for total C_{max} and total AUC_{last} were [REDACTED] and [REDACTED] respectively indicating minimal accumulation in plasma. Comparable pharmacokinetic (PK) parameters were observed for the free assay following 10 mg/kg/week repeated iv administration of MEDI1341.

In Good Laboratory Practice (GLP) 13-week repeat-dose toxicokinetic studies in rats and monkeys, systemic exposure was generally dose proportional. Evidence of [REDACTED]-fold accumulation of MEDI1341 was observed between Week 1 and Week 13 in rats in all dose groups and mostly in the lowest dose group in monkeys. [REDACTED] were detected for rats in the [REDACTED] and [REDACTED] mg/kg/week dose groups for [REDACTED] and [REDACTED] animals, respectively and in [REDACTED] monkeys across all dose groups. [REDACTED] animals were excluded from the non-compartmental analysis. In monkey CSF, MEDI1341 concentrations [REDACTED] with observed CSF/serum ratios, expected for an IgG.

In GLP [REDACTED]-week repeat-dose toxicokinetic studies in rat and monkey, MEDI1341 serum exposure generally increased in a dose proportional manner. Evidence of [REDACTED]-fold accumulation of MEDI1341 systemic exposure was observed in the [REDACTED] mg/kg/twice-weekly dose group in cynomolgus monkey. Less than [REDACTED]-fold accumulation in systemic exposure was observed in Week [REDACTED] for the [REDACTED] mg/kg/twice-weekly dose group in monkeys and the [REDACTED] and [REDACTED] mg/kg/twice-weekly dose groups in rats.

The toxicity profile of MEDI1341 has been evaluated in combined safety pharmacology and toxicity studies in 2 pharmacologically relevant species, the rat (rodent) and the cynomolgus monkey (non-rodent) in vivo. Toxicity studies of [REDACTED] and 13 weeks duration have been completed in both species. Engagement of the α -synuclein target was demonstrated in both plasma and CSF in the 13-week studies. The [REDACTED]-week studies were completed after the 13-week studies, in order to define MEDI1341 potential toxicity at significantly higher exposures to those achieved in the 13-week studies. In addition, binding of MEDI1341 to human tissue ex vivo has been assessed. MEDI1341 binding in ocular tissues ex vivo was also investigated in human, rat, and monkey tissues.

In 13-week rat and monkey toxicity studies, there were no MEDI1341-related adverse changes in any of the parameters evaluated. In the 13-week study in monkeys, MEDI1341-related acute inflammation was observed following histopathological examination of the most recently injected vein. This finding was noted at the end of the treatment phase only, indicating reversibility, and was consistent with a skin reaction to an injected protein and was not considered adverse. Similar injection site reactions were not observed in the [REDACTED]-week study in monkeys at higher exposures. At the time of initial evaluation of the 13-week studies, there were no other MEDI1341-related histopathology findings in any of the tissues assessed in rats

or monkeys, and the no-observed-adverse-effect level (NOAEL) was therefore considered to be [REDACTED] mg/kg/week (the [REDACTED]) in both species.

Dose levels for the subsequent [REDACTED]-week toxicity studies (rat: [REDACTED] and [REDACTED] mg/kg twice weekly [total dose [REDACTED] and [REDACTED] mg/kg/week]; monkey: [REDACTED] and [REDACTED] mg/kg twice weekly [total dose [REDACTED] and [REDACTED] mg/kg/week]) were selected in order to achieve a [REDACTED]-fold exposure margin over the highest anticipated clinical dose in the single-ascending dose clinical study.

Histopathological examination of the rat tissues revealed a finding in the ocular sections affecting all animals in both MEDI1341 dose groups. This was characterized as increased cellularity of the sclera and/or mononuclear cell infiltration around small vessels at the corneo-scleral junction. The finding was not considered adverse based on histopathology and other ocular evaluations included in the study (NOAEL of [REDACTED] mg/kg/twice weekly). Due to the presence of this finding, ocular sections from the previous 13-week rat and monkey studies were re-examined. The absence of ocular findings was confirmed in the 13-week monkey study. However, a similar change was observed at [REDACTED] and [REDACTED] mg/kg/week in the rat 13-week study (no-observed-effect level [NOEL] of [REDACTED] mg/kg/week). The findings were noted at a lower incidence and severity, and there were no ocular findings in rats dosed at [REDACTED] mg/kg/week for 13 weeks followed by a 13-week treatment-free period, suggesting reversibility. The ocular finding was not considered adverse and the NOAEL in both 13-week studies remain as originally stated. The ocular finding was also confirmed to be absent in the [REDACTED]-week monkey study.

In a cross-reactivity study using an extensive panel of normal human tissue cryosections as well as brain cryosections from individuals with Parkinson's disease, the majority observed MEDI1341 staining was cytoplasmic in nature and was judged of no toxicologic relevance as the cytoplasmic compartment is considered to be unavailable to monoclonal antibodies in vivo. In ocular tissue, similar staining was observed with MEDI1341 in the human, cynomolgus monkey, and Sprague-Dawley rat.

As of 09 May 2019, a first-time-in-human (FTIH) study (D6340C00001) is ongoing. The study is designed to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of single doses of MEDI1341 in healthy male and female volunteers. A total of 25 subjects, across 3 dose-level cohorts, have participated in the dose-escalation study to date and have received a single iv dose of either MEDI1341 (doses up to 400 mg) or placebo.

PPD

The trial was subsequently re-initiated and N=24 subjects were enrolled. The study remains blinded.

Overall, MEDI1341 has been well tolerated following single iv doses up to 400 mg and there have been no clinically important safety findings to date [REDACTED]

2. INTRODUCTION

2.1 Drug description

MEDI1341 is a high-affinity, α -synuclein specific, fully human monoclonal antibody, formatted as an IgG1 that specifically binds the C-terminal region of human α -synuclein. It is engineered for reduced effector function by virtue of a triple mutation introduced into the fragment crystallizable (Fc) region of the antibody. MEDI1341 recognizes both the monomeric and aggregated forms of α -synuclein, and it recognizes disease relevant, pathological forms of α -synuclein in the brain tissue of patients with PD.

2.2 Background and rationale for the development of MEDI1341

2.2.1 Parkinson's Disease

Parkinson's disease is a slowly progressive and debilitating age-related movement disorder affecting more than 1% of people over 65 years of age. Parkinson's disease is the second most common neurodegenerative condition after Alzheimer's disease. It is estimated that more than 10 million people worldwide may be living with PD. In the United States (US) alone, around 60000 new PD cases are diagnosed each year. The total economic burden of PD is estimated to be approximately \$25 billion per year in the US (Source: [Parkinson's Disease Foundation 2016](#)).

The defining pathological hallmarks of PD are Lewy bodies and Lewy neurites, which are insoluble inclusions of aggregated proteins found inside neuron cell bodies and axons, respectively, of the PD brain revealed upon postmortem histopathological examination. The major protein component of Lewy bodies and Lewy neurites is an aggregated form of α -synuclein, called fibrils.

2.2.2 Alpha-synuclein

There is human genetic linkage between the gene that encodes α -synuclein and PD; missense mutations in the α -synuclein gene and duplications/triplications of the wild-type α -synuclein gene cause familial PD, and a number of genome-wide association analyses have found common genetic variability at the α -synuclein locus (chromosome 4q21) that significantly increases susceptibility for the development of PD. This pathological and genetic evidence strongly suggests that α -synuclein plays a key causative role in PD.

Postmortem histopathological studies in PD indicate that the progressive neurodegeneration observed may result from the spreading of α -synuclein 'Lewy' pathology between neuroanatomically connected brain regions. Early evidence came from the observation that Lewy bodies were present in fetal nigral neurons which had been grafted into the brain of PD patients several years before as a therapeutic measure ([Kordower and Brundin 2009](#); [Li et al 2008](#)). In support of this theory, recent scientific studies have demonstrated that pathological forms of α -synuclein can transfer between neurons via a release and uptake mechanism involving an extracellular phase. There is a growing body of in vitro and in vivo scientific evidence generated from experimental models of α -synucleinopathy to suggest that

immunotherapy with antibodies targeting α -synuclein have the potential to be disease-modifying in PD or dementia with Lewy Bodies (DLB) or multiple system atrophy (MSA), by blocking or slowing the pathological uptake of α -synuclein into recipient cells and preventing seeding and transmission of α -synuclein pathology between anatomically connected brain regions. In this way, antibodies targeting α -synuclein may slow disease progression and be of therapeutic benefit to patients with synucleinopathies such as PD, DLB, or MSA (Valera and Masliah 2013).

2.2.3 Current options for the treatment of Parkinson's Disease

Current drug therapies for PD are mainly focused on the treatment of the motor-related symptoms of the disease that result from the loss of dopaminergic neurons in the substantia nigra region of the brain, and include carbidopa-levodopa, dopamine (receptor) agonists, catechol-O-methyltransferase inhibitors, and monoamine oxidase type B inhibitors. There are currently no licensed or available therapies that can slow or prevent PD progression; thus, the availability of disease-modifying treatments is an important unmet medical need in PD.

2.2.4 Rationale for the use of MEDI1341 in the treatment of Parkinson's Disease

Systemic administration of MEDI1341 to rats via the iv route led to a CCI

MEDI1341-mediated reduction of free α -synuclein in CSF has similarly been demonstrated following iv administration to cynomolgus monkeys. MEDI1341 has also been characterized in a novel mouse model of α -synuclein accumulation and spread in which chronic passive immunization of mice with MEDI1341 by the intraperitoneal (ip) route strongly reduced axonal propagation and accumulation of α -synuclein in the brain. Based on these non-clinical data, MEDI1341 has the potential to sequester disease-relevant forms of α -synuclein in the brain, abrogate α -synuclein accumulation and spreading throughout the brain and thus slow disease progression and neurodegeneration in patients with PD.

2.2.5 Clinical plan

The first-in-human study (D6340C00001) is ongoing. It is designed as a randomized, double-blind, placebo-controlled, single-ascending dose study with iv MEDI1341 administered to male and non-fertile female healthy volunteers. The objective of the study is to assess the safety, tolerability, PK, pharmacodynamics, and immunogenicity of single doses of MEDI1341 in healthy volunteers, prior to advancing MEDI1341 into a separate multiple-dose study in patients with PD.

3. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATIONS

3.1 Drug substance

CCI



3.2 Drug product (including formulation and dosage/supply & storage)

3.2.1 Description

CCI



3.2.2 Components and composition

CCI



3.2.3 Instructions and precautions in handling

CCI



3.2.4 Storage conditions

CCI



3.2.5 Known structural similarities

CCI



4. NON-CLINICAL STUDIES

4.1 Non-clinical pharmacology

4.1.1 Primary pharmacodynamics

4.1.1.1 In vitro studies

Affinity

The equilibrium dissociation constant (K_D) of the MEDI1341 antibody for recombinant bacterially expressed CCI was calculated in the studies to be CCI pM using an Octet instrument. The solution phase K_D of MEDI1341 for bacterially expressed human α -synuclein was determined to be CCI pM using a KinExA instrument. The K_D of the Fab of MEDI1341 antibody was calculated to be CCI pM using the KinExA method.

Specificity

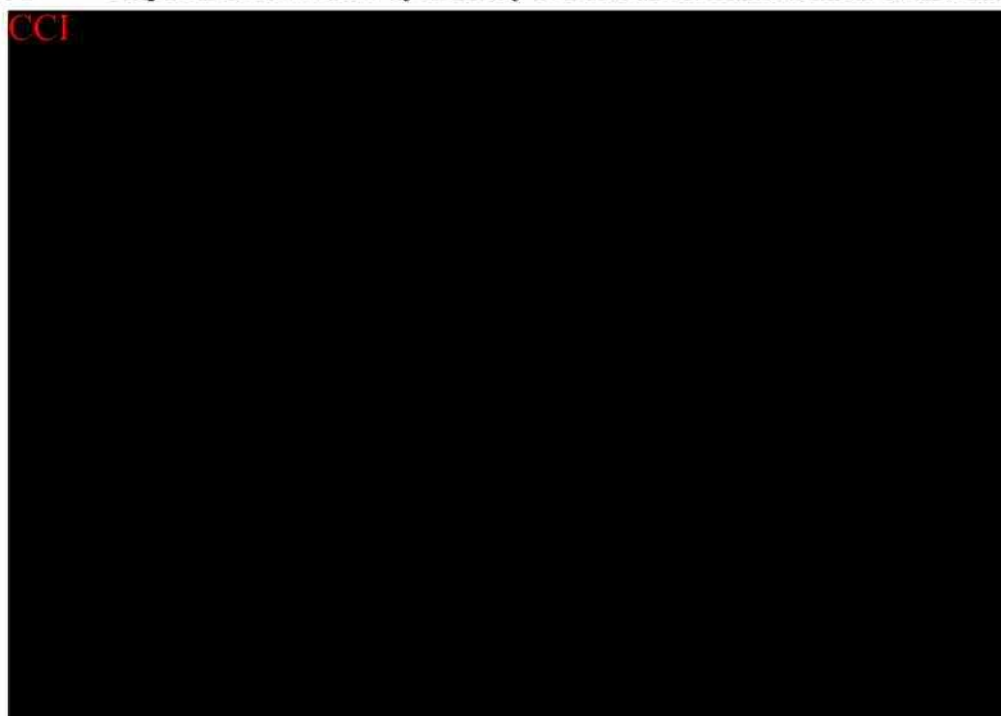
Specificity of MEDI1341 for rat, monkey, and human α -synuclein

The specificity of MEDI1341 for rat, cynomolgus monkey, and human α -synuclein was determined using a homogeneous time-resolved fluorescence (HTRF) biochemical epitope competition assay that measured the binding of biotinylated human α -synuclein to MEDI1341 in solution. Rat, monkey, and human α -synuclein were titrated into the assay and the selectivity of MEDI1341 was assessed by measuring the degree of inhibition of biotinylated human α -synuclein binding to MEDI1341. Half-maximal inhibitory concentration (IC_{50}) values were determined to be CCI, and CCI nM in rat, monkey, and human α -synuclein, respectively.

Specificity of MEDI1341 for native α -synuclein

The specificity of MEDI1341 for binding to native, endogenous human α -synuclein was determined by flow cytometry using α -synuclein positive (SHSY5Y neuroblastoma) and negative (BT20 breast cancer) cell lines. CCI

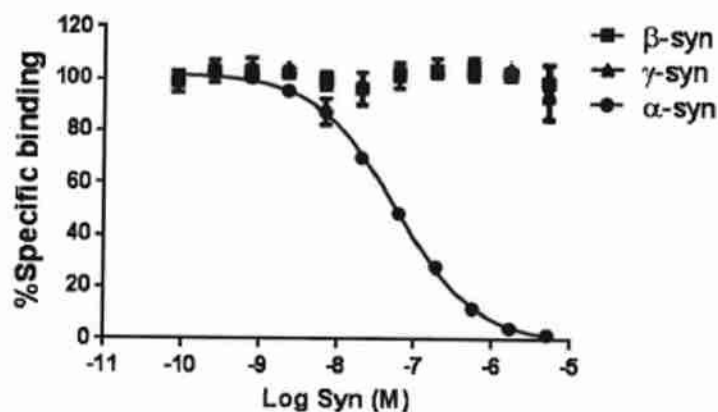
Figure 1 Representative flow cytometry results from human neuroblastoma cell line



Specificity of α -synuclein over β -synuclein and γ -synuclein

The specificity of MEDI1341 for α -synuclein over β -synuclein and γ -synuclein was determined using a HTRF epitope competition assay that measured the binding of biotinylated human α -synuclein to MEDI1341 in solution. No binding of MEDI1341 to β -synuclein and γ -synuclein was detected at the concentrations tested (up to $1 \mu\text{M}$), demonstrating that MEDI1341 is selective for α -synuclein (Figure 2).

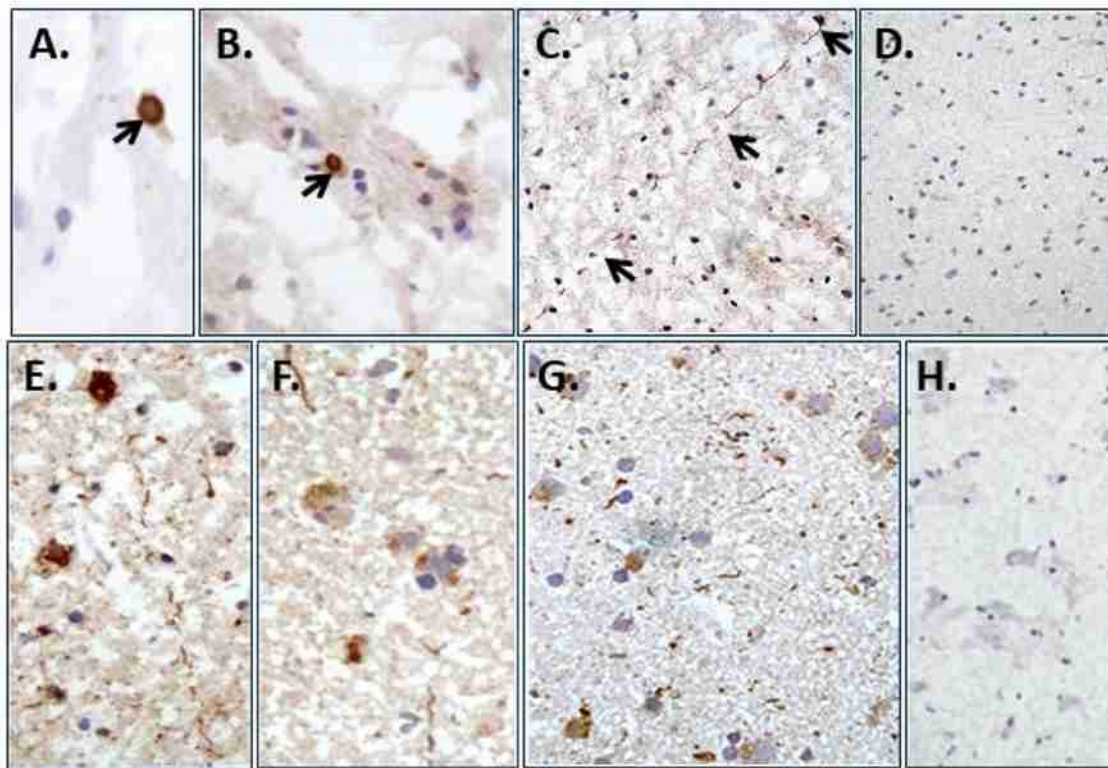
Figure 2 Representative graph of α -synuclein, β -synuclein, and γ -synuclein in MEDI1341 HTRF epitope competition assay



Specificity of MEDI1341 in disease relevant tissues

The specificity of MEDI1341 for disease relevant forms of human α -synuclein was determined by immunohistochemical staining of brain tissue from patients with Parkinson's disease. Results from the study demonstrate that MEDI1341 can recognize disease relevant pathological forms of human α -synuclein in Parkinson's disease brain tissue sections (Figure 3).

Figure 3 Representative immunohistochemistry images PD brain regions



Panels A, B, and C: show MEDI1341 staining both Lewy bodies (Panels A and B) and Lewy neurites (Panel C) of substantia nigra in Parkinson's disease (PD) brain tissue. **Panel D:** shows MEDI1341 demonstrates low level staining of α -synuclein in cells from the temporal cortex in a normal brain section. **Panels E, F, and G:** show MEDI1341 staining Lewy bodies, Lewy neurites and Lewy dots of the amygdala in Parkinson's disease brain tissue. **Panel H:** shows an isotype matched control antibody demonstrating no staining in the amygdala in Parkinson's disease brain tissue.

Specificity of MEDI1341 for aggregated human α -synuclein

The specificity of MEDI1341 for aggregated human α -synuclein was determined using a dissociation enhanced lanthanide fluorescence immunoassay (DELFI) antibody capture assay that measured the capture of aggregated human α -synuclein by MEDI1341 in a pair-wise enzyme-linked immunosorbent assay (ELISA). In this assay only aggregated human α -synuclein is captured and detected, since it presents multiple copies of the same epitope on a single aggregate. For monomeric α -synuclein, only one epitope is present, therefore the detecting second antibody cannot bind in the presence of capture antibody.

CCI

Figure 4 Representative graph showing capture of aggregated human α -synuclein by MEDI1341 in the DELFIA aggregated capture ELISA

CCI

MEDI1341 epitope characterization

Crude epitope mapping for MEDI1341 was conducted in an ELISA assay using commercially available α -synuclein truncates. These epitope binding studies demonstrated that MEDI1341 recognizes an epitope located in the C-terminal region of the α -synuclein protein between

CCI

4.1.1.2 In vivo studies

The effects of passive immunization of 3 anti- α -synuclein antibodies, on the spreading of α -synuclein aggregate pathology in a mouse model of α -synucleinopathy was assessed (Report: CNS13410010). Non-transgenic wildtype mice (non-tg) and human α -synuclein overexpressing transgenic mice (α -synuclein tg) were injected with a lentiviral vector expressing human α -synuclein (LV- α -synuclein) into the right hippocampus, and were then passively immunized weekly for 13 weeks with anti- α -synuclein antibodies: MEDI1341 (Aslo0452 ngl-3, which is a mouse version of MEDI1341 with retained effector function), or the effector null mutant version of MEDI1341 (MEDI1341 D265A, Aslo0452 ngl-3 D265A), or CCI or with an isotype control mouse IgG1 (NIP228). All test antibodies in the α -synuclein mouse spreading study were given by the ip route at a dose of 20 mg/kg weekly for 13 weeks. At the end of the immunization period, the mice were euthanized and their brains analyzed by immunocytochemistry with automated image analysis

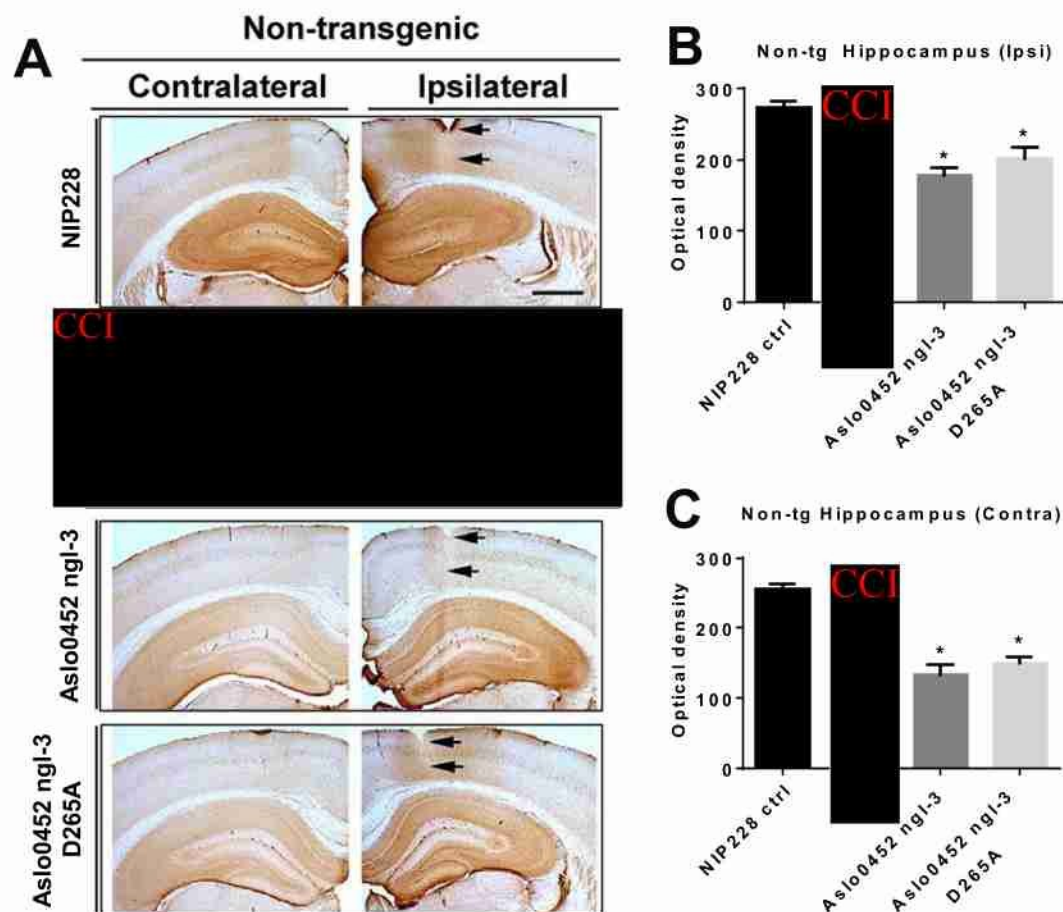
for levels of α -synuclein immunoreactivity ipsilateral and contralateral to the site of the LV- α -synuclein injection.

Assessment of the effect of anti- α -synuclein antibodies on hippocampal ipsilateral to contralateral spreading of LV- α -synuclein

In both non-tg mice and α -synuclein tg mice, α -synuclein immunoreactivity on the LV- α -synuclein injected ipsilateral side was intense in the neuropil and covered most of the surface of the hippocampus. The contralateral non-injected hippocampus of non-tg mice and α -synuclein tg mice also displayed high levels of α -synuclein immunoreactivity, indicating that the LV-expressed α -synuclein had spread from the injected right hippocampus to the left hippocampus. In this LV- α -synuclein injection mouse model, previous experiments have shown that only expressed α -synuclein protein spreads to the contralateral side with no evidence of transfer of the lentivirus itself, as determined by polymerase chain reaction (PCR) analysis.

Comparison of the ipsilateral and contralateral hippocampal levels of LV-expressed α -synuclein in non-tg mice that were passively immunized with the tested antibodies, indicate that **CCI**) does not block the dissemination of α -synuclein in this α -synuclein spreading model. However, passive immunization of mice with either MEDI1341 or the effector null D265A mutant version of MEDI1341 robustly blocks the spreading of α -synuclein in this mouse model of α -synucleinopathy (Figure 5).

Figure 5 MEDI1341 blocks α -synuclein spreading in non-transgenic mice



ANOVA = analysis of variance; contra = contralateral; ipsi = ipsilateral; SEM = standard error of mean.

A: Non-tg mice injected with LV- α -synuclein into the right hippocampus (black arrows) were passively immunized with 13 weekly doses of anti- α -synuclein mouse IgG1 antibodies: MEDI1341 (Aslo0452 ngl-3), MEDI1341 D265A (Aslo0452 ngl-3 D265A; effector null mutant), CCI or with NIP228 isotype control antibody, followed by determination of α -synuclein spreading by immunocytochemistry with SYN-1 and automated image analysis.

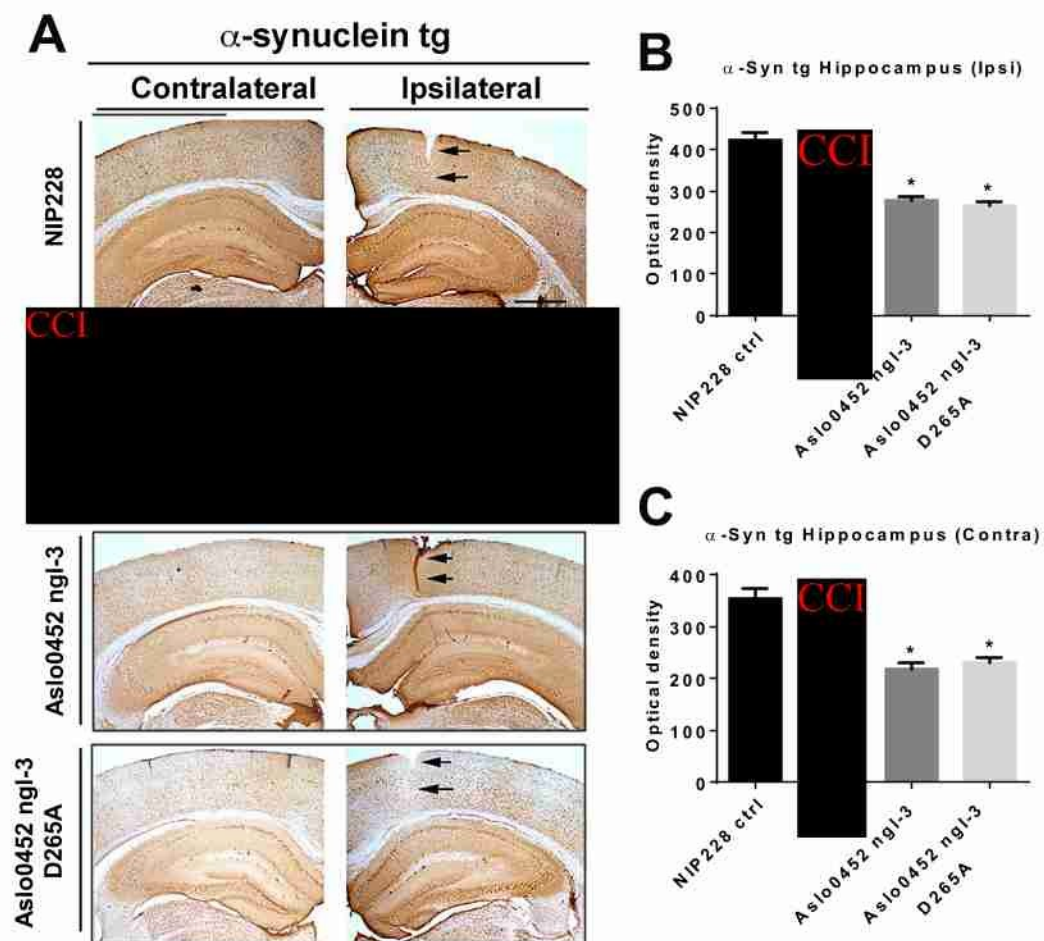
B: Quantification of α -synuclein immunoreactivity data obtained from immunocytochemical analysis of ipsilateral hippocampal coronal sections represented in A.

C: Quantification of α -synuclein immunoreactivity data obtained from immunocytochemical analysis of contralateral hippocampal coronal sections represented in A.

Each column is the mean $\pm$ SEM value of 10 independent antibody treatments (n=10 mice per antibody treatment group). *P<0.05 vs NIP228 ctrl; 1-way ANOVA with Dunnett's post-test.

Similar results were obtained when the LV- α -synuclein vector was injected into the right hippocampus of α -synuclein tg mice. Passive immunization with MEDI1341 or MEDI1341 D265A CCI, led to a robust and statistically significant reduction in both the ipsilateral and contralateral levels of α -synuclein immunoreactivity in the hippocampus when compared to NIP228-treated α -synuclein tg mice (Figure 6).

Figure 6 **MEDI1341 blocks α -synuclein spreading in α -synuclein transgenic mice**



ANOVA = analysis of variance; contra = contralateral; ipsi = ipsilateral; SEM = standard error of mean.

A: α -synuclein tg mice injected with LV- α -synuclein into the right hippocampus (black arrows) were passively immunized with weekly doses of anti- α -synuclein mouse IgG1 antibodies: MEDI1341 (Aslo0452 ngl-3), MEDI1341 D265A (Aslo0452 ngl-3 D265A; effector null mutant), CCI or with NIP228 isotype control antibody, for 13 weeks, followed by determination of α -synuclein spreading by immunocytochemistry with SYN-1 and automated image analysis.

B: Quantification of α -synuclein immunoreactivity data obtained from immunocytochemical analysis of ipsilateral hippocampal coronal sections represented in A.

C: Quantification of α -synuclein immunoreactivity data obtained from immunocytochemical analysis of contralateral hippocampal coronal sections represented in A.

Each column is the mean $\pm$ SEM value of 10 independent antibody treatments (n=10 mice per antibody treatment group).

*P<0.05 vs NIP228 ctrl; 1-way ANOVA with Dunnett's post-test.

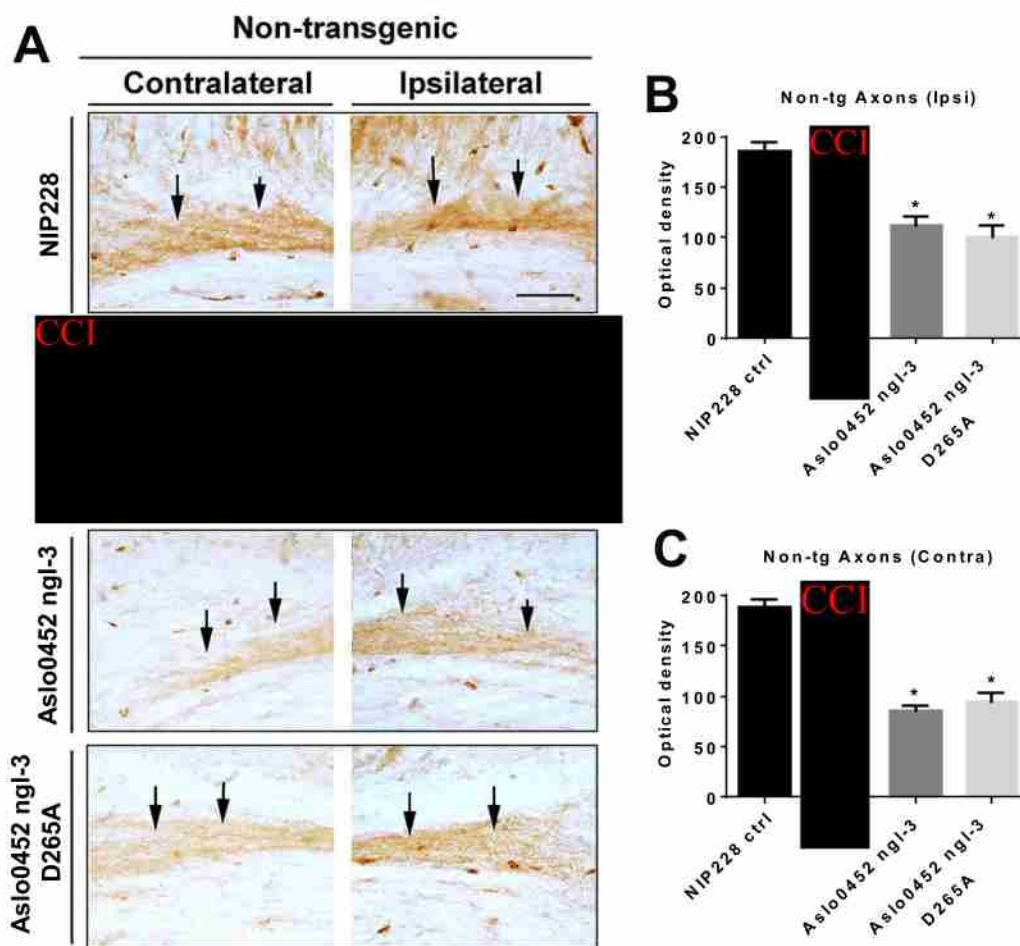
Assessment of the effect of MEDI1341 on Ipsilateral to contralateral transaxonal spreading of LV α -synuclein

At higher magnification, LV-expressed α -synuclein immunoreactive deposits were observable along both ipsilateral axons of the injected side and contralateral axons of the non-injected side of non-tg mice, suggesting that α -synuclein spreading to the contralateral hippocampus may principally occur along axons (trans-axonal spreading). Both the ipsilateral and contralateral levels of axonal α -synuclein deposits in non-tg mice passively immunized with either MEDI1341 antibody or MEDI1341 D265A, were significantly lower than the levels of axonal α -synuclein deposits in non-tg mice treated with NIP228 isotype control mouse IgG.

CCI [REDACTED] These data indicate that passive immunization of mice with either MEDI1341 or the effector null D265A mutant version of MEDI1341 clears axonal α -synuclein deposits and robustly blocks the ipsilateral-to-contralateral transfer of α -synuclein along axons in this lentiviral- α -synucleinopathy mouse model (Figure 7).

Very similar results were obtained when the LV- α -synuclein vector was injected into the right hippocampus of α -synuclein tg mice. Passive immunization with MEDI1341 or MEDI1341 D265A, **CCI** [REDACTED], led to a robust and statistically significant reduction in both the ipsilateral and contralateral levels of α -synuclein immunoreactivity along axons when compared to NIP228-treated α -synuclein tg mice (Figure 8).

Figure 7 MEDI1341 reduces deposition and spreading of lentivirally-expressed α -synuclein along axons



ANOVA = analysis of variance; contra = contralateral; ipsi = ipsilateral; SEM = standard error of mean.

A: Non-tg mice injected with LV- α -synuclein into the right hippocampus were passively immunized with 13 weekly doses of anti- α -synuclein mouse IgG1 antibodies: MEDI1341 (Aslo0452 ngl-3), MEDI1341 D265A (Aslo0452 ngl-3 D265A), **CCI** or with NIP228 isotype control antibody, followed by immunocytochemical analysis of α -synuclein deposits along ipsilateral and contralateral trans-hippocampal axons (black arrows).

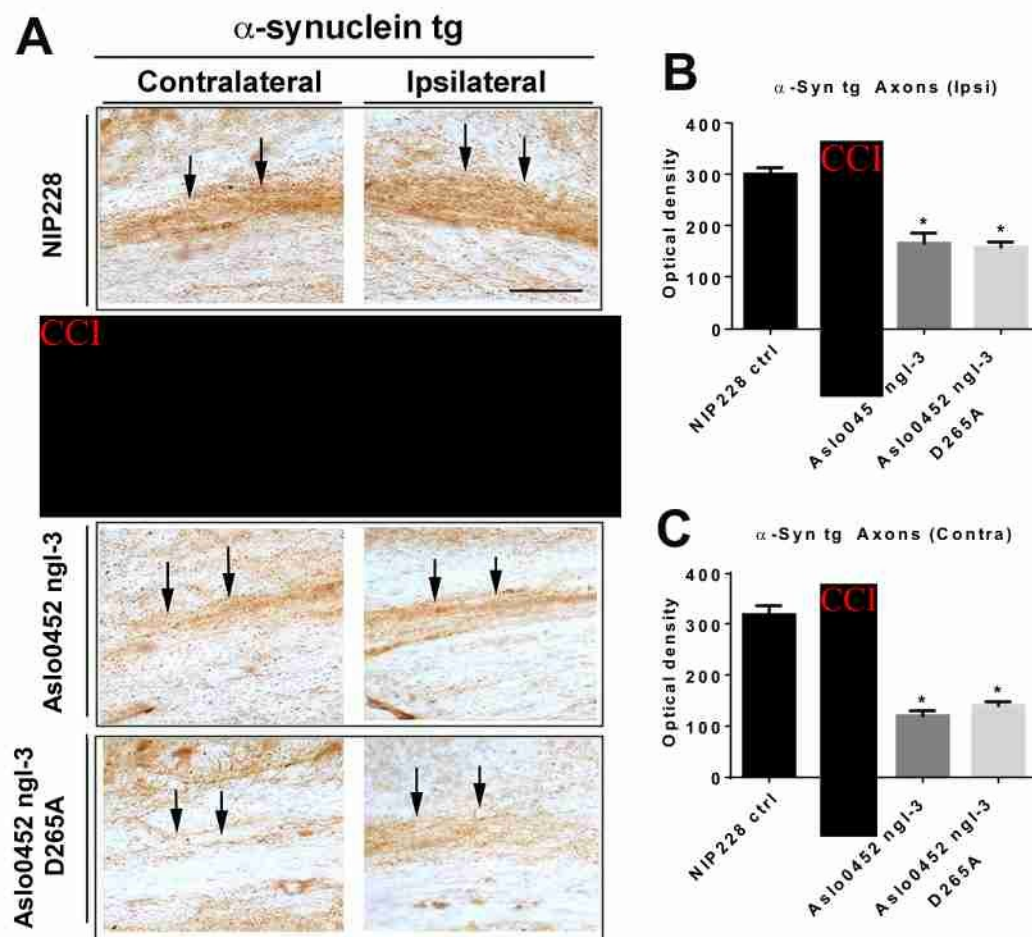
B: Quantification of ipsilateral axonal α -synuclein deposits determined by immunocytochemistry with SYN-1 and automated image analysis.

C: Quantification of contralateral axonal α -synuclein deposits determined by immunocytochemistry with SYN-1 and automated image analysis.

Each column is the mean $\pm$ SEM value of 10 independent antibody treatments (n=10 mice per antibody treatment group).

*P<0.05 vs NIP228 ctrl; 1-way ANOVA with Dunnett's post-test.

Figure 8 **MEDI1341 reduces deposition and spreading of lentivirally-expressed α -synuclein along axons in α -synuclein transgenic mice**



ANOVA = analysis of variance; α -syn tg = α -synuclein transgenic mice; Contra = contralateral; Ipsi = ipsilateral; SEM = standard error of mean.

A: α -synuclein tg mice injected with LV- α -synuclein into the right hippocampus were passively immunized with weekly doses of anti- α -synuclein mouse IgG1 antibodies: MEDI1341 (Aslo0452 ngl-3), MEDI1341 (Aslo0452 ngl-3 D265A), **CCI** or with NIP228 isotype control antibody, for 13 weeks, followed by immunocytochemical analysis of α -synuclein deposits along ipsilateral and contralateral trans-hippocampal axons (black arrows).

B: Quantification of ipsilateral axonal α -synuclein deposits determined by immunocytochemistry with SYN-1 and automated image analysis.

C: Quantification of contralateral axonal α -synuclein deposits determined by immunocytochemistry with SYN-1 and automated image analysis.

Each column is the mean $\pm$ SEM value of 10 independent antibody treatments (n=10 mice per antibody treatment group).

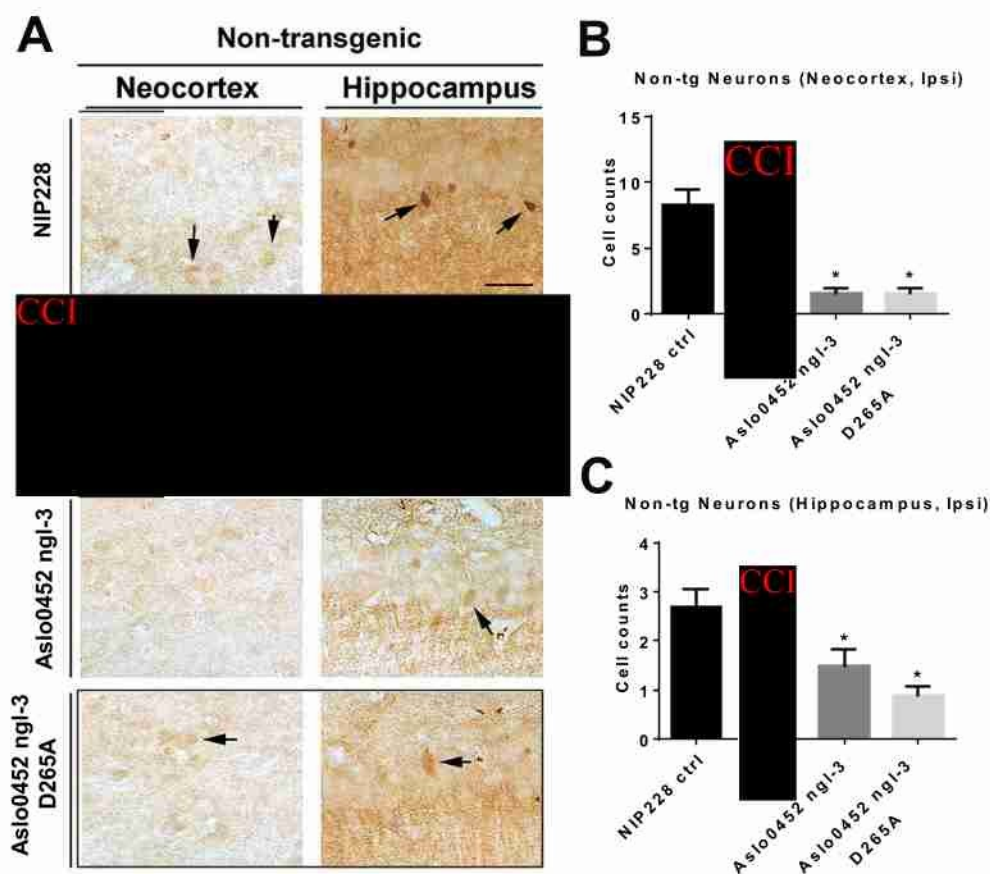
* P<0.05 vs NIP228 ctrl; 1-way ANOVA with Dunnett's post-test.

Assessment of the effect of MEDI1341 on α -synuclein deposits in neuropil and neurons

In LV- α -synuclein-injected non-tg mice, at higher magnification, intense α -synuclein immunoreactivity was detected in the neuropil of the ipsilateral hippocampus and to a lesser extent in the neuropil of the ipsilateral neocortex. In addition, intense deposits of α -synuclein were detected in a number of identifiable neuronal cell bodies (soma) in the CA1 region of the ipsilateral hippocampus and weaker α -synuclein immunoreactivity was detected in layer 5 neurons of the ipsilateral neocortex. Non-tg mice treated with either MEDI1341 antibody or MEDI1341 D265A had significantly reduced numbers of ipsilateral CA1 neurons and ipsilateral layer 5 neurons containing α -synuclein deposits compared to NIP228 isotype control mouse IgG-treated non-tg mice, CCI. The intensity of α -synuclein immunoreactivity in the neuropil and neurons of the ipsilateral CA1 region of the hippocampus and layer 5 region of the neocortex was also noticeably lower in MEDI1341-treated and MEDI1341 D265A-treated non-tg mice compared to NIP228 isotype control mouse IgG-treated non-tg mice (Figure 9).

Similar results were obtained when the LV- α -synuclein vector was injected into the right hippocampus of α -synuclein tg mice; treatment with MEDI1341 or MEDI1341 D265A CCI led to a statistically significant decrease in the numbers of neurons containing strong α -synuclein immunoreactivity in the ipsilateral CA1 hippocampal and layer 5 neocortical regions, as well as in the contralateral CA1 hippocampal region, when compared to NIP228 isotype control antibody-treated α -synuclein tg mice (Figure 10).

Figure 9 **MEDI1341 reduces α -synuclein deposition in CA1 hippocampal neurons and layer 5 neocortical neurons**



ANOVA = analysis of variance; contra = contralateral; ipsi = ipsilateral; SEM = standard error of mean.

A: Non-tg mice injected with LV- α -synuclein into the right hippocampus were passively immunized with weekly doses of anti- α -synuclein mouse IgG1 antibodies: MEDI1341 (Aslo0452 ngl-3), MEDI1341 D265A (Aslo0452 ngl-3 D265A), **CCI** or with NIP228 isotype control antibody, for 13 weeks, followed by immunocytochemical analysis of α -synuclein deposits in ipsilateral CA1 hippocampal neurons and ipsilateral layer 5 neocortical neurons (black arrows).

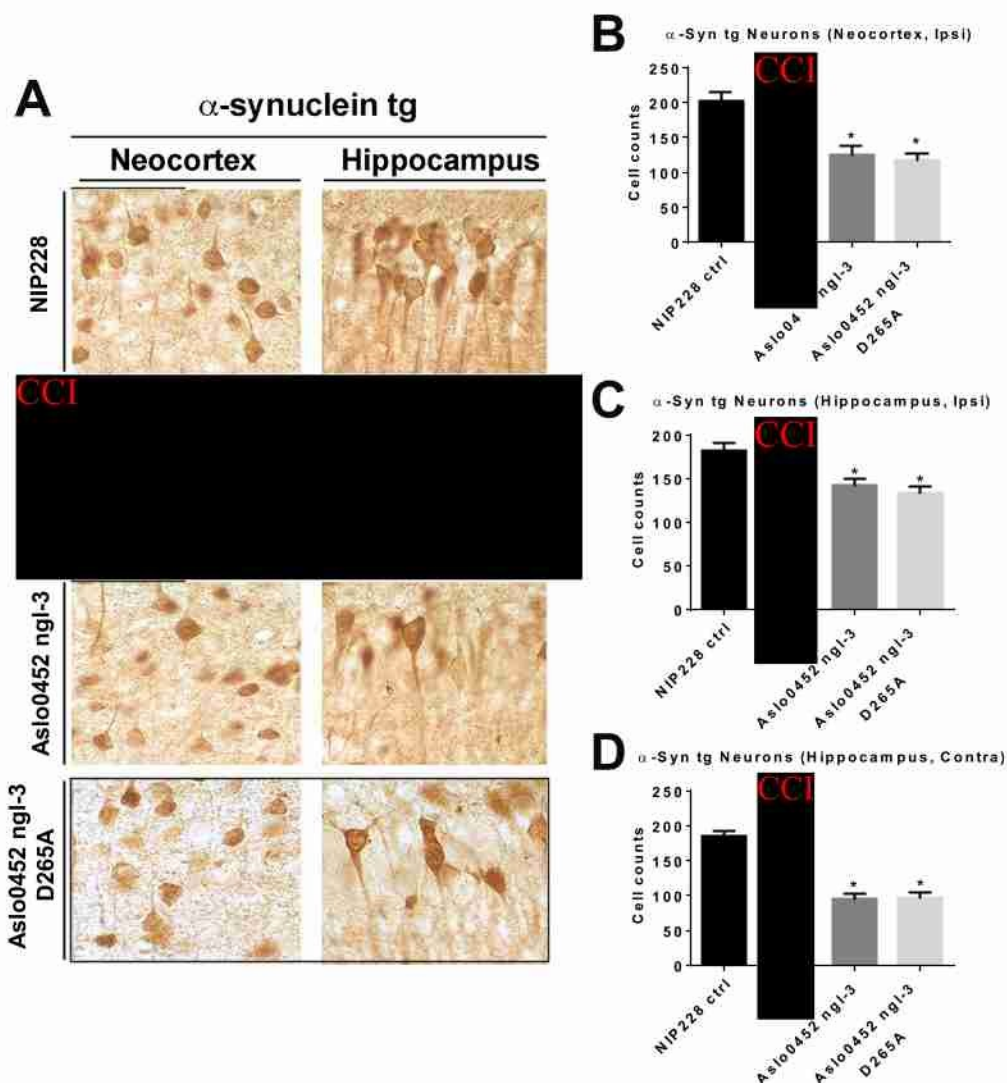
B: Quantification of α -synuclein deposits in ipsilateral layer 5 neocortical neurons determined by immunocytochemistry with SYN-1 and automated image analysis.

C: Quantification of α -synuclein deposits in ipsilateral CA1 hippocampal neurons determined by immunocytochemistry with SYN-1 and automated image analysis.

Data shown represents the number of α -synuclein positive cells (neurons) per 0.1 sq mm. Each column is the mean $\pm$ SEM value of 10 independent antibody treatments (n=10 mice per antibody treatment group).

*P<0.05 vs NIP228 ctrl; 1-way ANOVA with Dunnett's post-test.

Figure 10 **MEDI1341 reduces α -synuclein deposition in CA1 hippocampal neurons and layer 5 neocortical neurons in α -synuclein transgenic mice**



ANOVA = analysis of variance; contra = contralateral; ipsi = ipsilateral; SEM = standard error of mean.

A: α -synuclein tg mice injected with LV- α -synuclein into the right hippocampus were passively immunized with weekly doses of anti- α -synuclein mouse IgG1 antibodies: MEDI1341 (Aslo0452 ngl-3), MEDI1341 (Aslo0452 ngl-3 D265A), **CCI** or with NIP228 isotype control antibody, for 13 weeks, followed by immunocytochemical analysis of α -synuclein deposits in ipsilateral CA1 hippocampal neurons and ipsilateral layer 5 neocortical neurons.

B: Quantification of α -synuclein deposits in ipsilateral layer 5 neocortical neurons determined by immunocytochemistry with SYN-1 and automated image analysis.

C: Quantification of α -synuclein deposits in ipsilateral CA1 hippocampal neurons determined by immunocytochemistry with SYN-1 and automated image analysis.

D: Quantification of α -synuclein deposits in contralateral CA1 hippocampal neurons determined by immunocytochemistry with SYN-1 and automated image analysis.

Data shown represents the number of α -synuclein positive cells (neurons) per 0.1 sq mm. Each column is the mean $\pm$ SEM value of 10 independent antibody treatments (n=10 mice per antibody treatment group).

*P<0.05 vs NIP228 ctrl; 1-way ANOVA with Dunnett's post-test.

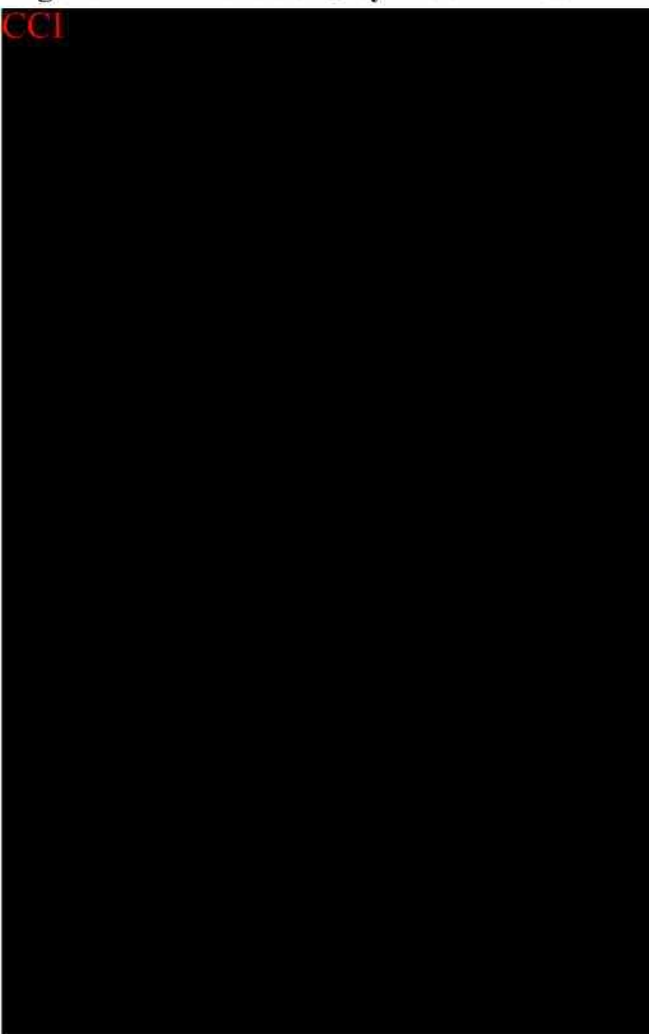
4.1.1.3 Pharmacodynamic biomarker analysis

GLP rat and monkey studies

Once weekly iv doses of **CCI**, or **CCI** mg/kg MEDI1341 were administered to male and female Sprague-Dawley rats and cynomolgus monkeys for 13 weeks (Reports AB21095 and AB21096). Toxicology data from this study are summarized in [Section 4.3.2](#).



Figure 11 Levels of α -synuclein in CSF



B: Monkey Free α -synuclein (Study AB21096 [BS001397-85])

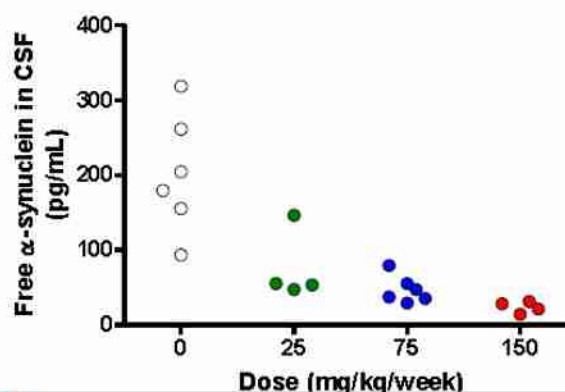


Figure 12 Total α -synuclein plasma concentration from the first 6 hours after dose

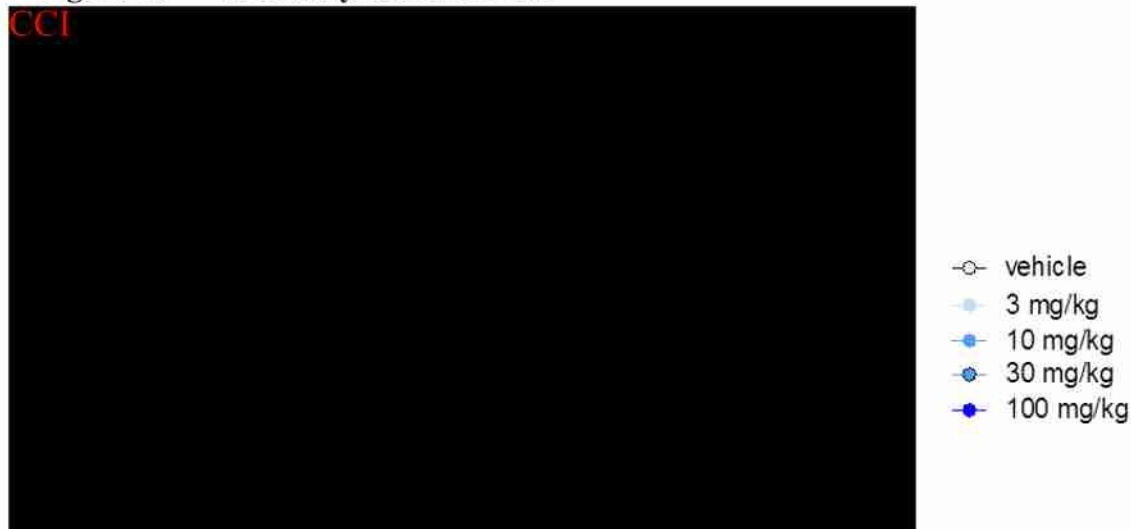


Non-GLP rat studies

Free α -synuclein concentrations in rat CSF were determined after administration of 3, 10, 30, or 100 mg/kg MEDI1341 by single iv (bolus) injection (BS001216-65 [BOL 142-2 {Key 1054}])).

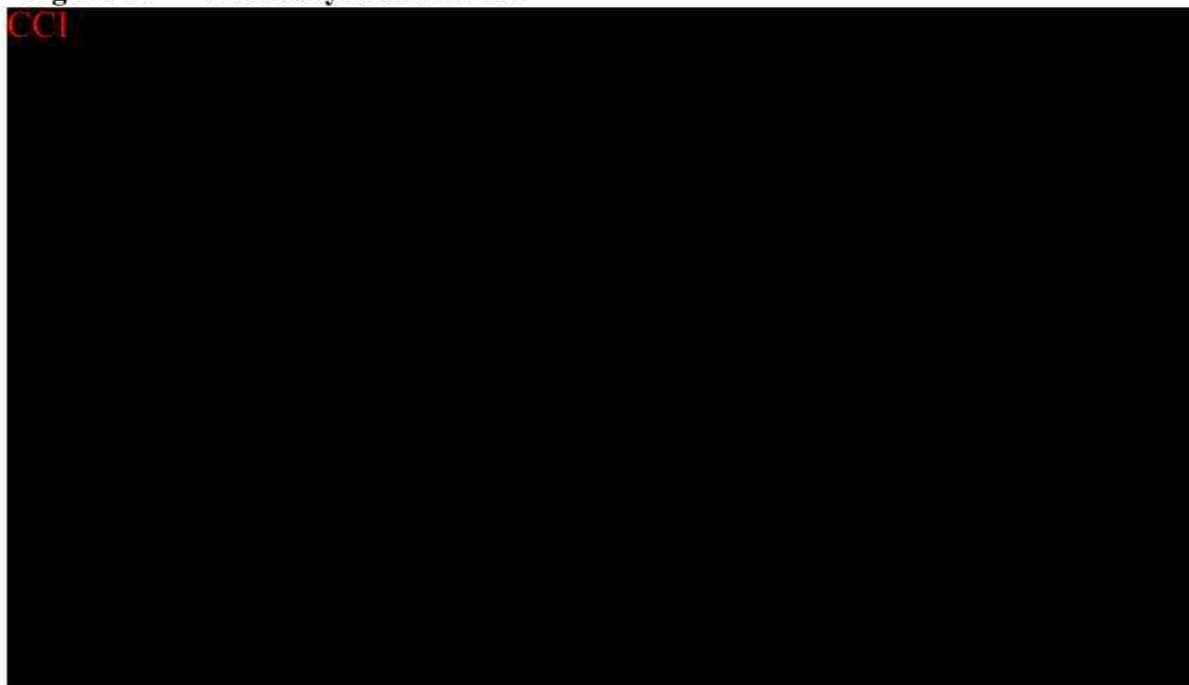
As observed in the GLP toxicology studies ([Section 4.3.2](#)), CCI

Figure 13 Free α -synuclein in CSF



Using in vivo microdialysis to sample brain ISF in rats, MEDI1341 (30 mg/kg iv) CCI

Figure 14 Free α -synuclein in ISF



Data shown are mean $\pm$ Standard Error of Mean.

Closed symbols = 30 mg/kg iv MEDI1341; open symbols = vehicle; LLOQ = CCI pg/mL;

ULOQ = CCI pg/mL.

ISF = interstitial fluid; iv = intravenous; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.

4.1.2 Secondary pharmacodynamics

Secondary pharmacodynamics studies with MEDI1341 were not conducted.

4.1.3 Safety pharmacology

No stand-alone safety pharmacology studies were conducted with MEDI1341. Safety pharmacology endpoints were assessed in the GLP toxicology studies with MEDI1341 in Sprague-Dawley rats and cynomolgus monkeys (Reports: AB21095, AB21096, AB22290, and AB22301). These studies are summarized in [Section 4.3.2](#).

4.1.4 Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies with MEDI1341 were not conducted.

4.2 Non-clinical pharmacokinetics and drug metabolism

4.2.1 Absorption

No studies to assess the absorption of MEDI1341 have been conducted to date.

4.2.2 Distribution

No formal distribution studies have been conducted to date, however the PK of MEDI1341 in the CSF of Sprague-Dawley rats have been investigated (Report: BOL142 PK analysis; data presented in [Section 4.2.6.1](#)). In summary, following a 3, 10, 30, or 100 mg/kg iv dose to rats, the exposure of MEDI1341 (AUC_{last}) in CSF was 0.3% to 0.4% of that observed in plasma. Following repeat dose administration to cynomolgus monkeys for 13 weeks (Report AB21096; data presented in [Section 4.3.2.2](#)), the concentration of MEDI1341 in CSF increased proportionally with dose. The CSF exposure compared to serum exposure suggested approximately 0.2% CNS penetration by MEDI1341 in cynomolgus monkey, confirming distribution of MEDI1341 to the CNS compartment consistent with that expected for an IgG.

4.2.3 Metabolism

No studies have been conducted.

4.2.4 Excretion

No studies have been conducted.

4.2.5 Pharmacokinetic drug interactions

No studies have been conducted.

4.2.6 Other pharmacokinetic studies

4.2.6.1 Single dose pharmacokinetics

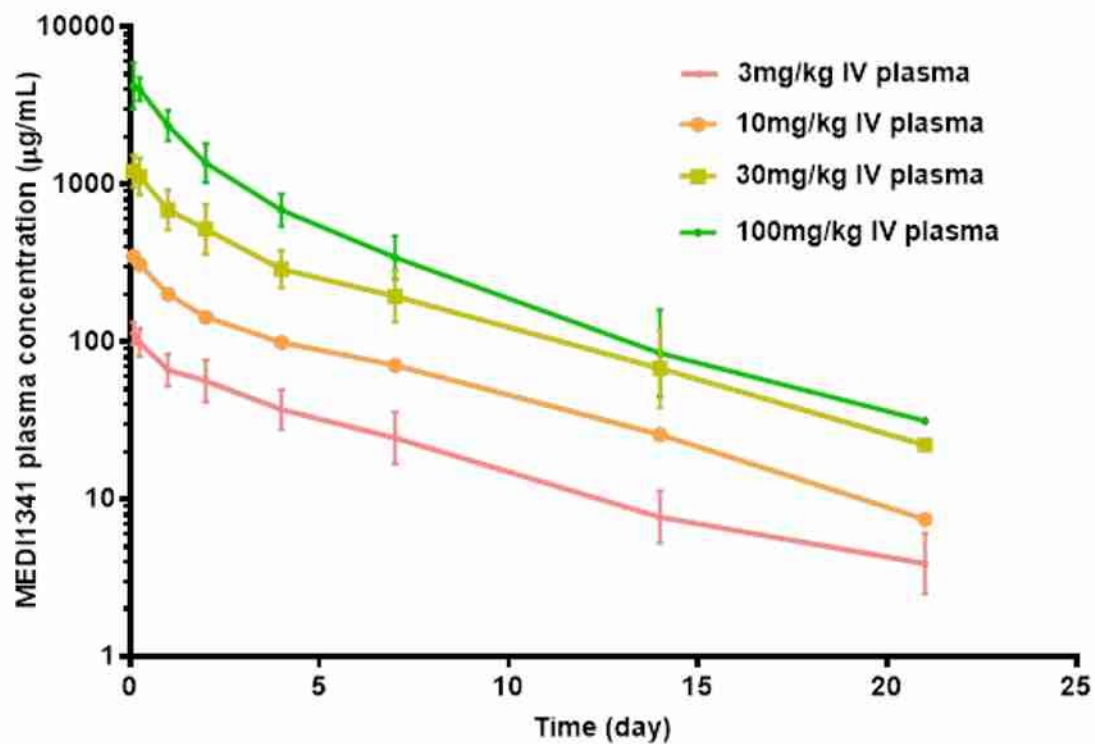
Pharmacokinetics of MEDI1341 in the rat following single intravenous administration

The PK and pharmacodynamics of total MEDI1341 were determined in male Sprague-Dawley rats following single 3, 10, 30, or 100 mg/kg iv administration (Report: BOL142 PK analysis).

Following administration of a single iv dose of 3 mg/kg, MEDI1341 exhibited a mean CL of 6.53 mL/day/kg and a mean V_z of 44.2 mL/kg that resulted in a $t_{1/2}$ of 4.79 days. Comparable mean CL and V_z values were determined after iv administration at 10, 30, and 100 mg/kg.

Following single iv administration, mean MEDI1341 C_{max} increased in a dose proportional manner from CC1 $\mu\text{g/mL}$ at 3 mg/kg to CC1 $\mu\text{g/mL}$ at 100 mg/kg. Mean AUC_{last} increased in a dose proportional manner between 3 mg/kg and 30 mg/kg with mean AUC_{last} values of CC1 $\mu\text{g}\cdot\text{day/mL}$ and CC1 $\mu\text{g}\cdot\text{day/mL}$ determined at these dose levels respectively. Mean MEDI1341 AUC_{last} increased in a slightly less than dose proportional manner between 30 mg/kg and 100 mg/kg with a mean AUC_{last} of CC1 $\mu\text{g}\cdot\text{day/mL}$ observed following 100 mg/kg administration. The plasma concentration-time profiles of MEDI1341 are presented in [Figure 15](#). The mean PK of MEDI1341 determined in this study is presented in [Table 1](#).

Figure 15 Plasma concentration-time profiles of MEDI1341 after intravenous administration of MEDI1341 in rats



Data are presented as mean plasma concentration ($\mu\text{g/mL}$) $\pm$ standard deviation.

Table 1 Mean plasma pharmacokinetic parameters after intravenous administration of MEDI1341 in rats

Mean parameter±SD	Dose (mg/kg)			
	3	10	30	100
t _{max} (day)	CCI			3
C _{max} (µg/mL)				
C _{trough} (µg/mL)				
AUC _{last} (µg•day/mL)				
AUC _{inf} (µg•day/mL)				
CL (mL/day/kg)				
t _{1/2} (day)				
V _z (mL/kg)				

AUC_{inf} = area under curve extrapolated to infinity; AUC_{last} = area under curve extrapolated to last measured time point; CL = clearance; C_{max} = maximum observed concentration; C_{trough} = last measurable time point; SD = standard deviation; t_{max} = time of C_{max}; t_{1/2} = half-life; V_z = terminal volume of distribution.

Following administration of a single 3 mg/kg iv dose of MEDI1341, a mean CSF C_{max} of CCI µg/mL was observed. Mean MEDI1341 CSF C_{max} increased in a dose proportional manner with mean C_{max} values of CCI µg/mL, CCI µg/mL and CCI µg/mL observed at 10, 30, and 100 mg/kg, respectively. The mean AUC_{last} in CSF increased in a less than dose proportional manner between 3 and 100 mg/kg iv administration.

Following 3 mg/kg iv administration, a mean CSF AUC_{last} of CCI µg•day/mL was observed; this increased to CCI µg•day/mL following a 100 mg/kg dose. Following a 3 mg/kg dose, comparing mean AUC_{last} in CSF to mean AUC_{last} in plasma, indicates that the CSF exposure of MEDI1341 was 0.4% of that observed in plasma. Comparable CSF/plasma data was observed following 10, 30, and 100 mg/kg administration, with AUC_{last} in CSF being 0.3% of the plasma AUC_{last}. The CSF concentration-time profiles of MEDI1341 are presented in Figure 16. The mean CSF PK of MEDI1341 determined in this study is presented in Table 2.

Figure 16 CSF concentration-time profiles of MEDI1341 after intravenous administration of MEDI1341 in rats

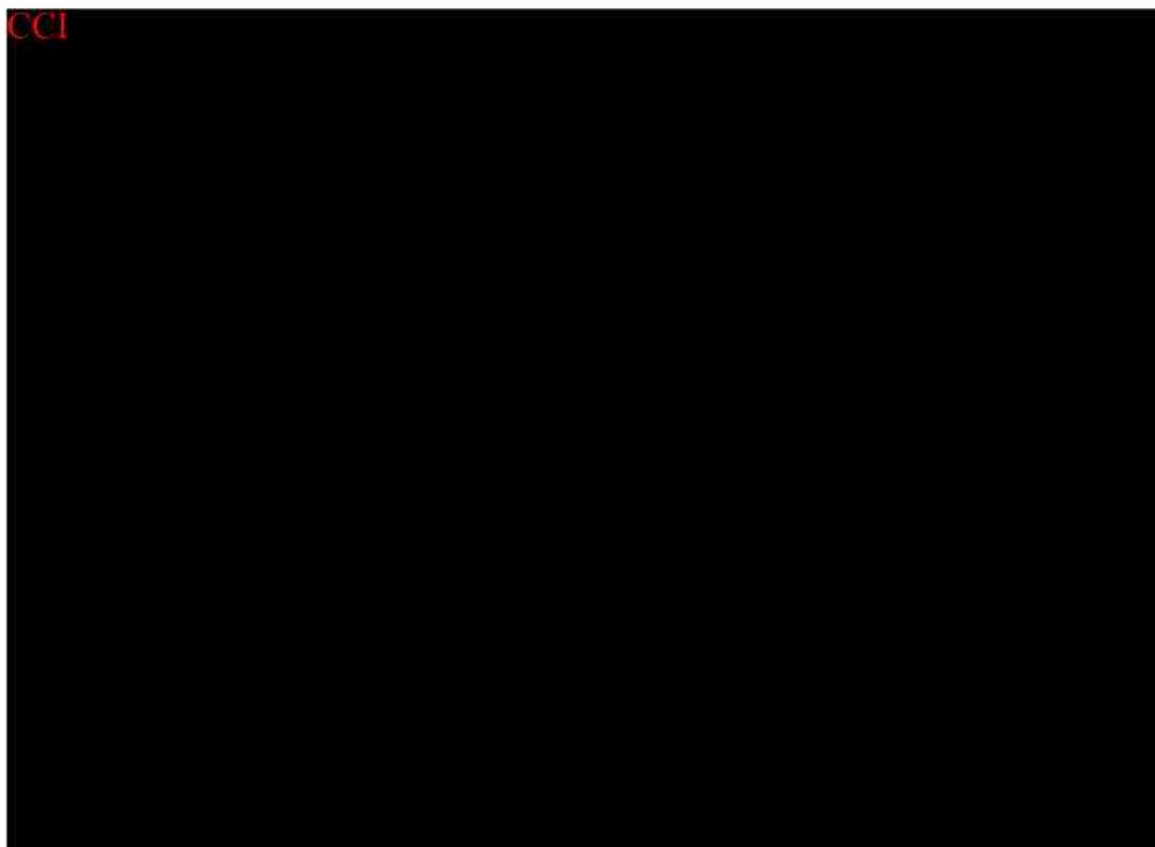


Table 2 Mean CSF pharmacokinetic parameters after a single intravenous administration of MEDI1341 in rats

Mean parameter±SD	Dose (mg/kg)			
	3	10	30	100
t _{max} (day)	CCI			
C _{max} (µg/mL)				
C _{trough} (µg/mL)				
AUC _{last} (µg·day/mL)				

AUC_{last} = area under curve extrapolated to last measured time point; C_{max} = maximum observed concentration; CSF = cerebrospinal fluid; C_{trough} = last measurable time point; t_{max} = time of C_{max}.

Pharmacokinetics of MEDI1341 in rat following high dose intravenous administration

Three groups (n=1 per group) of male Sprague-Dawley (CD) rats received iv doses of MEDI1341 at CCI mg/kg on Day 1 and Day 8, with the aim to evaluate the serum PK of MEDI1341 at higher doses than tested previously. Blood samples were collected up to 7 days post the Day 1 MEDI1341 administration (0.021, 0.25, 1, 2, 4, 7 days), with an

additional sample taken 24 hours after a second iv administration on Day 8. Serum was prepared from the blood samples.

Following single iv administration of MEDI1341 in male Sprague-Dawley rats, MEDI1341 serum C_{max} increased in a dose proportional manner. MEDI1341 exposure AUC extrapolated to infinity (AUC_{inf}) increased in a dose proportional manner between [REDACTED] and [REDACTED] mg/kg but increased in a sub-proportional manner between [REDACTED] and [REDACTED] mg/kg. Following single iv administration of MEDI1341 in male Sprague-Dawley rats at [REDACTED], and [REDACTED] mg/kg, MEDI1341 mean C_{max} were [REDACTED], and [REDACTED] $\mu\text{g/mL}$, respectively. The corresponding values for AUC_{inf} were [REDACTED], and [REDACTED] $\mu\text{g}\cdot\text{day/mL}$ for [REDACTED], and [REDACTED] mg/kg doses, respectively (Table 3).

Following a second iv administration (Day 8) of MEDI1341 at the same dose levels of [REDACTED] [REDACTED] or [REDACTED] mg/kg, observed concentrations 24 hours after dosing were similar to the observed concentrations 24 hours after the first iv administration (Day 1), showing no accumulation of compound when dosed intravenously with a 1-week dosing interval.

Table 3 Mean serum pharmacokinetic parameters after a single high dose intravenous administration of MEDI1341 in rats

Mean parameter $\pm$ SD	Dose (mg/kg)
	[REDACTED]
t_{max} (day)	[REDACTED]
C_{max} ($\mu\text{g/mL}$)	[REDACTED]
C_{trough} ($\mu\text{g/mL}$)	[REDACTED]
AUC_{last} ($\mu\text{g}\cdot\text{day/mL}$)	[REDACTED]
AUC_{inf} ($\mu\text{g}\cdot\text{day/mL}$)	[REDACTED]
CL (mL/day/kg)	[REDACTED]
$t_{1/2}$ (day)	[REDACTED]
V_z (mL/kg)	[REDACTED]

AUC_{inf} = area under curve extrapolated to infinity; AUC_{last} = area under curve extrapolated to last measured time point; CL = clearance; C_{max} = maximum observed concentration; C_{trough} = last measurable time point; SD = standard deviation; t_{max} = time of C_{max} ; $t_{1/2}$ = half-life; V_z = terminal volume of distribution.

Pharmacokinetics of MEDI1341 in the monkey following single and repeat intravenous administration

The total and free PK and pharmacodynamic profiles of MEDI1341 have been investigated in male cynomolgus monkeys (n=█/dose group) following iv administration of MEDI1341 at single doses of 1, 10, and 30 mg/kg (Report: 8304343). The 10 mg/kg group of animals also received repeat iv doses of MEDI1341 on Day █ and 35. The pharmacodynamic data from this study are summarized in [Section 4.1.1.3](#). The total and free pharmacokinetics parameters of MEDI1341 on Day 1 and Day 35 are summarized in [Table 4](#).

Total MEDI1341

Following iv administration of 1, 10, and 30 mg/kg MEDI1341, total MEDI1341 plasma exposure increased slightly more than dose proportionally after the first dose. The mean C_{max} increased from ███ μg/mL at █ mg/kg to ███ μg/mL at 30 mg/kg, while AUC_{last} increased from ███ μg•day/mL to ███ μg•day/mL over the same dose range.

Following 10 mg/kg iv administration on Day 1, the mean total MEDI1341 C_{max} and AUC_{last} were ███ μg/mL and ███ μg•day/mL, respectively. On Day 36 a mean C_{max} of ███ μg/mL and AUC_{last} of ███ μg•day/mL were observed. The AI for C_{max} and AUC_{last} were ███ and ███ respectively, indicating minimal accumulation in plasma upon 10 mg/kg/week repeated dosing of MEDI1341.

On Day 1, a mean total CL of ███ mL/day/kg and a mean total V_z of ███ mL/kg were determined, resulting in a mean $t_{1/2}$ of ███ days. Following 10 mg/kg/week iv administration, on Day 36, MEDI1341 exhibited a mean total CL of ███ mL/day/kg and a mean V_z of ███ mL/kg, resulting in a mean $t_{1/2}$ of ███ days.

Free MEDI1341

Following Day 1 iv administration, MEDI1341 free systemic CL was determined to be ███ mL/day/kg, with a V_z of ███ mL/kg, resulting in a $t_{1/2}$ of ███ days.

Following single iv administration of 1, 10, and 30 mg/kg, free MEDI1341 plasma exposure increased dose proportionally. The mean free C_{max} increased from ███ μg/mL at █ mg/kg to ███ μg/mL at 30 mg/kg, while free AUC_{last} increased from ███ μg•day/mL to ███ μg•day/mL over the same dose range. Following a 10 mg/kg/week repeat dose, the AI for free C_{max} and free AUC_{last} were ███ and ███, respectively, indicating minimal accumulation in plasma upon repeat dosing.

Table 4 Mean total plasma pharmacokinetic parameters after intravenous administration of MEDI1341 in monkeys

Mean Parameter ± SD	Dose (mg/kg/week)					
	CCI					
	Total	Free	Total	Free	Total	Free
Day 1:	CCI					
t _{max} (day)						
C _{max} (µg/mL)						
C _{last} (µg/mL)						
AUC _{last} (µg•day/mL)						
CL (mL/day/kg)						
t _{1/2} (day)						
V _{ss} (mL/kg)						
V _z (mL/kg)						
Day 35:						
t _{max} (day)						
C _{max} (µg/mL)						
C _{last} (µg/mL)						
AUC _{last} (µg•day/mL)						
CL _{ss} (mL/day/kg)						
t _{1/2} (day)						
V _{ss} (mL/kg)						
V _z (mL/kg)						

- = no samples collected; AUC_{last} = area under curve extrapolated to last measured time point; CL = clearance; C_{last} = last measurable concentration; CL_{ss} = steady state clearance; C_{max} = maximum observed concentration; C_{trough} = last measurable time point; SD = standard deviation; t_{max} = time of C_{max}; t_{1/2} = half-life; V_{ss} = steady state volume of distribution; V_z = terminal volume of distribution.

Pharmacokinetics of MEDI1341 in cynomolgus monkey following high dose intravenous administration

The aim of the study was to evaluate the serum PK of MEDI1341 following high dose iv administration at a dose level of **CCI**, or **CCI** mg/kg on Day 1 and Day 8, in 3 groups of female cynomolgus monkeys. The test formulations were administered intravenously with a 30 minute infusion for groups 1 and 2 (**CCI** and **CCI** mg/kg, respectively) and 60 minutes for group 3 (**CCI** mg/kg). Blood samples were collected up to 7 days post dose (0.021, 0.25, 1, 4, 7 days), with 1 additional sample taken 24 hours after a second intravenous administration.

Over the iv dose range tested in female cynomolgus monkeys, MEDI1341 serum exposure increased in an approximately dose proportional manner after a single iv administration of MEDI1341, with approximately linear increases in both C_{max} and AUC_{last} (Table 5).

Following iv administration of MEDI1341 at **CCI**, and **CCI** mg/kg, mean AUC_{last} were **CCI**, and **CCI** $\mu\text{g}\cdot\text{day}/\text{mL}$, respectively, and mean C_{max} were **CCI**, and **CCI** $\mu\text{g}/\text{mL}$, respectively. The corresponding t_{max} were **CCI**, and **CCI** day after the start of infusion following intravenous administration of MEDI1341 at **CCI**, and **CCI** mg/kg, respectively. The t_{max} consistently corresponded to the first samples taken after the end of the iv infusion period at each dose level, with the differences in reported t_{max} due to delay in blood sampling at **CCI** mg/kg and a longer duration of infusion at **CCI** mg/kg, compared to **CCI** mg/kg.

Following a second iv administration (Day 8) of MEDI1341 at the same dose level of **CCI** **CCI** or **CCI** mg/kg, observed concentrations 1 day after dosing were similar to the observed concentrations 1 day after the first iv administration (Day 1), showing little to no accumulation of compound when dosed intravenously with a 1-week dosing interval.

Table 5 Mean serum pharmacokinetic parameters after a single high dose intravenous administration of MEDI1341 in cynomolgus monkey

Mean parameter $\pm$ SD	Dose (mg/kg)
	CCI
t_{max} (day)	
C_{max} ($\mu\text{g}/\text{mL}$)	
C_{trough} ($\mu\text{g}/\text{mL}$)	
AUC_{last} ($\mu\text{g}\cdot\text{day}/\text{mL}$)	
AUC_{inf} ($\mu\text{g}\cdot\text{day}/\text{mL}$)	

AUC_{inf} = area under curve extrapolated to infinity; AUC_{last} = area under curve extrapolated to last measured time point; CL = clearance; C_{max} = maximum observed concentration; C_{trough} = last measurable time point; SD = standard deviation; t_{max} = time of C_{max} ; $t_{1/2}$ = half-life; V_z = terminal volume of distribution.

4.2.6.2 Repeat dose toxicokinetics

Repeat-dose GLP toxicokinetic studies were conducted with MEDI1341 in Sprague-Dawley rats and cynomolgus monkeys.

Repeat-dose toxicokinetic studies in rats

GLP toxicokinetic study of MEDI1341 in rat following once weekly intravenous administration for █ weeks

The toxicokinetics of MEDI1341 were investigated following iv administration of █ and █ mg/kg/twice weekly (ie, █ and █ mg/kg/week) of MEDI1341 to male and female Sprague-Dawley rats for █ weeks (Report: AB22290). MEDI1341 was administered twice weekly to rats (n=█/gender per dose level) by slow (5 minutes, █ mL/kg) iv bolus, at doses of █ or █ mg/kg (total dose █ and █ mg/kg/week). Blood samples were taken at 0.5, 2, 24, 72 hours (before 2nd weekly administration) post the end of the iv infusion on Days 1 and █, and 0.5, 2, 24, and 96 hours post-end of the iv infusion on Days 4 and █. The C_{max} and AUC_{last} values were calculated on a weekly basis following quantification of MEDI1341 in Week 1 and Week █ serum samples. Toxicology data from this study are summarized in [Section 4.3.2.1](#).

No gender differences in toxicokinetics were observed in the MEDI1341 dosed groups during the study, therefore the data has been combined for both genders.

Following twice weekly administration of MEDI1341, mean C_{max} and AUC_{last} values generally increased in proportion to the dose of MEDI1341 between █ and █ mg/kg/week in both sampling occasions. Following repeat twice daily dosing no accumulation was observed, with Week █ C_{max} and AUC_{last} values comparable to the corresponding values observed on Week 1 at █ or █ mg/kg/twice weekly (total dose █ and █ mg/kg/week) ([Table 6](#)).

Table 6 Toxicokinetic parameters following [REDACTED]-week administration of MEDI1341 to rat

Mean parameter	Dose (mg/kg/twice weekly)
Week 1:	[REDACTED]
C_{max}^a (µg/mL)	
AUC_{inf} (µg•h/mL)	
AUC_{last}^b (µg•day/mL)	
Week [REDACTED]	
C_{max}^a (µg/mL)	
AUC_{inf} (µg•h/mL)	
AUC_{last}^b (µg•day/mL)	

^a C_{max} was the maximum serum concentration of MEDI1341 observed over a weekly dosing period.

^b AUC_{last} was calculated over a weekly dosing period with the final PK sample being collected at 96 hours post the end of the intravenous infusion of the 2nd weekly dose.

AUC_{inf} = area under curve extrapolated to infinity; AUC_{last} = area under curve extrapolated to last measured time point; C_{max} = maximum observed concentration; NR = not reported.

GLP toxicokinetic study of MEDI1341 in rats following once weekly intravenous administration for 13 weeks

The toxicokinetics and [REDACTED] of MEDI1341 were investigated following once weekly iv administration of [REDACTED], or [REDACTED] mg/kg/week MEDI1341 to male and female Sprague-Dawley rats for 13 weeks (Report: AB21095). Toxicology data from this study are summarized in Section 4.3.2.1.

No gender differences in the toxicokinetics of MEDI1341 were observed during the study, therefore data are presented as a mean of both genders. At the end of Week 1, the exposure of MEDI1341 (in terms of C_{max} and AUC_t) increased in a dose proportional manner. At the end of Week 13, MEDI1341 C_{max} and AUC_t increased in a linear manner between [REDACTED] and [REDACTED] mg/kg/week, however a sub-proportional increase in exposure was observed between [REDACTED] and [REDACTED] mg/kg/week. There was evidence of minimal accumulation observed between Week 1 and 13 for all dose groups.

At the end of Week 1, CL was determined to be [REDACTED], and [REDACTED] mL/day/kg at [REDACTED], and [REDACTED] mg/kg/week, respectively. Volume of distribution ranged between [REDACTED] and [REDACTED] mL/kg. Half-life ranged from [REDACTED] to [REDACTED] days at the end of Week 1 and a $t_{1/2}$ of [REDACTED] days was estimated for the [REDACTED] mg/kg/week dose group at Week 13 (Table 7).

[REDACTED] were detected in animals from the [REDACTED] mg/kg/week group. In the [REDACTED] mg/kg/week group, [REDACTED] animals out of [REDACTED] animals ([REDACTED]%) tested [REDACTED] and [REDACTED] animals ([REDACTED]%) in the [REDACTED] mg/kg/week dose group. Only [REDACTED] animals tested [REDACTED] on more than

1 occasion. In the [REDACTED] mg/kg/week dose group, there were no major differences in MEDI1341 concentration between the [REDACTED] animals at Week 13. In the [REDACTED] mg/kg/week dose group, with the exception of [REDACTED], serum MEDI1341 concentrations at Week 13 were significantly lower for [REDACTED]. [REDACTED] were excluded from the non-compartmental analysis.

Table 7 Toxicokinetic parameters following 13-week administration of MEDI1341 to rats

Mean parameter	Dose (mg/kg/week)
Week 1:	[REDACTED]
t_{max} (h)	
C_{max} (µg/mL)	
AUC_{inf} (µg•day/mL)	
AUC_{last} (µg•day/mL)	
$t_{1/2}$ (days)	
Week 13:	[REDACTED]
t_{max} (h)	
C_{max} (µg/mL)	
AUC_{inf} (µg•day/mL)	
AUC_{last} (µg•day/mL)	
$t_{1/2}$ (days)	

AUC_{inf} = area under curve extrapolated to infinity; AUC_{last} = area under curve extrapolated to last measured time point; C_{max} = maximum observed concentration; N/C = not calculated; t_{max} = time of C_{max} ; $t_{1/2}$ = half-life.

Repeat-dose toxicokinetic studies in cynomolgus monkey

GLP toxicokinetic study of MEDI1341 in cynomolgus monkey following once weekly intravenous administration for [REDACTED] weeks

The toxicokinetics of MEDI1341 were investigated following iv administration of [REDACTED] and [REDACTED] mg/kg/twice weekly (ie, [REDACTED] and [REDACTED] mg/kg/week) of MEDI1341 to male and female cynomolgus monkeys for [REDACTED] weeks (Report: AB22301). MEDI1341 was administered twice weekly to cynomolgus monkeys (n=[REDACTED]/gender per dose level) at iv doses (60 minutes infusion, [REDACTED] mL/kg) of [REDACTED] or [REDACTED] mg/kg (total dose [REDACTED] or [REDACTED] mg/kg/week). Blood samples were taken at 0.5, 2, 24, 72 hours (before 2nd weekly administration) post the end of the iv infusion on Days 1 and [REDACTED] and 0.5, 2, 24, and 96 hours post-end of the iv infusion on Days 4 and [REDACTED]. The C_{max} and AUC_{last} values were calculated on a weekly basis following quantification of

MEDI1341 in Week 1 and Week [REDACTED] serum samples. Toxicology data from this study are summarized in Section 4.3.2.2.

All animals dosed with MEDI1341 were exposed to MEDI1341. No gender differences in toxicokinetics were observed in the MEDI1341 dosed groups during the study, therefore the data has been combined for both genders.

From [REDACTED] mg/kg/week to [REDACTED] mg/kg/week, mean C_{max} and mean AUC_{last} increased in proportion to the dose of MEDI1341 following a single dose and after repeated twice weekly dosing. Following repeat twice weekly doses of MEDI1341, systemic exposure was generally greater at [REDACTED] mg/kg/week compared to the observed exposure after a single dose and comparable (within [REDACTED]-fold) between sampling occasions at [REDACTED] mg/kg/week.

Table 8 Toxicokinetic parameters following [REDACTED]-week administration of MEDI1341 to cynomolgus monkey

Mean parameter	Dose (mg/kg/twice weekly)
Week 1:	[REDACTED]
C_{max}^a (µg/mL)	
AUC_{last}^b (µg•day/mL)	
Week [REDACTED]	
C_{max}^a (µg/mL)	
AUC_{last}^b (µg•day/mL)	

^a C_{max} was the maximum serum concentration of MEDI1341 observed over a weekly dosing period.

^b AUC_{last} was calculated over a weekly dosing period with the final PK sample being collected at 96 hours post the end of the intravenous infusion of the 2nd weekly dose.

AUC_{last} = area under curve extrapolated to last measured time point; C_{max} = maximum observed concentration.

GLP toxicokinetic study of MEDI1341 in monkeys following once weekly intravenous administration for 13 weeks

The toxicokinetics, [REDACTED] and PD of MEDI1341 were assessed in a 13-week repeat-dose toxicology study in cynomolgus monkeys with a 13-week recovery period (Report: AB21096), toxicology data are summarized in Section 4.3.2.2.

No gender differences in toxicokinetics were observed during the study therefore the data has been combined for both genders.

At Week 1 and 13, exposure in the 25 to 150 mg/kg/week dose range increased proportionally in terms of both C_{max} and AUC_t . At Week 1, CL , V_z , and $t_{1/2}$ were also consistent across doses. This could not be confirmed in the 150 mg/kg/week dose group, as terminal $t_{1/2}$ and related parameters could not be accurately calculated, and therefore could not be reported.

Based on a comparison of exposure during Week 1 and Week 13, MEDI1341 does not appear to accumulate in cynomolgus monkey after 13 weeks of weekly intravenous administration across the 25 to 150 mg/kg/week dose range (Table 9).

CC1 animals out of CC1 developed CC1 to MEDI1341 CC1 (%). CC1 were not detected during Week 1. There was no significant difference in C_{max} or AUC_t between the CC1 animals during Week 13. Except for CC1 in the lowest dose group, which showed a significantly lower exposure than the remaining animals and was therefore excluded from the calculation of the toxicokinetic parameters. The majority of CC1 animals were found in the CC1 mg/kg/week dose group (CC1 animals), with CC1 confirmed in each of the other dose groups.

The concentration of MEDI1341 in CSF increased proportionally with dose. The CSF/serum ratio suggested approximately 0.2% CNS penetration by MEDI1341 in cynomolgus monkey, confirming distribution of MEDI1341 to the CNS compartment consistent with that expected for an IgG.

Table 9 Toxicokinetic parameters following 13-week administration of MEDI1341 to monkeys

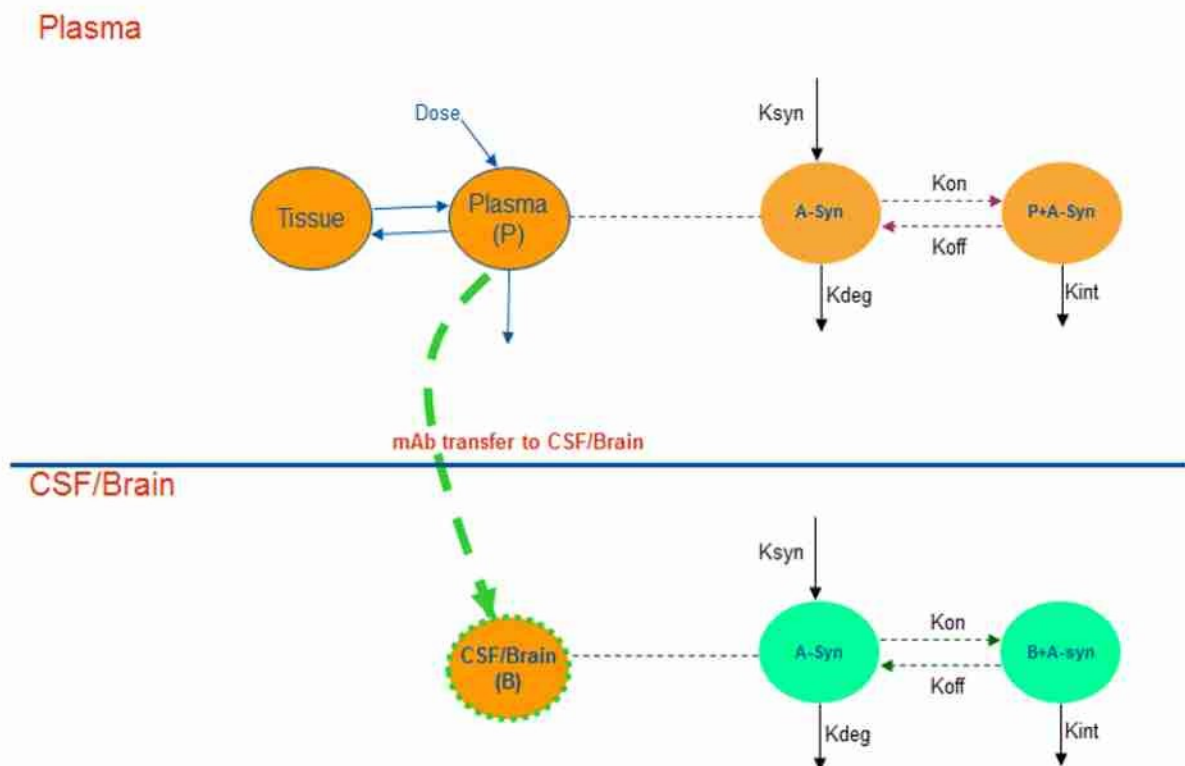
Mean parameter	Dose (mg/kg/week)		
	25	75	150
Week 1:	CC1		
C_{max} (µg/mL)			
AUC_{inf} (µg•day/mL)			
AUC_{last} (µg•day/mL)			
Week 13:	CC1		
C_{max} (µg/mL)			
AUC_{inf} (µg•day/mL)			
AUC_{last} (µg•day/mL)			

AUC_{inf} = area under curve extrapolated to infinity; AUC_{last} = area under curve extrapolated to last measured time point; C_{max} = maximum observed concentration; N/C = not calculated.

4.2.6.3 Human pharmacokinetic predictions

The pharmacokinetic/pharmacodynamic (PK/PD) model used for prediction of human PK and pharmacodynamics for MEDI1341 is represented in Figure 17.

Figure 17 PK/PD model describing the PK of MEDI1341 by a 2-compartment model and PD of α -synuclein



A-syn = α synuclein concentration in plasma and brain; B = mAb concentration in CSF/brain;
B + α -synuclein = Drug + α synuclein complex in brain; Kint = Internalization rate for P+A-syn and B+A-syn complexes; Kon & Koff = Association and dissociation rate constants of mAb for α -synuclein; Ksyn & Kdeg = Synthesis and degradation rate constants for α synuclein in plasma and brain; P = mAb concentrations plasma; P+A-syn = Drug+ α -synuclein complex in plasma; PK/PD = pharmacokinetic/pharmacodynamic.

The predicted MEDI1341 exposure at the proposed doses for the next cohorts are based on a preliminary population 2-compartment PK model. The population PK model was developed for MEDI1341 using the preliminary human PK data of the 3 available cohorts.

The PK/PD model accounts for complete MEDI1341 bioavailability after iv administration, brain penetration based on observed CSF:serum ratio, nonspecific clearance, and binding and clearance through α -synuclein pathways. The pharmacodynamic component of the model incorporates the binding of antibody to soluble α -synuclein and the resulting reductions in plasma and CSF/brain α -synuclein levels, accounting for MEDI1341-specific properties such as α -synuclein binding affinity and dissociation. The basal levels of α -synuclein in CSF and plasma were based on the observed data in the 3 clinical cohorts.

The sensitivity of model predictions to α -synuclein $t_{1/2}$ and K_D were investigated to identify a set of parameters that best fit the observed levels of α -synuclein in CSF and plasma. The $t_{1/2}$ of α -synuclein appears to be shorter than previously assumed but there was notable uncertainty in PD model. A plausible parameter set was chosen to simulate α -synuclein

suppression in CSF over a range of doses. The PK/PD parameter values used are summarized in Table 10. Predicted exposures and α -synuclein suppression in CSF are shown in Table 11.

Table 10 Key pharmacokinetic/pharmacodynamic parameters

Parameter	Value	Unit
Central compartment volume of distribution	CCI	L
Peripheral compartment volume of distribution		L
Human clearance		L/day
Human inter-compartmental clearance		L/day
MEDI1341 brain penetration		%
MEDI1341 binding off rate		1/d
MEDI1341 affinity (K_D)		nM
Human $t_{1/2}$ of α -synuclein in plasma		day
Human $t_{1/2}$ of α -synuclein in brain		day
Human α -synuclein basal levels in plasma		nM
Human α -synuclein basal levels in brain		nM

K_D = equilibrium dissociation constant; $t_{1/2}$ = half-life.

Table 11 Predicted human exposure and α -synuclein suppression in CSF

IV Dose (mg) ^c	Human exposure ^a		α -synuclein suppression in CSF (%) ^b	
	C_{max} (μ g/mL)	AUC (μ g•day/mL)	7 Days Post-dose (Day 8)	14 Days Post-dose (Day 15)
CCI				

^a Predicted exposure using population PK model fitted to clinical data at 70, 210 and 400 mg (cohorts 1, 2 and 3).

^b Predicted from PK/PD model.

^c Planned single doses for cohorts 4, 5 and 6.

AUC = area under the concentration time curve; C_{max} = maximum observed concentration;

CSF = cerebrospinal fluid; iv = intravenous.

4.3 Toxicology

4.3.1 Single-dose toxicity

No stand-alone single-dose toxicity studies were performed with MEDI1341. Toxicity following a single dose was evaluated as a component of the 13-week repeat-dose toxicity studies in the rat and cynomolgus monkey (AB21095 and AB21095; see [Section 4.3.2](#)). No

MEDI1341-related adverse effects were observed in either species following the first dose of MEDI1341 at doses up to [REDACTED] mg/kg iv.

4.3.2 Repeated-dose toxicity

Repeat-dose GLP studies were conducted with MEDI1341 in Sprague-Dawley rats and cynomolgus monkeys.

4.3.2.1 Repeat-dose toxicity studies in rats

A [REDACTED]-week intravenous toxicity study in rats

A GLP-compliant, repeat-dose toxicity study was conducted in male and female Sprague-Dawley rats (n=[REDACTED]/sex/dose group, aged approximately 11 weeks at treatment initiation) to assess the potential toxicity and toxicokinetics of MEDI1341 (Report: AB22290). MEDI1341 was administered twice weekly by slow (5 minutes, [REDACTED] mL/kg) iv bolus, at doses of [REDACTED] or [REDACTED] mg/kg (total dose [REDACTED] and [REDACTED] mg/kg/week) for [REDACTED] weeks (total of at least [REDACTED] doses). Control animals received vehicle [REDACTED]. Scheduled necropsies were conducted 2 days after the final dose (Day [REDACTED]).

All animals dosed with MEDI1341 were exposed to MEDI1341. Mean C_{max} and AUC from first dose to last observation values generally increased in proportion to the dose of MEDI1341 between [REDACTED] and [REDACTED] mg/kg twice weekly, in both sexes and sampling occasions. Time to peak serum concentrations (median t_{max}) following twice weekly administration of MEDI1341 was observed between [REDACTED] and [REDACTED] hours after the start of the 1st or 2nd (72 hours after 1st) weekly administration on both occasions. Systemic exposures in Week [REDACTED] were generally similar compared to corresponding values on Week 1. There was no evidence of a sex difference in exposure at both dose levels and occasions.

Twice weekly iv administration of MEDI1341 to Sprague-Dawley (CD) rats for [REDACTED] weeks was well tolerated. There were no unscheduled deaths and no MEDI1341-related changes in body weight, food consumption, ophthalmology, CNS parameters, organ weights or macroscopic findings.

MEDI1341-related changes in hematology parameters consisted of dose-related minimally lower absolute neutrophil counts in males and females at [REDACTED] and [REDACTED] mg/kg twice weekly. MEDI1341-related changes in clinical chemistry parameters consisted of minimally dose-related lower phosphate in females and minimally to mildly higher cholesterol, triglycerides, globulin, albumin (females only), total protein and glucose concentrations in both sexes at [REDACTED] and [REDACTED] mg/kg twice weekly without dose relationship. None of these changes were considered to be adverse considering their small magnitude, the absence of impact on health status and the absence of microscopic correlates. Relation to MEDI1341 was considered equivocal for the minimal to moderate increase in urinary protein-to-creatinine ratios noted in [REDACTED] females treated at [REDACTED] mg/kg twice weekly without any serum clinical chemistry and microscopic correlates of renal function impairment.

MEDI1341-related microscopic findings included minimal to moderate increased cellularity of the sclera and/or minimal mononuclear cell infiltration in the eyes of animals given CCI and CCI mg/kg twice weekly, incidence/severity being dose-related (Table 12).

Table 12 **MEDI1341-related ocular microscopic changes in 12-week intravenous toxicity study in rat**

	Dose (mg/kg/twice weekly)					
	CCI					
Sex	Male (n)	Female (n)	Male (n)	Female (n)	Male (n)	Female (n)
CCI						

- indicates absence of change.

Increased cellularity of the sclera was characterized by an increased number and/or prominence of scleral mesenchymal cells with variable width. Mononuclear cell infiltration, mainly lymphocytes, was characterized by a perivascular distribution and was generally most notable around small vessels at the corneo-scleral junction. Mononuclear cell infiltration was not observed in the internal ocular structures or cornea.

Immunohistochemical (IHC) staining (human IgG and rat IgM, IgG, and complement component 3) did not show evidence of granular deposits in the ocular tissue from any of the affected animals examined that could be interpreted as potential immune complex deposition.

CCI

CCI

Within the limitations of the evaluations conducted in this study, the ocular findings were not considered to be adverse based on the following:

- (i) there was no morphologic evidence of altered function in the ocular tissues due to the increased scleral cellularity;
- (ii) adjacent tissues (retinal pigment epithelium, retina, episclera) all appeared unaffected by the increased cellularity of the sclera and choroid;
- (iii) the increased cellularity of the sclera was not accompanied by any evidence of degeneration, necrosis or pathologic inflammation (neutrophils, edema, etc);
- (iv) there were no MEDI1341-related findings at ophthalmological examination (indirect ophthalmoscopy on Day CCI
- (v) there were no signs of impaired eye function during clinical observations or ophthalmological examination.

The NOAEL was therefore considered to be CCI mg/kg twice weekly (C_{max} CCI $\mu\text{g/mL}$ and AUC_{last} CCI $\mu\text{g}\cdot\text{day/mL}$ in Week CCI

A 13-week intravenous toxicity study in rat followed by a 13-week treatment-free period

A GLP-compliant, repeat-dose toxicity study was conducted in male and female Sprague-Dawley rats ($n=$ CCI /gender, aged approximately CCI weeks at treatment initiation) to assess the potential systemic, local toxicity and toxicokinetics of MEDI1341 (Report: AB21095). MEDI1341 was administered once weekly by iv bolus, at doses of CCI, or CCI mg/kg/week for 13 weeks (total of CCI doses). Control animals received vehicle CCI. Scheduled necropsies were conducted 2 or 3 days after the final dose (Day CCI). Additional cohorts of animals (CCI animals/gender/group) were included in control and high dose groups to assess reversibility of potential MEDI1341-related effects, and CCI /gender/group to assess toxicokinetics. These additional cohorts of animals were retained for a 13-week treatment-free period following the CCI weekly doses and were then terminated on Day CCI.

The systemic exposure of MEDI1341 was generally dose proportional, except for a CCI increase in exposure, which was observed in Week 13 between CCI and CCI mg/kg/week doses. A -fold accumulation of MEDI1341 was observed between Week 1 and Week 13. CCI were detected for CCI animals in the CCI /kg/week dose group and CCI animals in the CCI mg/kg/week dose group. MEDI1341 exposure was impacted CCI in the CCI mg/kg/week dose group, and CCI from this dose group were therefore excluded from toxicokinetic analysis. Consistent with the anticipated binding of MEDI1341 to circulating α -synuclein, CSF levels of free α -synuclein were decreased in CCI following CCI weekly administrations. Plasma levels of total α -synuclein (bound to MEDI1341) following administration of MEDI1341 showed an CCI during the treatment period. The toxicokinetics of MEDI1341 are summarized in Section 4.2.6.2.

There was no mortality during the study and there were no MEDI1341-related adverse clinical signs or ophthalmological findings in male or female rats throughout the treatment and treatment-free periods. No MEDI1341-related effects on body weight were observed and no overt treatment-related effect was noted on food consumption over the treatment period. In the modified Irwin test, no MEDI1341-related neuro-behavioral findings were noted at 1 hour post-dose on Day 1, Day CCI, and Day CCI nor at the end of the treatment-free period (Day CCI).

There were no toxicologically relevant changes noted in hematological and coagulation parameters, serum clinical chemistry or urinary parameters neither at the end of the 13-week treatment period, nor at the end of the treatment-free period in any dose groups. There were no treatment-related changes in organ weights, nor any macroscopic or histopathological treatment-related findings. Cytological evaluation of the bone marrow showed that MEDI1341 exposure did not cause any change in the individual and group mean myeloid: erythroid (M:E) ratio and the absolute and relative myeloid, erythroid precursors and lymphoid cell counts.

Upon further, post-study microscopic examination, MEDI1341-related minimal bilateral increased cellularity, sometimes associated with minimal mononuclear cell infiltration, was observed in the sclera of the eye, mainly at the corneo-scleral junction, in rats treated at CCI or CCI mg/kg/week (Table 13).

Table 13 MEDI1341-related ocular microscopic changes in 13-week intravenous toxicity study in rat

	Dose (mg/kg/week)							
	CCI							
Sex	Male (n)	Female (n)	Male (n)	Female (n)	Male (n)	Female (n)	Male (n)	Female (n)
CCI								

Table 13 **MEDI1341-related ocular microscopic changes in 13-week intravenous toxicity study in rat**

Sex	Dose (mg/kg/week)							
	Male (n)	Female (n)	Male (n)	Female (n)	Male (n)	Female (n)	Male (n)	Female (n)
CCI								

- indicates absence of change.

The increased cellularity was characterized by an increased number and/or prominence of round or fusiform cells at the corneo-scleral junction. Minimal mononuclear cell infiltration accompanied the increased cellularity in CCI treated at $\square$ mg/kg/week and in CCI and CCI at $\square$ mg/kg/week.

There were no MEDI1341-related microscopic changes in the other compartments of the eyes. No MEDI1341-related microscopic changes were observed in the eyes from rats previously treated at $\square$ mg/kg/week and sacrificed at the end of the 13-week recovery period, suggesting reversibility. These histopathological changes were considered non-adverse in view of the absence of any accompanying change in adjacent tissues/compartments (such as the retina, uvea and episclera), or morphologic evidence of altered function in the tissues due to the increased cellularity, or any evidence of a pathological inflammatory component (neutrophils, edema, necrosis, etc).

The NOAEL for MEDI1341 in this study was considered to be $\square$ mg/kg/week (C_{max} $\square$ μ g/mL and AUC_{last} $\square$ μ g•day/mL in Week 13).

4.3.2.2 Repeat-dose toxicity studies in monkeys

A $\square$ -week intravenous toxicity study in monkeys followed by an $\square$ -week treatment-free period

A GLP-compliant, repeat-dose toxicity study was conducted in male and female cynomolgus monkeys (aged between 29 to 55 months at initiation of treatment) to assess the potential toxicity and toxicokinetics of MEDI1341 (Report: AB22301). MEDI1341 was administered twice weekly by the iv route (60 minutes infusion, $\square$ mL/kg) to 1 group of $\square$ male and $\square$ female cynomolgus monkeys at $\square$ mg/kg (total dose: $\square$ mg/kg/week) and to 1 group of $\square$ male and $\square$ female cynomolgus monkeys at $\square$ mg/kg (total dose: $\square$ mg/kg/week) for $\square$ weeks (a total of $\square$ administrations). A control group of $\square$ male and $\square$ female cynomolgus monkeys was administered the vehicle CCI by the same route. $\square$ male and $\square$ female monkeys per

group were necropsied 2 or 3 days after the last dose (Day CCI); CCI monkeys from the group receiving CCI mg/kg twice weekly were necropsied at the end of the -week recovery period (Day CCI) to assess reversibility of potential MEDI1341-related effects.

All animals dosed with MEDI1341 were exposed to MEDI1341. No MEDI1341 was detected in control animals. From CCI to CCI mg/kg twice weekly, mean C_{max} and mean $AUC_{(0-170)}$ increased in proportion to the dose of MEDI1341 following a single dose and after repeated twice weekly dosing. Following repeated twice weekly doses of MEDI1341, systemic exposure was generally greater at CCI mg/kg twice weekly compared to exposure after a single dose and comparable between sampling occasions at CCI mg/kg twice weekly. There was no sex difference in the exposure of MEDI1341 in monkeys.

There were no deaths related to the administration of MEDI1341 during the study and no systemic or local clinical signs were attributed to MEDI1341. There were no effects of MEDI1341 on body weight, hematology parameters, urine parameters and urine chemistry and no ophthalmological changes. MEDI1341-related clinical chemistry findings consisted of a minimally higher cholesterol levels, a mildly higher triglycerides in females only at CCI mg/kg twice weekly and a minimally higher globulins in males at CCI and CCI mg/kg twice weekly and in females at CCI mg/kg twice weekly. Except for cholesterol in females that remained minimally higher at CCI mg/kg twice weekly, all parameters had reversed at the end of the recovery period and were considered not adverse. There was no effect of MEDI1341 on arterial blood pressure, heart rate, quantitative echocardiogram (ECG) parameters, ECG waveforms and respiratory parameters determined at the end of the 1-hour infusion at CCI or CCI mg/kg twice weekly, evaluated on Day 1 and Day CCI in males and females.

There were no macroscopic or organ weight changes related to MEDI1341. There were no microscopic findings at CCI mg/kg twice weekly. Microscopic findings at CCI mg/kg twice weekly were limited to subacute inflammation/inflammatory cell infiltration (granulocytes or mixed cells) noted in several organs of CCI (gastrointestinal tissues and lymph node, urinary bladder, vagina, eyes, heart, lungs, synovial capsule, injection site), decrease of bone marrow cellularity, mild chronic inflammation of skeletal muscle, thymus atrophy, mild lymphoid depletion and moderate histiocytosis in the mesenteric lymph node. These changes were considered unlikely to be direct effects of MEDI1341 and could in part be consistent with spontaneous findings commonly observed in cynomolgus monkeys (Chamanza et al, 2010), and/or an inflammatory reaction secondary to immune complex formation (Rojko et al, 2014). There were no hematological findings CCI in suggesting an ongoing inflammatory process (no noticeable increase of white blood cells count or fibrinogen). The exposure of CCI was significantly reduced in Week 1 when compared with other CCI from the same group, which could suggest CCI. In the absence of in-life impact and microscopic signs of degenerative changes, the findings CCI were considered not adverse.

Staining of the eyes for MEDI1341 and monkey IgG and IgM confirmed the presence of MEDI1341 in the sclera and other ocular tissues, with the level of MEDI1341 in the sclera and cornea appearing similar to the levels of endogenous IgG.

Twice weekly iv administration of MEDI1341 to cynomolgus monkeys for [REDACTED] weeks at [REDACTED] or [REDACTED] mg/kg twice weekly was well tolerated. MEDI1341-related clinical pathology findings were all considered to be non-adverse changes and consisted of minimally higher cholesterol and triglycerides (females only) at [REDACTED] mg/kg twice weekly and minimally higher globulin at both dose levels in males and at [REDACTED] mg/kg twice weekly in females. At [REDACTED] mg/kg twice weekly, subacute or chronic inflammation/inflammatory cell infiltration noted in several organs of [REDACTED] could be part of an inflammatory reaction secondary to immune complex formation.

In conclusion, the NOAEL was considered to be [REDACTED] mg/kg twice weekly (Week [REDACTED] C_{max} [REDACTED] $\mu\text{g/mL}$, AUC_{last} [REDACTED] $\mu\text{g}\cdot\text{day/mL}$).

A 13-week intravenous toxicity study in monkey followed by a 13-week treatment-free period

The potential toxicity of MEDI1341 was investigated in a 13-week GLP study in cynomolgus monkeys ($n=[REDACTED]$ /gender, aged between [REDACTED] months at initiation of treatment) following iv administration (given alternately each week in the left or right saphenous vein) of MEDI1341 at doses of [REDACTED], and [REDACTED] mg/kg/week for 13 weeks (a total of [REDACTED] administrations, Report: AB21096). Control animals received a [REDACTED] vehicle. Scheduled necropsies were conducted 3 days after the final dose (Day [REDACTED]). Additional cohorts of monkeys [REDACTED] were dosed with the vehicle or [REDACTED] mg/kg/week MEDI1341 for 13 weeks, but were retained for an additional 13-week treatment-free period (with termination on Day [REDACTED]) to assess reversibility of potential MEDI1341-related effects.

MEDI1341 exposure in plasma increased in a [REDACTED] in Week 1 and Week 13. Accumulation ([REDACTED] fold) was seen at the [REDACTED] mg/kg/week dose between Weeks 1 and 13. [REDACTED] were detected in [REDACTED] animals across the dose groups; however, exposure to MEDI1341 was only affected [REDACTED] animals in the [REDACTED] mg/kg/week dose group, and exposure data from [REDACTED] was not included in the toxicokinetic analysis. Concentration of MEDI1341 in CSF [REDACTED]. Consistent with the anticipated binding of MEDI1341 to circulating α -synuclein, CSF levels of free α -synuclein were decreased [REDACTED] following [REDACTED] weekly administrations. Plasma levels of total α -synuclein (bound to MEDI1341) showed an increase in each MEDI1341 dose group compared with vehicle treated animals over time. The toxicokinetics of MEDI1341 are summarized in [Section 4.2.6.2](#).

There were no MEDI1341-related adverse clinical signs or effects on survival, body weights, food consumption, neuro-behavioral examinations, cardiovascular endpoints (as assessed by electrocardiography and blood pressure), respiratory rate, hematology, coagulation parameters, clinical chemistry, immunophenotyping, urinalysis parameters, ophthalmoscopy,

organ weights or macroscopic aspects of organs and tissues. Perivenous hemorrhagic infiltration at the injection site was noted for a few days after injection in most animals including controls and was considered procedural. In addition, MEDI1341-related acute inflammation (graded minimal to mild) was observed following histopathological examination of the most recently injected vein. This finding was not strictly MEDI1341 dose-related, but was not observed in control animals. However, there was no inflammation in injection site tissues in recovery animals or in the right saphenous vein (which was not injected on Day CCI) and there was no evidence of changes in systemic lymphocyte subsets as determined by immunophenotyping. This finding was consistent with a local immune reaction to an injected human protein, and was not considered adverse. There were no other MEDI1341-related histopathology findings in any of the tissues assessed nor any effect on the bone marrow following cytological evaluation.

In conclusion, there were no MEDI1341-related adverse effects in cynomolgus monkeys following a total of CCI administrations of CCI, or CCI mg/kg/week by iv bolus. Therefore, the NOAEL for MEDI1341 in this study was considered to be CCI mg/kg/week (Week 13 C_{max} CCI $\mu\text{g/mL}$, AUC_{last} CCI $\mu\text{g}\cdot\text{day/mL}$).

4.3.3 Genotoxicity (Mutagenicity)

In accordance with ICH S6 (R1) guidelines, genotoxicity testing has not been conducted and is not planned as these studies are not applicable to biotechnology-derived large protein products. MEDI1341 is not expected to cross the nuclear or mitochondrial membranes and interact directly with DNA or other chromosomal materials.

4.3.4 Carcinogenicity

In accordance with ICH S6 (R1) guidelines, carcinogenicity studies have not been conducted and are not planned at this time. If warranted, appropriate strategies to assess carcinogenic potential (with justification and feasibility of any proposed approaches) may be formally addressed later in the development of MEDI1341.

4.3.5 Reproductive and development toxicity

A formal evaluation of the potential reproductive and developmental toxicity of MEDI1341 has not been conducted at this time. However, histopathological evaluation of male and female reproductive organs and tissues was conducted in sexually mature rats and sexually immature cynomolgus monkeys in the CCI and 13-week repeat-dose toxicity studies (Section 4.3.2). No adverse findings were noted in either gender, in either species following detailed light microscopy assessment of cervix, ovaries, oviducts, uterus, vagina, epididymides, seminal vesicles, testes, and uterus. An evaluation of the impact of MEDI1341 exposure on embryofetal development, fertility and perinatal and postnatal development will be considered later in the development of MEDI1341.

4.3.6 Local tolerance

A dedicated local tolerance study has not been conducted with MEDI1341. However, in-life observations of the injection sites and detailed histopathological examination, have been

conducted in repeat-dose toxicity studies in both rat and cynomolgus monkey (see [Section 4.3.2](#)). No MEDI1341-related macroscopic or histopathological changes were observed at the injection sites in rats. In cynomolgus monkeys, transient procedural perivenous hemorrhagic inflammation was noted following dosing in most animals. In addition, minimal-mild transient MEDI1341-related acute inflammation, consistent with a skin reaction to an injected protein, was observed microscopically in the most recently injected vein.

4.3.7 Other Studies

4.3.7.1 Tissue cross-reactivity study of MEDI1341

The potential cross-reactivity of MEDI1341 was determined in human tissues (Report: MEDI1341-6022-2016). In order to detect binding, MEDI1341, was applied to cryosections of normal human tissues (1 donor per tissue) as well as human PD and normal control brain tissue at 2 concentrations (1 and 1 µg/mL). A monoclonal human IgG1 antibody with a different antigenic specificity than that of MEDI1341, designated r347 triple mutant (TM), was used as a control.

MEDI1341 stained a variety of tissue elements in the human tissues including neurons and their processes, glial cells and their processes, ganglion cells, Lewy bodies, retinal cells, resident, migrating, and/or infiltrating mononuclear cells, mast cells, hematopoietic precursor cells, epithelium, endothelium, spindle cells, extracellular material, glomerular tuft cells, ovarian stromal cells, granulosa lutein cells, placental decidual cells, and interstitial Leydig cells. All observed MEDI1341 staining of neurons and their processes, glial cells and their processes, ganglion cells, Lewy bodies, retinal cells, resident, migrating, and/or infiltrating mononuclear cells, hematopoietic precursor cells, endothelium, some epithelium, and extracellular material was judged expected based on literature reports of α -synuclein expression at these sites. The observed staining of mast cells, some epithelium, spindle cells, glomerular tuft cells, ovarian stromal cells, granulosa lutein cells, placental decidual cells, and interstitial Leydig cells was judged unexpected as no literature was available describing α -synuclein expression at these sites. However, the observed unexpected as well as the majority of expected staining was cytoplasmic in nature and was judged of no toxicologic relevance as the cytoplasmic compartment is considered to be unavailable to monoclonal antibodies in vivo.

4.3.7.2 Ocular tissue cross-reactivity study of MEDI1341

The objective of this study was to determine the potential cross reactivity of MEDI1341 with cryosections of human, non-human primate (cynomolgus monkey), and rat (Sprague-Dawley) ocular tissues (Report: 20171178). In order to detect binding, MEDI1341 was applied to cryosections of human, cynomolgus monkey, and Sprague-Dawley rat ocular tissues (1 donor per species) at 2 concentrations (1 and 1 µg/mL). In addition, MEDI1341 was substituted with a monoclonal human IgG1 antibody, which has a different antigenic specificity from that of MEDI1341, designated r347-TM (control article). One of the following positive control antibodies was applied to the human, cynomolgus monkey, or Sprague-Dawley rat ocular tissues at 1 concentration (1 µg/mL) for comparison: Ms anti-Synuclein (LB 509) for human

tissues, Ms anti-Synuclein (4D6) for monkey tissues, or Ms anti-Synuclein (4B12) for rat tissues. The positive control antibodies were substituted with a monoclonal mouse IgG1 κ antibody, which has a different antigenic specificity from that of the positive control antibodies, designated MsIgG1 (negative control antibody). Tissue staining with positive and negative controls indicated that the assays were sensitive and specific.

Staining with MEDI1341 was observed in the human, monkey and rat ocular tissues as summarized below:

- Cytoplasmic elements:
 - Epithelium of the lens, cornea, conjunctiva, and ciliary body
 - Lens fibres
 - Vascular and/or intrinsic smooth myocytes
 - Spindloid cells (in the cornea, sclera, ciliary body, iris, and/or choroid)
 - Neuroepithelium in the retina (all layers)
 - Skeletal myocytes (monkey and rat only, tissue element not present in human samples)

Staining with the Ms anti-Synuclein antibodies was observed in the human and cynomolgus monkey ocular tissues as summarized below:

- Cytoplasmic elements:
 - Epithelium of the lens (monkey only), cornea, conjunctiva, and ciliary body
 - Lens fibres
 - Spindloid cells (in the ciliary body, human only)
- Nuclei in the following:
 - Neuroepithelium in the retina (monkey only)
- No staining was observed with the Ms anti-Synuclein antibody (4B12) in the Sprague-Dawley rat eye.

Similar staining was observed with MEDI1341 in the human, cynomolgus monkey, and Sprague-Dawley rat eye. The minor differences in staining between the human and animal tissues are likely related to individual donor/section variation. The staining with the positive control antibodies in the human and monkey eye was less frequent and less intense than the staining observed with MEDI1341 in the same elements.

4.3.8 Anticipated safety margins

Human exposure for the proposed Cohorts 4, 5, and 6 will not exceed **CCI** $\mu\text{g}\cdot\text{day}/\text{ml}$ (AUC) or **CCI** $\mu\text{g}/\text{ml}$ (C_{max}). These exposures incorporate a **CCI**-fold safety margin relative to the exposures achieved at NOAEL in the **CCI**-week GLP rat toxicology study. This human exposure also provides for **CCI**-fold (AUC) and **CCI**-fold (C_{max}) safety margins relative to the exposures achieved at NOAEL in the **CCI**-week GLP cynomolgus monkey toxicology study.

Table 14 presents the predicted exposures for the planned MEDI1341 doses of **CCI** and **CCI** mg and safety margins relative to the NOAELs from the **CCI**-week monkey and rat studies.

Table 14 Proposed MEDI1341 human doses, predicted exposures, and margins to cynomolgus monkey and rat data

Human dose (mg)	Human exposure ^a		Safety margin compared to monkey exposure at █-week NOAEL (█ mg/kg/twice weekly)		Safety margin compared to rat exposure at █-week NOAEL (█ mg/kg/twice weekly)	
	C _{max} (µg/mL)	AUC (µg·day/mL)	Multiple of C _{max} ^b (█ µg/mL)	Multiple of AUC ₀₋₁ ^c (█ µg·day/mL)	Multiple of C _{max} ^b (█ µg/mL)	Multiple of AUC ₀₋₁ ^c (█ µg·day/mL)
█ (Cohort 4)	█					
█ (Cohort 5)						
█ (Cohort 6)						

^a All human doses will be administered by intravenous infusion.

^b C_{max} was the maximum serum concentration of MEDI1341 observed over a weekly dosing period (Week █).

^c AUC₀₋₁ was calculated over a weekly dosing period (Week █) with the final PK sample collected at █ hours post the end of the intravenous infusion of the 2nd weekly dose.

AUC = Area under the concentration-time curve; AUC₀₋₁ = AUC from from zero to the last measurable concentration; C_{max} = Maximum concentration;
NOAEL = No-observed-adverse-effect limit.

5. EFFECTS IN HUMANS

As of 09 May 2019, the FTIH study with MEDI1341 (D6340C00001) is ongoing. No other clinical studies have been undertaken with MEDI1341. The clinical data presented in the following subsections are from the ongoing study. The study remains blinded.

5.1 Pharmacokinetics, pharmacodynamics, and immunogenicity

An interim analysis of draft PK/PD and immunogenicity data from the first 3 cohorts from Study D6340C00001 has been conducted.

5.1.1 Pharmacokinetics

The interim PK analysis was conducted using draft serum MEDI1341 data and nominal dose, infusion duration, and blood sampling times.

Following single iv infusion of 70, 210, or 400 mg MEDI1341, maximum serum concentrations of MEDI1341 were generally observed at the end of the 1-hour infusion; the median t_{max} was 1 hour after start of infusion at the 70- and 210-mg dose levels. At the 400-mg dose level, median t_{max} was 9 hours after the start of infusion with individual subject t_{max} values ranging from 1 to 73 hours after the start of infusion. Late t_{max} values were not expected based on route of administration and PK observations from lower dose levels. However, no bioanalytical or sample handling/labelling issues could be identified on further investigation.

CCI [REDACTED] Arithmetic mean (SD) apparent terminal elimination half-life ($t_{1/2\lambda z}$) values were similar across the 70-, 210-, and 400-mg MEDI1341 dose levels (19.8 [7.54] days, 16.8 [2.84] days and 17.4 [1.71] days, respectively). The PK parameters are summarized in Table 15.

Between-subject variability as measured by geometric mean CV% was generally moderate for AUCs and C_{max} with values across all dose levels ranging from 13.7% to 24.9% and 19.3% to 57.4%, respectively.

Table 15 Pharmacokinetic parameters of serum MEDI1341 following single intravenous administration of MEDI1341 to healthy subjects

PK parameter	Statistic	70 mg (N=6)	210 mg (N=6)	400 mg (N=5)
AUC _{0-∞} (µg*day/mL)	Geo mean	65.5	225	458
	(Geo CV%)	(13.7)	(24.9)	(21.2)
C_{max} (µg/mL)	Geo mean	11.5	43.1	65.0

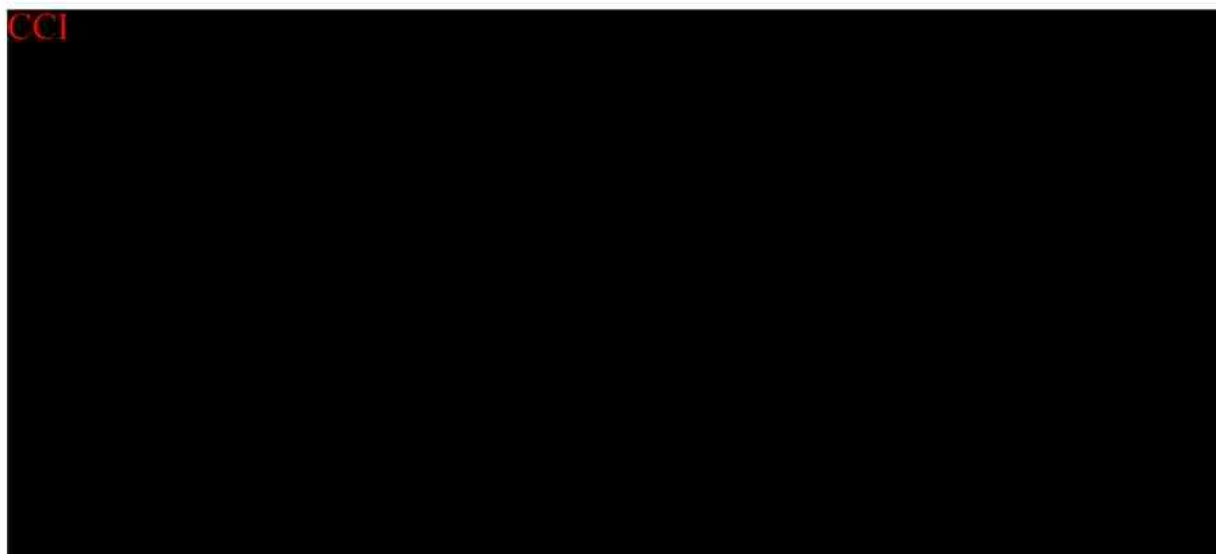
Table 15 Pharmacokinetic parameters of serum MEDI1341 following single intravenous administration of MEDI1341 to healthy subjects

PK parameter	Statistic	70 mg (N=6)	210 mg (N=6)	400 mg (N=5)
$t_{\max}$ (h)	(Geo CV%)	(30.4)	(19.3)	(57.4)
	Median	1.00	1.00	9.00
	(Min-Max)	(1.00-9.00)	(1.00-9.00)	(1.00-73.00)
$t_{1/2\lambda z}$ (day)	Mean	19.8	16.8	17.4
	(SD)	(7.54)	(2.84)	(1.71)
CL (L/day)	Geo mean	1.07	0.933	0.874
	(Geo CV%)	(13.7)	(24.9)	(21.2)
V_{ss} (L)	Geo mean	16.8	13.4	14.2
	(Geo CV%)	(47.6)	(20.6)	(20.2)

Notes: All PK and PD data for 1 subject on 400 mg were excluded from descriptive statistics since this subject had notably lower exposure to MEDI1341 in serum.

AUC_{0-∞} = area under curve from zero to infinity; CL = clearance; C_{max} = maximum observed concentration; t_{max} = time of C_{max}; geo = geometric; t_{1/2λz} = apparent terminal elimination half-life; V_{ss} = steady state volume of distribution.

Figure 18 Loglinear plot of arithmetic mean (+SD) serum concentrations of MEDI1341 vs time following single intravenous administration of 70 mg, 210 mg, or 400 mg MEDI1341 to healthy male and female subjects, Day 1 through Day CCI



Note: Subject **PPD** (400 mg) was excluded from descriptive statistics since this subject had notably lower exposure to MEDI1341 in serum.

Increases in AUC from time zero to infinity ($AUC_{0-\infty}$) and C_{max} were **CCI** from 70 mg to 210 mg (Table 16). The further increase in MEDI1341 dose from 210 mg to 400 mg resulted in a **CCI** in C_{max} but an approximate **CCI** in $AUC_{0-\infty}$.

Table 16 Effect of increasing dose on the pharmacokinetics of MEDI1341

Dose	70 mg	210 mg	400 mg
Dose increment	CCI		
Increase in C_{max}			
CCI C_{max}			
Increase in $AUC_{0-\infty}$			
CCI $AUC_{0-\infty}$			

Notes: All PK and PD data for 1 subject on 400 mg were excluded from descriptive statistics since this subject had notably lower exposure to MEDI1341 in serum.

CCI and calculated using geometric mean values.

- = not applicable; $AUC_{0-\infty}$ = area under curve from zero to infinity; C_{max} = maximum observed concentration;

The CSF MEDI1341 concentration on Day **CCI** was below the limit of quantitation at the 70-mg MEDI1341 dose level for half of the subjects. At the 210-mg dose level, CSF/serum MEDI1341 concentration ratios on Day **CCI** were **CCI**% for all subjects, with values ranging from **CCI**% to **CCI**% (geometric mean value of **CCI**%). At the 400-mg dose level, CSF/serum MEDI1341 concentration ratios were assessed on Day **CCI** the geometric mean was **CCI**% with an individual subject range of **CCI**% to **CCI**%.

5.1.2 Pharmacodynamics

The effect of MEDI1341 on free CSF α -synuclein is shown in [Figure 19](#). At MEDI1341 doses of 70 and 210 mg, the observed median percentages of α -synuclein suppression in CSF on Day **CCI** were **CCI**% and **CCI**%, respectively. At the MEDI1341 dose of 400 mg, the observed median percentage of α -synuclein suppression in CSF on Day **CCI** was **CCI**%.

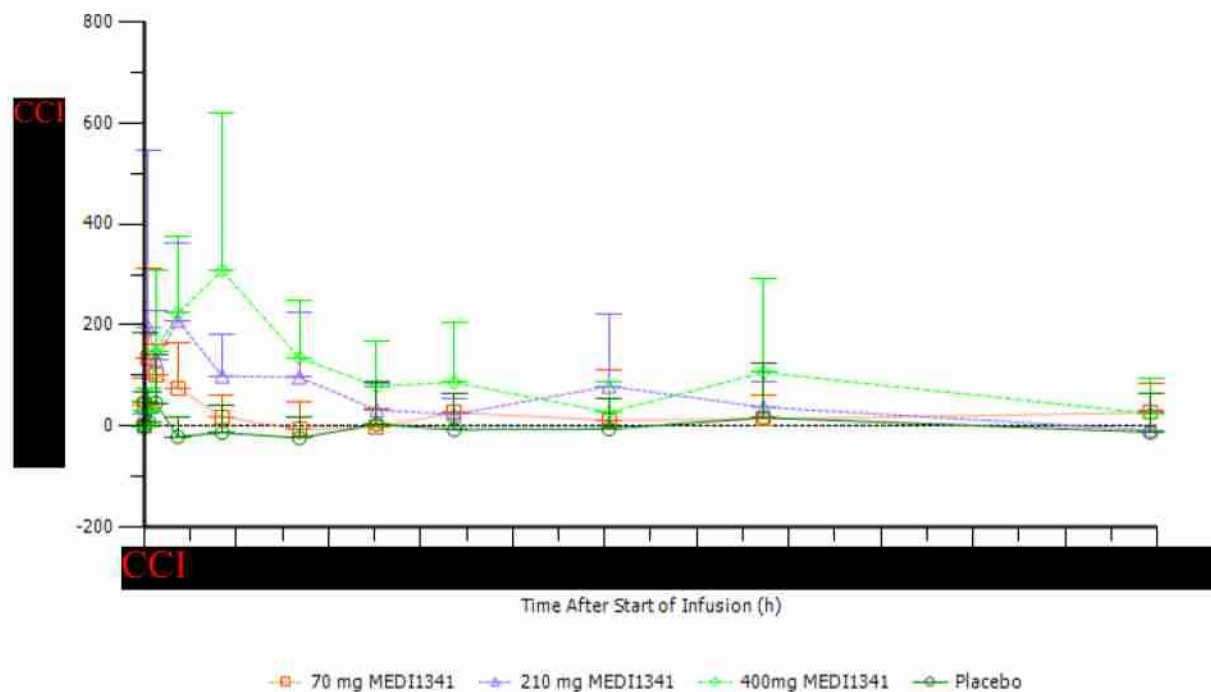
Figure 19 Individual subject and median percent change from baseline for free α -synuclein in CSF on Study Day **CC1** (400 mg) or 29 (70 mg and 210 mg)



Following a single iv infusion of 70, 210, or 400 mg MEDI1341, the percent change from baseline for total α -synuclein in plasma **CC1** (Figure 20). **CC1**
The greatest increase in arithmetic mean percent change from baseline was observed on Day **CC1** post-dose for the 70-mg dose, on Day **CC1** for the 210-mg dose, and on Day **CC1** for the 400-mg dose with respective mean (SD) values of **CC1**%, **CC1**%, and **CC1**%.

Following a single iv infusion of placebo, arithmetic mean percent change from baseline for total α -synuclein in plasma ranged from **CC1**% to **CC1**% for all time points with high between-subject variability observed.

Figure 20 Arithmetic mean (SD) percent change from baseline for total α -synuclein in plasma following single intravenous administration of placebo, 70 mg, 210 mg, or 400 mg MEDI1341 to healthy male and female subjects



5.1.3 Immunogenicity

In cohorts CCI results were observed for:

- Pooled placebo: CCI had titer values of CCI on Days CCI respectively.
- 70 mg MEDI1341: 1 subjects were borderline positive on Days CCI or only Day CCI.
- 210 mg MEDI1341: 1 subject was borderline positive on Days 1 and CCI and 1 subjects had respective titer values of CCI and CCI on both Days CCI.
- 400 mg MEDI1341: no subjects were borderline positive or positive through Day CCI.

None of the subjects with the CCI results appeared to exhibit differences in MEDI1341 exposure and pharmacodynamic (α -synuclein) results.

5.2 Safety and efficacy

A total of 25 healthy volunteer subjects, across 3 dose-level cohorts, have participated in the first-in-human dose-escalation study to date and have received a single iv dose of either MEDI1341 (doses up to 400 mg) or placebo. Doses higher than 400 mg have not been explored to date, as the maximum dose level was capped by previously-defined exposure limits and safety margins based on cynomolgus monkey toxicology data available at the time

that the study was initiated. Estimates of overall cumulative subject exposure for MEDI1341 are provided in Table 17.

PPD

The study was subsequently re-initiated and N=24 subjects were enrolled. Of these, N= [REDACTED] received iv MEDI1341 across 3 cohorts at doses of 70 mg (N=[REDACTED]), 210 mg (N=[REDACTED]), or 400 mg (N=[REDACTED]) and [REDACTED] subjects received placebo (N=[REDACTED] per cohort). Dose-escalation proceeded across the cohorts as planned and subjects were followed-up for 13 weeks after dosing.

Table 17 Estimated cumulative subject exposure

Treatment	Number of subjects ^{a,b}
MEDI1341	[REDACTED]
Placebo	[REDACTED]
Note: PPD	
[REDACTED] The treatment assignment for all other subjects (N=24) remains blinded.	
^a Cumulative numbers from initiation of the first interventional clinical study (D6340C00001) up to 09 May 2019.	
^b Numbers are based on knowledge of applied randomisation schemes for subjects with dosing data available from 1 ongoing study as of 09 May 2019.	

While treatment assignment for the 24 subjects remains blinded, single iv infusions of either MEDI1341 or placebo have been generally well tolerated across the 3 cohorts. No medically-important or clinically significant changes or trends for changes related to administration of investigational product have been identified across any of the safety endpoints over the course of the trial to date. Safety endpoints included physical and neurological examinations, adverse event profiling, vital signs, electrocardiogram monitoring, safety laboratory tests (hematology, clinical chemistry and urinalysis), cognitive assessments (Montreal Cognitive Assessment) and Colombia-Suicide Severity Rating Scale.

Overall, a total of 33 adverse events have been reported across 11 subjects. Of these, 28 treatment-emergent adverse events (TEAEs) were reported across 8 subjects (Table 18). The most common TEAEs have been headache, nausea, and vomiting. Most TEAEs were mild in intensity and assessed as not related to administration of the study product. No deaths have been reported. No subjects were discontinued from the study as a result of a TEAE.

[REDACTED] SAEs have been reported in the FTIH study as follows:

- PPD

PPD

- PPD

Following completion of MEDI1341 dosing at the 400 mg dose level in humans (Cohort 3), new toxicology data from a █-week high dose rat toxicity study of MEDI1341 indicated the presence of an ocular histopathological change, described as increased cellularity of the sclera/choroid (minimal-moderate) with minimal perivascular mononuclear cell infiltration (thought to comprise cells predominantly of the macrophage-lineage) at the corneo-scleral junction (summarized in non-clinical [Section 4.3.2.1](#)). Due to the unusual nature of this finding, ocular sections from the original 13-week rat toxicity study were re-evaluated and the change was also found to be present at the CCI dose levels, albeit at a lower incidence and severity. CCI

█ No immediate risk to the study participants was anticipated, because:

- the subjects had received only a single dose of study medication,
- no ocular findings have been noted in cynomolgus monkey toxicity studies (█-week toxicity study with twice weekly MEDI1341 dosing up to CCI mg/kg [up to total dose CCI mg/kg/week] and a 13-week toxicity study with once weekly MEDI1341 dosing up to CCI mg/kg/week), representing CCI-fold (AUC) and CCI-fold (C_{max}) safety margins for the human exposure in the current trial relative to the exposures achieved at NOAEL in the █-week GLP cynomolgus monkey toxicology study
- the ocular findings have only been detected in the rat and were considered to be non-adverse with some evidence of reversibility following a 13-week recovery period, and
- the estimated exposures in the highest dose cohort (400 mg) were several fold (CCI lower than the exposures achieved at the NOEL in the 13-week repeat-dose rat toxicology study (CCI mg/kg/week).

PPD

PPD

AstraZeneca (AZ) made the decision to suspend immediate plans for further dosing of MEDI1341 to human subjects until additional non-clinical investigations had been undertaken to further understand the nature of the rodent ocular pathology, and to evaluate the possible relevance to humans including consultation with independent veterinary and clinical ophthalmic experts to support the evaluation. Additionally, participants from the completed cohorts were subsequently scheduled to undergo an ad hoc ophthalmic follow-up examination, which has been achieved for all 25 subjects over a period of between CCI months since their dosing date. CCI of the subjects were noted to have normal ophthalmic examinations. CCI of the subjects PPD

Overall, MEDI1341 has been well tolerated in single iv doses up to 400 mg across 3 cohorts of subjects (N= CCI subject exposures to MEDI1341 to date) and there have been no clinically important safety findings to date CCI

Table 18 **Number (%) of subjects with at least 1 treatment-emergent adverse event (TEAE) – MEDI1341 first-in-human study (D6340C00001)**

System organ class	Adverse event term	Cohort 1 (N=███ MEDI1341 70 mg or placebo N (%))	Cohort 2 (N=███ MEDI1341 210 mg or placebo N (%))	Cohort 3 (N=███ MEDI1341 400 mg or placebo N (%))
Subjects with any TEAE		3 (33.3%)	1 (12.5%)	4 (50%)
Blood and lymphatic system disorders	Lymphadenopathy	0	0	1 (12.5%)
Cardiac disorders	Palpitations	1 (11.1%)	0	0
	Arrhythmia	1 (11.1%)	0	0
	Tachyarrhythmia	0	0	1 (12.5%)
Eye disorders	Eye pruritus	1 (11.1%)	0	0
	Asthenopia	0	0	1 (12.5%)
Gastrointestinal disorders	Nausea	0	1 (12.5%)	2 (25%)
	Vomiting	0	1 (12.5%)	1 (12.5%)
	Dysphagia	0	0	1 (12.5%)
	Paraesthesia oral	0	0	1 (12.5%)
General disorders and administration site reactions	Injection site bruising	1 (11.1%)	0	0
	Chest discomfort	0	0	1 (12.5%)
Infections and infestations	Sinusitis	1 (11.1%)	0	0
	Upper respiratory tract infection	1 (11.1%)	0	0
	Procedural pain	1 (11.1%)	0	0

Table 18 **Number (%) of subjects with at least 1 treatment-emergent adverse event (TEAE) – MEDI1341 first-in-human study (D6340C00001)**

System organ class	Adverse event term	Cohort 1 (N=■ MEDI1341 70 mg or placebo N (%))	Cohort 2 (N=■ MEDI1341 210 mg or placebo N (%))	Cohort 3 (N=■ MEDI1341 400 mg or placebo N (%))
Injury, poisoning and procedural complications	Post lumbar puncture syndrome	0	0	1 (12.5%)
Musculoskeletal and connective tissue disorders	Back pain	0	0	1 (12.5%)
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness	0	0	1 (25%)
Nervous system disorders	Headache	0	1 (12.5%)	2 (12.5%)
Nervous system disorders	Paraesthesia	0	0	1 (12.5%)
Skin and subcutaneous tissue disorders	Pruritus	0	0	1 (12.5%)
Vascular disorders	Flushing	1 (11.1%)	0	0

^a PPD

Cohort 1 was later re-initiated with N=■ subjects.

Note: Adverse events (AEs) designated as non-treatment emergent [as the start date was pre-dose] are not included in the table. Five (5) non-treatment emergent AEs were reported: elevated blood creatine phosphokinase (1), contusion (1), abrasion (1), post-lumbar puncture syndrome (1) and back pain (1).

6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATORS

MEDI1341 is a high-affinity, α -synuclein specific, fully human monoclonal antibody, formatted as an IgG1 that specifically binds the C-terminal region of human α -synuclein. It is engineered for reduced effector function by virtue of a triple mutation introduced into the fragment crystallizable (Fc) region of the antibody. MEDI1341 recognizes both the monomeric and aggregated forms of α -synuclein, and it recognizes disease relevant, pathological forms of α -synuclein in the brain tissue of patients with PD.

The FTIH study for MEDI1341 (D6340C00001) is ongoing. It is designed as a randomized, double-blind, placebo-controlled, single-ascending dose study with iv MEDI1341 administered in male and non-fertile female healthy volunteers. As of 09 May 2019, safety, tolerability, PK and pharmacodynamics for MEDI1341 have been evaluated following single doses of 70, 210, or 400 mg MEDI1341 across 3 cohorts of subjects (N=■ per cohort; N=■ received MEDI1341 and N=■ received placebo per cohort). The Phase I clinical development program plans to evaluate MEDI1341 at higher single dose levels in the healthy volunteer FTIH study and, in a separate study, following multiple ascending doses administration to PD patients.

6.1 Rationale for development

The background and rationale for the development of MEDI1341 are summarized in [Section 2](#).

6.2 Indication to be studied

MEDI1341 is being developed as a therapeutic antibody for the treatment of patients with PD.

6.3 Non-clinical safety data

MEDI1341 is cross-reactive to both rat and cynomolgus monkey α -synuclein; therefore, these species are considered pharmacologically relevant species in which to assess the safety of MEDI1341, as per International Conference on Harmonization (ICH) S6 R(1) guidelines.

The non-clinical safety of MEDI1341 has been evaluated in ■ and 13-week combined safety pharmacology and repeat-dose toxicity studies in rats and cynomolgus monkeys, conducted according to GLP standards. The ■-week studies were completed after the 13-week studies, in order to explore potential MEDI1341 toxicity at significantly higher exposures to those achieved in the 13-week studies. In addition, binding of MEDI1341 to human tissue ex vivo has been assessed. MEDI1341 binding in ocular tissues ex vivo was also investigated in human, rat, and monkey.

In 13-week rat and monkey toxicity studies, there were no MEDI1341-related adverse changes in any of the parameters evaluated. Engagement of the α -synuclein target was demonstrated in both plasma and CSF. In the 13-week study in monkeys, MEDI1341-related acute

inflammation was observed following histopathological examination of the most recently injected vein. This finding was noted at the end of the treatment phase only, indicating reversibility, was consistent with skin reaction to an injected protein and was not considered adverse. Similar injection site reactions were not observed in the █-week study in monkeys. At the time of evaluation of the 13-week studies, there were no other MEDI1341-related histopathology findings in any of the tissues assessed in rats or monkeys, and the NOAEL was therefore considered to be █ mg/kg/week (the █) in both species. Exposure at the NOAEL in rats was █ µg/mL for C_{max} and █ µg•day/mL for AUC_{last} . In monkeys, exposure at the NOAEL was █ µg/mL for C_{max} and █ µg•day/mL for AUC_{last} .

Dose levels for the subsequent █-week toxicity studies (rat: █ and █ mg/kg twice weekly; monkey: █ and █ mg/kg twice weekly) were selected in order to achieve a █-fold exposure margin over the highest anticipated clinical dose in the single-ascending dose study. Histopathological examination of the rat tissues revealed an unusual/rare change in the ocular sections affecting all animals in both MEDI1341 dose groups. This was characterized as increased cellularity of the sclera and/or mononuclear cell infiltration generally most notable around small vessels at the corneo-scleral junction, but was not considered adverse based on the evaluations included in the study. Due to the nature of this finding, ocular sections from the previous 13-week rat and monkey studies were re-examined. There were no ocular findings in the 13-week monkey study. However, a similar change was observed at █ and █ mg/kg/week in the rat 13-week study (NOEL = █ mg/kg/week), albeit at a lower incidence and severity. There were no ocular findings in rats dosed at █ mg/kg/week for 13 weeks followed by a 13-week treatment-free period, suggesting reversibility. The ocular finding was not considered adverse and the NOAEL in both 13-week studies remain as originally stated. The ocular finding was also confirmed to be absent in the █-week monkey study. Exposure at the NOAEL in the █-week study in rats was █ µg/mL for C_{max} and █ µg•day/mL for AUC_{last} . In monkeys, exposure at the NOAEL was █ µg/mL for C_{max} and █ µg•day/mL for AUC_{last} .

In a cross-reactivity study using an extensive panel of normal human tissue cryosections as well as brain cryosections from individuals with PD, the majority observed MEDI1341 staining was cytoplasmic in nature and was judged of no toxicologic relevance as the cytoplasmic compartment is considered to be unavailable to monoclonal antibodies in vivo. MEDI1341 ex vivo binding in ocular tissues from human, rat and monkey showed no species differences.

Further details are provided in [Section 4](#) (Non-clinical studies).

6.4 Clinical experience with anti- α -synuclein antibodies

Data from the first reported assessment of an anti- α -synuclein antibody (PRX002) in humans have been published ([Schenk et al 2017](#)). PRX002 is a monoclonal IgG1 antibody designed to preferentially target soluble and insoluble aggregated forms of α -synuclein. Forty healthy participants received single iv doses of up to 30 mg/kg and no dose-limiting toxicities were reported. Pharmacokinetic exposures were dose proportional and associated with a

dose-dependent reduction in free serum α -synuclein within 1 hour of administration. Multiple ascending-doses of PRX002 were subsequently evaluated in 80 patients with idiopathic PD (Jankovic et al 2018). The patients received 3 iv doses (up to 60 mg/kg), followed by a 3-month observational period. No serious or severe TEAEs were reported. The TEAEs with an incidence greater than placebo in 5% or more of PRX002-treated patients, regardless of relationship to PRX002, included constipation, infusion-related reactions, diarrhea, peripheral edema, post-lumbar puncture syndrome and upper respiratory tract infection. PRX002 was also reported to be CNS penetrant (mean concentration of 0.3% relative to serum across all dose levels). Results also showed a rapid, dose- and time-dependent mean reduction of free serum α -synuclein of up to 97% after a single dose. Based on the Phase 1 clinical evaluation, PRX002 appears to be generally safe and well tolerated in doses that fully suppress α -synuclein in the periphery and that are distributed to the CNS compartment. While it is not yet known whether PRX002 engages extracellular aggregated α -synuclein in the brain, the antibody is currently being evaluated for efficacy in a 52-week trial in patients with early PD and participants receive monthly iv doses up to 4500 mg (PASADENA trial; Clinical Trials.gov identifier NCT03100149).

The human derived anti- α -synuclein monoclonal antibody BIIB054, which binds to a N-terminal epitope on α -synuclein with selectivity for aggregated forms of the protein (Weihofen et al 2019), is also undergoing Phase 2 evaluation for efficacy in patients with PD and is being administered in doses up to 3500 mg iv every 4 weeks (SPARK trial, NCT03318523). Data from the Phase 1 program for BIIB054 have not been published in the peer-reviewed literature. However, data from abstracts and conference presentations would indicate that single doses of the antibody up to 45 mg/kg were safe and well tolerated in PD patients. BIIB054 penetrates the central compartment (CSF-serum ratio up to 0.4%) and there is evidence to indicate that it engages α -synuclein in the plasma (Brys et al 2017; Brys et al 2018).

Collectively, the available data achieved with the investigational immunotherapeutics PRX002 and BIIB054 indicate that serum α -synuclein can be safely modulated in humans.

6.5 Previous human experience

The ongoing study (D6340C00001), is the first human study undertaken with MEDI1341 and the study remains blinded at this time. Single-ascending doses of MEDI1341 (70, 210, and 400 mg) administered iv to healthy volunteers have been evaluated across 3 cohorts of subjects to date. CCI [REDACTED] subjects have been exposed to MEDI1341 and N=[REDACTED] subjects have received placebo. No medically-important or clinically significant changes or trends for changes related to administration of investigational product have been identified across any of the clinical or laboratory safety endpoints over the course of the trial to date. CCI [REDACTED] TEAEs were reported across [REDACTED] subjects (details provided in Section 5). The most common TEAEs have been headache, nausea and vomiting. CCI [REDACTED] SAEs were reported: PPD [REDACTED]

Following the availability of new toxicology data for MEDI1341 that revealed the presence of ocular pathology in rats, all subjects participating in the FTIH study underwent ad hoc follow-up ophthalmic examinations at between CCI months post-dose of MEDI1341 or placebo. CCI of these subjects were noted to have 'glaucomatous optic discs'. Based on expert opinion, it is not thought that these findings are related to exposure to investigational product.

MEDI1341 PK data indicate CCI. Terminal elimination half-lives were comparable across the single doses (mean range CCI days). As expected, CCI in plasma total α -synuclein have been observed, although there is high between-subject variability for these data. The highest increases for total α -synuclein (approximately CCI%) have been observed at CCI days post-dose at the 400-mg dose level. MEDI1341 was quantifiable in CSF at the 210 and 400-mg dose levels and therefore appears to be CNS penetrant (CSF/serum concentration ratio individual range was CCI% to CCI% at the 400-mg dose level). Pharmacodynamic data achieved to date indicate MEDI1341 CCI of free α -synuclein in the CSF. Observed maximum median percentage of α -synuclein suppression was CCI% at Day CCI after the 400-mg dose (Section 5.1.2). While these pharmacodynamic data provide early evidence of target engagement in the central compartment, this has been CCI for the CCI compared with predictions from a PK/PD model. A more comprehensive evaluation of human PK/PD would require administration of MEDI1341 at higher dose levels. With respect to CCI data has been observed for CCI subjects exposed to MEDI1341 at the 70- and 210-mg dose levels. CCI of the subjects CCI results appeared to exhibit differences in MEDI1341 exposure and pharmacodynamic results or safety parameters.

MEDI1341 was well tolerated and shown to have an acceptable safety profile at the dose levels explored (70, 210, and 400 mg iv or placebo) across N=25 subjects. Further dose escalation in the FTIH study was stopped by AstraZeneca pending an evaluation of new non-clinical toxicology data in relation to rodent ocular pathology. In the context of this evaluation, there have been no findings in the clinical study to date that would preclude further administration of MEDI1341 to humans in the setting of the Phase 1 study proposals incorporating an appropriate risk-mitigation strategy (Section 6.7).

Further details are provided in Section 5.2.

6.6 Safety margins

Human exposure for the proposed Cohorts 4, 5, and 6 will not exceed CCI $\mu\text{g}\cdot\text{day}/\text{ml}$ (AUC) or CCI $\mu\text{g}/\text{ml}$ (C_{max}). These exposures incorporate a CCI-fold safety margin relative to the exposures achieved at NOAEL in the CCI-week GLP rat toxicology study. This human exposure also provides for CCI-fold (AUC) and CCI-fold (C_{max}) safety margins relative to the exposures achieved at NOAEL in the CCI-week GLP cynomolgus monkey toxicology study.

6.7 Risk-benefit analysis and risk mitigation

MEDI1341 may have risks similar to those reported with other anti- α -synuclein antibodies, and, to a lesser extent, those reported with iv immunoglobulin (ivIg) therapies in general. Potential risks include CCI

Other adverse reactions reported with the use of ivIg therapy include headache, fatigue, hypotension, dyspnea, fever, nausea, vomiting, meningitis (including aseptic meningitis), exacerbation of chronic renal impairment, myocardial infarction, angina, infusion site erythema, thrombosis, chills, myalgia, reversible encephalopathy with cerebral vasospasm, skin reaction, pulmonary embolism, deep vein thrombosis, stroke, retinal arterial or venous occlusion and changes in blood laboratory findings (Gold et al 2007; Elovaara et al 2008). The doses that are typically used for ivIg therapies are in the range of 1 to 2 g/kg (Gold et al 2007). Doses that have been used for investigational anti- α -synuclein immunotherapeutics undergoing clinical development to date (PRX002 and BIIB054) are in the range of 0.3 to 60 mg/kg (Schenk et al 2017). Clinical data from studies of PRX002 and BIIB054 indicate that systemic α -synuclein can be safely modulated in humans.

Exposure to MEDI1341 has been observed to be related to the occurrence of ocular pathology in 2 rat toxicology studies (see non-clinical Section 4.3.2.1), described as increased cellularity of the sclera with perivascular mononuclear cell infiltration at the corneo-scleral junction. The findings appear to be exposure and dose-related. Equivalent findings have not been observed in the cynomolgus monkey toxicity studies. Although the rat ocular pathology findings have been reported as non-adverse, it is appreciated that this judgement has been made within the context of the specified endpoints for the respective general toxicology studies and the clinical relevance is unknown. Some evidence of reversibility of the pathology is appreciated from the recovery period incorporated into the 13-week study. Overall, it is acknowledged that the mechanism(s) underpinning the observed rodent pathology, as well as the potential clinical relevance to humans, remain unknown at present. From a clinical perspective, the rodent ocular findings are considered to be of potential clinical concern and an appropriate risk-mitigation strategy, which includes ophthalmic monitoring, has been implemented to support further Phase 1 evaluation of MEDI1341 in humans.

It is not expected that Phase 1 participants will benefit directly from participation in the studies. However, significant potential scientific benefits can be anticipated from exploration of PK/PD and safety over a higher dose range for MEDI1341, as the resulting data would provide a rational basis for the selection of appropriate doses for subsequent clinical development of MEDI1341 as a disease-modifying therapeutic targeting α -synuclein. Planned human exposure in the MEDI1341 Phase 1 program is of limited duration compared to the available repeat-dose toxicology studies and is therefore expected to minimize any potential risk of ocular toxicity. The Phase 1 studies comprise (i) administration of single doses at levels higher than 400 mg iv to healthy volunteers (single-ascending dose study), and (ii)

subsequent administration of no more than 3 repeat doses to relevant patient populations (multiple-ascending dose study).

No clinically significant ophthalmic adverse events have been reported, or other safety issues identified, for the Phase 1 participants who have received single doses of MEDI1341 up to 400 mg CCI. The eligibility criteria for subjects participating in further clinical studies should incorporate appropriate exclusions with respect to ophthalmic risk factors or pre-existing clinically relevant ophthalmic conditions. As part of the clinical monitoring strategy, ophthalmic patient-reported outcomes, assessments of visual acuity and comprehensive ophthalmic examinations should be implemented at baseline and at follow-up for the remainder of the single-ascending dose study and for the subsequent multiple-ascending dose study, pending further evaluation of risk-benefit profile.

Recognizing the limitations of the current understanding of the ocular findings in rats, the clinical exposure do not exceed a -fold safety margin in relation to the NOAEL exposure (AUC) achieved in the -week rat study and an -fold safety margin in relation to the NOAEL exposure (AUC) achieved in the -week cynomolgus monkey study.

Dose selection and escalation decisions across cohorts should be undertaken by a Dose Escalation Committee and based on a cohort-by-cohort review of all relevant safety, PK and pharmacodynamic data in the context of pre-defined stopping criteria. A cohort-by-cohort review of PK and relevant pharmacodynamic data is implemented: (i) to ensure that exposure predictions for the next planned cohort will not exceed pre-defined limits of human exposure, and (ii) to enable the PK/PD relationship to be explored on an interim basis, such that no further dose-escalation will occur once a near-maximal level of free α -synuclein suppression has been achieved in the central compartment (defined as a mean suppression of % for the cohort, as measured in CSF at the relevant trough time-point). For the ongoing FTIH study, single dose-level escalations should be restricted to no greater than -fold from one cohort to the next higher dose-level cohort.

6.8 Treatment for overdose and adverse reactions

In the event of a known or suspected overdose, vital signs should be monitored and symptomatic and supportive treatment should be provided in accordance with local standards of accepted medical practice. Referral to an appropriate high-dependency or critical care facility should be considered as required. There is no known specific antidote to MEDI1341.

6.9 Conclusion

By virtue of its capacity to engage disease relevant, pathological forms of α -synuclein, MEDI1341 presents a potential opportunity for the development of a disease-modifying therapeutic for PD and other related pathologies, for which there is an unmet medical need. At this stage of development, significant potential scientific benefits can be anticipated from exploration of safety and PK/PD over a higher dose range for MEDI1341 in the setting of the single dose escalation study (healthy volunteers) and a planned multiple-ascending dose study

(patient populations), as the resulting data will inform dose selection for subsequent efficacy trials.

Based on the available information regarding the risks for MEDI1341 and the risk mitigation measures implemented in the ongoing FTIH clinical study, the potential risks to exposing healthy study subjects to MEDI1341 in the context of single-dose escalation are considered acceptable.

7. REFERENCE SAFETY INFORMATION FOR ASSESSMENT OF EXPECTEDNESS OF SERIOUS ADVERSE REACTIONS

No serious adverse reactions are considered to be expected by the sponsor for the purpose of expedited reporting of suspected unexpected serious adverse reactions (SUSARs) and identification of SUSARs in the “Cumulative Summary Tabulation of Serious Adverse Reactions” in the Development Safety Update Report for MEDI1341.

8. SUMMARY OF CHANGES TO THE INVESTIGATOR'S BROCHURE

This version of the investigator's brochure (Edition 3.0, dated 26 June 2019) has been updated from the previous edition (Edition 2.0) dated 15 November 2017. The cut-off date for changes to this update was 09 May 2019. Updates included in this edition are listed in the table below.

Section Number	Section Title	Revision
Not applicable	Title Page	Updated edition number and date
Not applicable	Glossary of Abbreviations and Definition of Terms	Updated
Global	Not applicable	Minor formatting, edition number, data cut-off date, and consistency changes updated throughout
Section 1	Summary	• Revised with Study D6340C00001 summary and status • Revised with updated pharmacokinetic, toxicokinetic, and toxicology data from rat and monkey studies
Section 2.2	Background and rationale for the development of MEDI1341	Clarifications to background information on Parkinson's Disease, α -synuclein, and current therapeutic options made.
Section 2.2.5	Clinical Plan	Revised text to reflect Study D6340C00001 status
Section 4.1.1.2	In vivo studies	Statement on doses used in in vivo pharmacology studies added
Section 4.2.6.1	Single Dose Pharmacokinetics; Subsection "Pharmacokinetics of MEDI1341 in Rat following High Dose Intravenous Administration"	New section added
Section 4.2.6.1	Single Dose Pharmacokinetics; Subsection "Pharmacokinetics of MEDI1341 in Cynomolgus"	New section added

Section Number	Section Title	Revision
	Monkey following High Dose Intravenous Administration"	
Section 4.2.6.2	Repeat Dose Pharmacokinetics; Subsection "GLP Toxicokinetic Study of MEDI1341 in Rat Following Once Weekly Intravenous Administration for █ Weeks"	New section added based on Report AB22290
Section 4.2.6.2	Repeat Dose Pharmacokinetics; Subsection "GLP Toxicokinetic Studies of MEDI1341 in Rats Following Once Weekly Intravenous Administration for 13 Weeks"	Section title revised
Section 4.2.6.2	Repeat Dose Pharmacokinetics; Subsection "GLP Toxicokinetic Study of MEDI1341 in Cynomolgus Monkey Following Once Weekly Intravenous Administration for █ Weeks"	New section added based on Report AB22301
Section 4.2.6.2	Repeat Dose Pharmacokinetics; Subsection "GLP Toxicokinetic study of MEDI1341 in Monkeys Following Once Weekly Intravenous Administration for 13 Weeks"	Section title revised; table footnotes added
Section 4.2.6.3	Human Pharmacokinetic Predictions	Section revised based on additional pharmacokinetic and toxicokinetic data
Section 4.3.2	Repeated-Dose Toxicity	Added summary of studies
Section 4.3.2.1	Repeat-Dose Toxicity Studies in Rats	• Added new subsection summarizing the █-week repeat-dose toxicity study in rats (Report: AB22290) • Revised summary of 13-week repeat-dose toxicity study in rats based on ocular microscopic changes
Section 4.3.2.2	Repeat-Dose Toxicity Studies in Monkeys	Added new subsection summarizing the █-week repeat-dose toxicity study in

Section Number	Section Title	Revision
		cynomolgus monkeys (Report: AB22301)
Section 4.3.5	Reproductive and Development Toxicity	Clarified █-week repeat-dose toxicity studies were conducted
Section 4.3.6	Local Tolerance	Revised text for consistency
Section 4.3.7.2	Ocular Tissue Cross-reactivity Study of MEDI1341	New Section added
Section 4.3.8	Anticipated Safety Margins	Revised with updated clinical dose rationale and non-clinical data from █-week and 13-week repeat-dose toxicity studies
Section 5	Effects in Humans	Revised text to reflect Study D6340C00001 status
Section 5.1	Pharmacokinetics, Pharmacodynamics, and Immunogenicity	New section added with data from Study D6340C00001, along with subsections 5.1.1 (Pharmacokinetics), 5.1.2 (Pharmacodynamics), and 5.1.3 (Immunogenicity)
Section 5.2	Safety and Efficacy	New section added with data from Study D6340C00001
Section 6	Summary of Data and Guidance for the Investigators	Revised with Study D6340C00001 summary and status
Section 6.2	Indication to be Studied	Revised to include other patient populations with relevant α -synuclein pathology
Section 6.3	Non-clinical Safety Data	Revised summary of 13-week toxicity studies and added summary of █-week toxicity studies
Section 6.4	Clinical Experience with Anti- α -synuclein Antibodies	Added information on investigational immunotherapeutics PRX002 and BIIB054
Section 6.5	Previous Human Experience	Revised with Study D6340C00001 summary and status
Section 6.6	Safety Margins	Revised with Study D6340C00001 and data from █-week and 13-week rat

Section Number	Section Title	Revision
		and monkey toxicokinetic and toxicology studies
Section 6.7	Risk-Benefit Analysis and Risk Mitigation	Revised based on available clinical and non-clinical data
Section 6.8	Treatment for Overdose and Adverse Reactions	Clarified treatment
Section 6.9	Conclusion	Revised based on available clinical and non-clinical data
Section 7	Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions	New section added
Section 8	Summary of Changes to the Investigator's Brochure	New section added
Section 9	References	References revised

9. REFERENCES

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