2. SYNOPSIS

Title of study: A Randomized, Double-blind, Placebo-controlled Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Ascending Doses of MEDI1341 in Subjects with Parkinson's Disease

Investigational product: MEDI1341

Sponsor: AstraZeneca Pharmaceuticals LP

Investigators: Beth Emmie Safirstei PPD

Publications: None.

Period of study: 04 August 2020 (date of first informed consent) to 05 January 2022 (date of last subject's last visit).

Phase of development: Clinical Phase 1

Objectives

The primary objective was to assess the safety and tolerability of multiple-ascending doses of MEDI1341 versus placebo in subjects with Parkinson's Disease (PD).

The secondary objectives were:

- To assess the pharmacokinetics (PK) of MEDI1341 in subjects with PD
- To assess the pharmacodynamics of MEDI1341 in subjects with PD
- To assess the immunogenicity of MEDI1341 in subjects with PD

The tertiary/exploratory objectives were:

CCI

Methodology:

The study was a multicenter, randomized, double-blind, placebo-controlled study of multiple ascending intravenous (IV) doses of MEDI1341 being conducted in male and female subjects aged 40 to 85 years (inclusive) and with PD. This study was planned to evaluate MEDI1341 in the intended patient population at an early stage of development. The study was designed to include up to 3 cohorts CCI, with 12 subjects in each, for a total of up to 36 randomized subjects.

Within each cohort, 9 subjects were to be randomized to receive MEDI1341, and 3 subjects were to be randomized to receive placebo. The study comprised a screening period, an 8-week double-blind treatment period, and a 13-week follow-up period. Each subject received three 60-minute IV infusions of MEDI1341 or placebo during the double-blind treatment period, with a period of 4 weeks (28 days) in between the infusions (ie, 1 infusion was administered on each of Days 1, 29, and 57). The placebo was included in the study to permit comparative assessment of the endpoints between MEDI1341 and placebo.

To minimize risk to the subjects, the Dose Escalation Committee (DEC) assessed unblinded clinical safety data and all relevant PK, pharmacodynamics, and immunogenicity data, accumulated up to at least the Day 85 timepoint (up to Day 99 for ophthalmic follow-up data), on a cohort-by cohort basis to be able to make decisions on further dose escalation. Also, after completion of Cohort 1 (MEDI1341 CCI), implementation of the planned higher doses was to be decided in the context of the totality of available nonclinical and clinical data. Based on new nonclinical data, the proposed Cohort 3 dose was updated CCI . After DEC review of study data from Cohort 1, the dose for Cohort 2 was then adjusted CCI to keep the predicted exposures for this dose level within a 10-fold safety margin of the prespecified exposure limits based on nonclinical data available at that time.

Although the safety profile was good following Cohort 2, the study was concluded without any further dose escalation to ensure that MEDI1341 exposures associated with higher potential dose levels above CCI did not exceed the 10-fold safety margin with respect to the nonclinical safety exposure limits. The study was therefore terminated after completion of the first 2 cohorts.

Number of subjects (planned and analyzed):

The study planned to enroll a total of up to 36 subjects. It was decided not to enroll subjects to a dose level beyond CCI per DEC decision. A total of 25 subjects received at least 1 dose of investigational medicinal product in this study: 7 on placebo, 9 on CCI , and 9 on CCI MEDI1341.

Diagnosis and main criteria for inclusion and exclusion:

Subjects who met the following criteria were included in the study:

Age

1. Subjects aged between 40 to 85 years (inclusive) on the day of randomization.

Type of Participant and Disease Characteristics

2. PPD (PPD of the protocol).
3. Parkinson's disease was at stages 1 to 3 using the Hoehn and Yahr scale as modified.
4. Subjects receiving medications for idiopathic PD were on a stable dosing regimen of their medication(s) for ≥1 month before randomization (and their ongoing

medications or dosing regimen were not changed for the duration of the study, barring unforeseen circumstances). For subjects who were not currently receiving medications to treat idiopathic PD, there was no expectation of a need to initiate the medications for the duration of the study).

Weight

5. Subjects had a body weight of 45 to 120 kg (inclusive), and a body mass index (BMI) of 18 to 34 kg/m^2 (inclusive) at screening and check-in for the first infusion.

Sex

6. Subjects were male or female. Female subjects were of nonchildbearing potential (postmenopausal and/or surgically sterile).

Reproduction

7. Postmenopausal women had ≥12 months of spontaneous amenorrhea and must have had a negative serum pregnancy test result at screening. Surgically sterile women were defined as those who have had a hysterectomy, bilateral ovariectomy (oophorectomy), salpingectomy, or bilateral tubal ligation. Women who were surgically sterile were required to provide documentation of the procedure by an operative report, ultrasound, or other verifiable medical documentation.
8. Men who were biologically capable of fathering children agreed and committed to use an adequate form of double-barrier contraception for the duration of the treatment period and for 5 half-lives (100 days) after the last administration of study intervention. A male subject was considered capable of fathering children even if his sexual partner was sterile or on contraceptives.
9. Men who were biologically capable of fathering children also agreed to refrain from sperm donation for the duration of the treatment period and for 5 half-lives or 90 days (whichever was longer) after the last administration of study intervention.

Informed Consent

10. Subjects in the investigator's opinion understood the nature of the study and provided signed and dated written informed consent before the conduct of any study-related procedures.

Other Inclusion Criteria

11. Subjects had to, in the opinion of the investigator, be able to participate in all scheduled evaluations, likely to be compliant, and likely to complete all required tests, including magnetic resonance imaging (MRI) brain scans and lumbar punctures (LPs). Note: The investigator assessed the physical and functional needs of the subject at screening, as participation in the study was contingent on the availability and willingness of a caregiver to attend with the subject at all study visits.
12. Subjects were able to read, write, and speak fluently in English and/or Spanish.

13. Subjects agreed to not post any personal medical data related to the study or information related to the study on any website or social media site (eg, Facebook, Twitter, Instagram) until the study has been completed.
14. Subjects had a Montreal Cognitive Assessment total score of ≥24.

Subjects who met any of the following criteria as stated in the protocol were excluded from the study:

Medical Conditions

1. In the opinion of the investigator, a recent clinically significant illness (other than PD), infection, medical/surgical procedure, or significant trauma that occurred within 30 days prior to screening, or between screening and randomization, that was likely to deteriorate, compromise the subject's safety or ability to complete the study, or compromise the interpretation of the study results (Note: a history of coronavirus disease 2019 [COVID-19] infection with unresolved medical sequelae was considered exclusionary).
2. Presence of a serious or unstable clinically significant illness, including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic or autoimmune disease (eg, multiple sclerosis), hematologic or other major diseases, which, in the judgment of the investigator, was poorly controlled or otherwise likely to deteriorate, compromise the subject's safety, ability to complete the study, or compromise the interpretation of the study results.
3. Significant neurological disease affecting the central nervous system (other than PD) that, in the opinion of the investigator, may have affected motor function or the ability to complete the study, including but not limited to progressive supranuclear palsy, multiple system atrophy (MSA; including MSA-P and MSA-C or other MSA terminology: striatonigral degeneration, olivopontocerebellar atrophy or autonomic failure), postencephalitic parkinsonism, metabolic diseases with parkinsonian signs and symptoms (eg, Wilson disease, manganese exposure) or other secondary forms of Parkinsonism, and ischemic or traumatic brain injury (including multiple episodes of head trauma, or head trauma resulting in protracted loss of consciousness within the 5 years prior to screening or between screening and randomization).
4. Brain MRI scan that showed clinically significant evidence of malignant, ischemic, demyelinating, structural, or degenerative brain disease or had findings that compromised the safety of LP.
5. Had undergone surgery for the treatment of PD (eg, pallidotomy, deep brain stimulation, fetal tissue transplantation) or had undergone any other brain surgery at any time, even for non-PD conditions.
6. Had history of epilepsy or seizures, except febrile childhood seizures.
7. Had history of transient ischemic attack, stroke, or any unexplained loss of consciousness within 1 year prior to screening or between screening and randomization.
8. Had presence of any psychiatric disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) or symptom if, in

the judgment of the investigator, the psychiatric disorder or symptom was likely to confound interpretation of the study results, affect motor function assessment, or affect the subject's ability to complete the study.

9. Had a diagnosis of intellectual disability (intellectual developmental disorder), mental retardation, or significant inherited cognitive impairment.
10. Suicidality, represented by answering "yes" to Question 4 or Question 5 on the C- SSRS, indicating active suicidal ideation with any intent to act, during the subject's lifetime, as assessed at screening, or between screening and randomization.
11. Suicidal behavior such that a determination of "yes" was made on the Suicidal Behavior section of the Columbia–Suicide Severity Rating Scale for "Actual Attempt," "Interrupted Attempt," "Aborted Attempt," or "Preparatory Acts or Behavior," during the subject's lifetime, as assessed at screening, or between screening and randomization.
12. Had history of alcohol or drug abuse or dependence (except nicotine dependence), as defined by the DSM-V, within 2 years prior to screening or between screening and randomization.
13. Within 1 year prior to screening, had any of the following: myocardial infarction; hospitalization for congestive heart failure; hospitalization for, or symptoms of unstable angina; unexplained syncope.
14. Had moderate or severe congestive heart failure, or known ejection fraction <40%.
15. Known significant structural heart disease (eg, significant valvular disease, hypertrophic cardiomyopathy) that was considered likely to lead to a deterioration of cardiac function over the course of the study.
16. Had history of cancer within 5 years prior to screening or between screening and randomization, with the exception of nonmetastatic basal and/or squamous cell carcinoma of the skin.
17. Had history of allergy/hypersensitivity to immunizations or immunoglobulins.
18. Any condition that, in the opinion of the investigator or medical monitor, made the subject unsuitable for the study.

Prior/Concomitant Therapy

19. Required treatment with another monoclonal antibody.
20. Used any investigational medicine, device, or biologic within 3 months or 5 half-lives of that intervention (whichever was longer) prior to screening.
21. Had undergone previous allogeneic bone marrow or stem cell transplant.
22. Used typical or atypical antipsychotic medication, or other medication with dopamine antagonist properties (eg, metoclopramide, domperidone), within 6 months prior to randomization.
23. Used immunosuppressive medication within 6 months prior to randomization. (Note: Inhaled and topical corticosteroids were permitted. Low-dose systemic corticosteroids [<10 mg per day prednisone or equivalent], for autoimmune disease that was

considered quiescent, in remission, or otherwise well-controlled were permitted). Other immunosuppressive drugs and biologics were contraindicated.

24. Received non-leukocyte-depleted whole blood transfusion within 6 months prior to screening.
25. Received any commercially available vaccine within 30 days prior to randomization. (Note: for COVID-19 vaccines authorized by the Food and Drug Administration for emergency use, this timeframe applied from last vaccination or booster dose, whichever was required to consider vaccination complete in line with applicable guidance).

Prior/Concurrent Clinical Study Experience

26. Participated in another study investigating: (a) Active or passive immunization against α-synuclein for PD, at any time prior to screening, or (b) Immunoglobulin G therapy within 6 months before screening.

Diagnostic Assessments

27. Any clinically significant abnormality as determined by investigator at screening or between screening and randomization in physical examination, vital signs, electrocardiograms (ECG), or clinical laboratory test results that may have compromised the subject's safety or ability to complete the study or compromise the interpretation of the study results.
28. Presence of any of the following MRI contraindications: pacemaker; cardiac defibrillator; spinal cord or vagus nerve stimulator; aneurysm clip; artificial heart valve; recent (within 1 year) coronary or carotid stent; ear implant; CSF shunt; other implanted medical device (eg, insulin pump); metal fragments or foreign objects in the eyes, skin, or body; claustrophobia which may have contraindicated a brain MRI scan.
29. Brain MRI findings (or historical radiologic reports, if available) that showed evidence of clinically significant structural brain disease which, in the opinion of the investigator, contraindicated the performance of LP.
30. Any spinal abnormality or other aspects (eg, tattoos) or other clinical findings (papilledema seen with ophthalmoscopy) that may have complicated or contraindicated LP, as judged by the investigator.
31. Ophthalmic abnormalities. The following were considered exclusionary:
    a) Congenital or acquired ophthalmic conditions (primary or secondary) that were considered poorly controlled within the last 12 months prior to screening, with or without treatment, or otherwise expected to lead to significant deterioration in visual acuity in the next 6 months after randomization.
    b) Specific ophthalmic conditions:
        i. Current or past history of inflammation affecting the uveal tract or sclera
        ii. Diabetic retinopathy

iii. Neovascular or exudative (wet) form of age-related macular degeneration
iv. Active central serous retinopathy (central serous chorioretinopathy)
v. Subjects with active autoimmune disease
vi. Subjects who had taken immunosuppressive drugs (other than low doses of systemic steroids [<10 mg per day of prednisone equivalent], for autoimmune disease that was considered inactive, in remission, or otherwise well-controlled). Other immunosuppressive drugs were contraindicated.
vii. Mature cataracts (Grade ⩾4 per the Lens Opacities Classification System III) or lower grade cataracts that were otherwise considered by the examining ophthalmologist to prevent adequate examination of the uveal tract or posterior ocular segment. (Note: Previous cataract surgery or an age-related cataract with age-appropriate lens opacification and no other important identified secondary causes [eg, diabetes, corticosteroids, vitamin deficiencies, trauma, radiation, or systemic fluid and electrolyte disturbances] was not necessarily exclusionary).

32. Aspartate aminotransferase or alanine aminotransferase concentrations >1.5 × the upper limit of normal (ULN) at screening, or between screening and baseline.
33. Estimated creatinine clearance <50 mL/min or creatinine >1.5 × ULN at screening.
34. Clinically significant vital signs abnormalities at screening or on Day 1, defined as (a) systolic blood pressure ≥160 mmHg, (b) diastolic blood pressure ≥90 mmHg (blood pressure assessed at rest; may be repeated up to 3 times), or (c) pulse rate <45 or >100 beats per minute (at rest).
35. Clinically significant abnormality in ECG rhythm, conduction, or morphology at screening or between screening and randomization, including but not limited to:
    a) Clinically significant ECG interval measured from the onset of the P wave to the onset of the QRS complex (PR [PQ]) interval prolongation (PR >220 msec)
    b) Intermittent second or third-degree atrioventricular (AV) block (AV block II Mobitz Type I, Wenckebach, while asleep or in deep rest was not exclusionary)
    c) Bundle branch block or intraventricular conduction delay with ECG interval measured from the onset of the QRS complex to the J point (QRS) interval duration ≥120 msec
    d) Electrocardiogram interval measured from the onset of the QRS complex to the end of the T wave interval corrected for heart rate using Fridericia's formula QT (QTcF) interval measurement >470 msec, or a shortened QTcF <340 msec, at screening or between screening and randomization, or a family history of long or short QT syndrome.
36. Positive serologic findings for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen, or hepatitis C virus antibodies, with relevant confirmatory testing conducted, where applicable, in accordance with Centers for Disease Control and Prevention guidance for HIV and viral hepatitis.

37. Current blood clotting or bleeding disorder, including clinically significant abnormal findings in laboratory tests of coagulation.

Other Exclusions

38. Poor venous access, such that IV drug delivery or PK/safety blood sampling was difficult.
39. Donated blood or plasma within 2 months prior to screening and until 2 months after the final follow-up visit.
40. A positive serum pregnancy test result at screening or prior to randomization.
41. Urine drug screen positive for a drug of abuse (except for permitted, prescribed opiates and /or benzodiazepines). A urine drug screen positive for cannabinoids was exclusionary unless there was a documented legitimate medical reason for the subject's cannabinoid use (eg, chronic pain) or the investigator and medical monitor agreed that the subject could abstain from use for the duration of the study.
42. Currently employed by the sponsor (AstraZeneca) or by a contract research organization or clinical study site participating in this study, or a first-degree relative of an AstraZeneca employee or of an employee at a participating contract research organization or clinical study site.

Test product, dose and mode of administration, batch/lot number:

Three 60-minutes IV infusion of CCI [redacted] MEDI1341 was administered every 4 weeks. The batch number was CCI [redacted].

Reference therapy, dose and mode of administration, batch/lot number:

Three 60-minutes IV infusion of placebo (saline) was administered every 3 weeks. The batch number was CCI [redacted].

Duration of treatment:

The study comprised a screening period, an 8-week double-blind treatment period, and a 13-week follow-up period. Each subject received MEDI1341 or placebo during the double-blind treatment period, with a period of 4 weeks (28 days) in between the infusions (ie, 1 infusion was administered on each of Days 1, 29, and 57).

Endpoints:

The primary endpoints were:

- Adverse events (AEs) and serious adverse events (SAEs)
- Vital signs, body weight measurements, and BMI
- Clinical chemistry, hematology, coagulation, and urinalysis test results

- Electrocardiograms (12-lead paper and digital recordings), including rhythm, heart rate, conduction, PR (PQ), QRS, the time elapsed between 2 consecutive R waves as measured by ECG, QT, and QTcF intervals, and overall evaluation
- Physical and neurological examinations
- Ophthalmic assessments
- Injection-site reaction assessments
- Columbia–Suicide Severity Rating Scale assessments
- Montreal Cognitive Assessment

The secondary endpoints were:

- Pharmacokinetic parameters such as maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the concentration-time curve from time zero to the end of the dosing interval ($AUC_{0-\tau}$), terminal elimination half-life ($t_{1/2\lambda z}$), clearance (CL), volume of distribution (V_d), and accumulation ratio (R_o)
- α-synuclein levels (total in plasma, free in CSF)
- Presence of antidrug antibodies (ADA)

Tertiary/exploratory endpoints were:

CCI [redacted]

Statistical methods:

Analysis populations:

The all-subjects analysis set included all subjects who signed the informed consent form and had any study assessment recorded in the database per the protocol.

The safety analysis set included all subjects who received at least 1 dose of study drug (MEDI1341, placebo) and for whom any postdose data were available.

The PK analysis set included all subjects for whom PK data were available. The PK analysis set included all evaluable PK data appropriate for the evaluation of interest from all subjects who received at least 1 dose of MEDI1341.

The pharmacodynamic analysis set included all subjects for whom pharmacodynamic data were available. The pharmacodynamic analysis set included all evaluable pharmacodynamic data appropriate for the evaluation of interest (eg, with no important protocol deviations or violations thought to significantly affect the result) from all subjects.

Statistical methodology:

Pharmacokinetics

The PK parameters were determined from the serum concentrations of MEDI1341 using noncompartmental procedures.

The PK analysis was carried out using actual blood sampling times postdose, wherever possible. If an actual time was missing, the sample concentration result was treated as missing unless there was scientific justification to include the result using the nominal time. The parameters such as C_{max}, time of the last quantifiable concentration (t_{last}), and t_{max} were obtained directly from the serum concentration-time profiles. If C_{max} occurred at more than 1 timepoint, t_{max} was assigned to the first occurrence of C_{max}. All the PK concentrations (serum and CSF) and parameters (serum) were listed.

Summary tables, mean (+standard deviation [SD]) figures, overlaying individual figures, and individual figures by treatment and time were provided for serum PK concentrations. Summary tables were provided for MEDI1341 CSF PK concentrations and CSF PK concentrations as a percentage of the serum PK concentrations of MEDI1341. All figures were produced on linear and semilogarithmic scales, with the exception of figures across all days, which were produced on the linear scale only.

A summary of serum and CSF PK concentrations was also provided by ADA study status.

Summary tables by treatment were provided for all serum PK parameters, with the exception of diagnostic regression-related PK parameters.

A statistical analysis was conducted to investigate the dose proportionality of $AUC_{0-\tau}$ and C_{max} on Days 1 and 57. Due to only 2 dose levels reported in the study, the power model was not used and instead the natural log-transformed PK parameters (normalized by dose administered) were analyzed using an analysis of variance model. The model included dose as a factor.

Pharmacodynamics

All pharmacodynamic variables, with changes from baseline and percentage changes from baseline, were listed. Individual figures by treatment and time were provided. Summary tables by treatment and timepoint were provided for all pharmacodynamic variables, with changes from baseline and percentage changes from baseline.

Arithmetic mean (+SD) figures by treatment and timepoint were provided for total α-synuclein (from plasma), with arithmetic mean (+SD) changes from baseline and arithmetic mean (+SD) percentage changes from baseline. Median figures by treatment and timepoint were provided for total α-synuclein (from plasma), with median changes from baseline and median percentage changes from baseline.

For free α-synuclein (from CSF), an arithmetic mean (+SD) percentage changes from baseline figure and median percentage changes from baseline figure by treatment and timepoint were provided.

Overlaying individual figures by treatment were provided for total α-synuclein (from plasma) by treatment. Overlaying individual figures were provided for free α-synuclein (from CSF) by treatment, with individual value markers flagged. A scatterplot (with median displayed) and boxplots by timepoint and treatment were provided for free α-synuclein (from CSF).

No formal pharmacodynamic parameter calculations or inferential statistical analyses were planned.

Safety

All safety data for the safety population were listed. All AEs were listed using the Medical Dictionary for Regulatory Activities Version 23.0 and assigned severity grades using CTCAE Version 5.0. The AE listings included onset time and duration. Onset time was calculated from the time of the start of the last given infusion for treatment-emergent adverse events (TEAEs) only.

The frequency of subjects with TEAEs and the number of TEAEs were summarized for the following categories:

- TEAEs (overall, serious, and leading to discontinuation) by treatment
- TEAEs by intensity and treatment
- Treatment-related TEAEs (overall, serious, and leading to discontinuation) by treatment
- Treatment-related TEAEs by intensity and treatment.

This summary was also provided by ADA study status.

The frequency of subjects was summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class (SOC), preferred term (PT), and treatment (this summary was also provided for TEAEs by ADA study status)
- Preferred term and treatment

Summary tables and boxplots by treatment and timepoint were provided for clinical chemistry, hematology, and coagulation parameters, with changes from baseline.

Summary tables and boxplots by treatment and timepoint with changes from baseline were provided for all vital signs parameters.

Summary - Conclusions:

<u>Pharmacokinetic results:</u>

Following the infusion of CCI [redacted] MEDI1341 on Day 1, the median t_{max} was approximately 1 hour after the start of infusion. All individual subject serum concentrations were measurable through Day 29, when the next infusion was to start.

Following the Day 57 infusion of CCI MEDI1341, the median t_{max} was approximately 1 hour after the start of infusion. At the dose levels of CCI, individual subject serum concentrations were measurable through Day 148 in all subjects after the last infusion on Day 57. Median t_{last} for both dose levels were similar: 90.5 versus 91.1 days for CCI dose levels, ranging from 84.1 to 97.0 days and 85.1 to 98.1 days for CCI dose levels, respectively.

The geometric mean $t_{1/2\lambda z}$ was similar between the 2 MEDI1341 groups: 18.2 days for the CCI dose level versus 19.5 days for the CCI dose level.

Geometric mean CL, V_d, and R_o appeared to be comparable between the 2 dose levels.

Dose proportionality was observed for AUC_{0-t} and C_{max}.

For both MEDI1341 groups, geometric mean CSF concentrations were 0.187% to 0.608% of their respective serum concentrations and appeared to increase with time from Day 61 to 85. The geometric mean CSF/serum concentration ratios appeared to be comparable between the 2 MEDI1341 dose levels.

Eleven percent of subjects treated with MEDI1341 developed treatment-emergent ADA (2/9 in the CCI cohort and 0/9 in the CCI cohort). Based on limited data, ADA had no impact on PK, pharmacodynamics, or safety.

Pharmacodynamic results:

Following the IV infusion of MEDI1341, the mean (SD) total α-synuclein in both the CCI groups showed an increase whilst no obvious trend was observed in the placebo group. After an increase in plasma total α-synuclein, the levels started to fall 7 days and 14 days following the IV infusion of CCI, respectively, on both Day 1 and 57.

Following the IV infusion of CCI MEDI1341, dose-dependent suppression of free α-synuclein in CSF was observed. The median percentage change of free α-synuclein from baseline was -75.2% (-81.9%, -13.0%) at Day 61 and was -59.0% (-80.3%, -37.6%) at Day 85 at the CCI dose level, which was higher compared to the CCI dose level.

Safety results:

Overall, 10 (40%) of the 25 subjects reported 27 TEAEs during the study. More MEDI1341-treated subjects experienced TEAEs compared to placebo.

The most frequently reported SOCs for TEAEs were gastrointestinal disorders (4 [16.0%] subjects) and general disorders and administration site conditions (3 [12.0%] subjects). The most frequently reported TEAEs were fall and nausea (2 [8.0%] subjects each).

No subjects reported TEAEs of severe/Grade 3 intensity. Most of the TEAEs were mild/Grade 1 in intensity.

No subjects experienced an SAE or a TEAE leading to discontinuation during the study.

Four treatment-related TEAEs of fatigue, headache, nausea, and rash were reported; all were reported in 1 (4.0%) subject from the MEDI1341 CCI group. All treatment-related TEAEs were mild/Grade 1 with the exception of moderate/Grade 2 fatigue.

Clinical laboratory evaluations, ECG data, physical, injection site and infusion reaction assessments, and ophthalmic assessments did not reveal any significant changes from baseline or trends for changes that would suggest that MEDI1341 negatively affected subject safety.

Montreal Cognitive Assessment CCI were all within the expected range, which indicated that clinical features of PD remained relatively stable during the study and were unaffected by treatment assignment.

Two of 18 (11.1%) subjects dosed with MEDI1341 developed treatment-emergent ADA. Based on limited data, ADA had no impact on PK, pharmacodynamics, or safety.

Overall, MEDI1341 was generally well tolerated.

Conclusions:

- MEDI1341 was found to have a good safety profile in comparison to placebo and was generally well tolerated following 3 repeat IV infusions CCI administered every 4 weeks. Two of 18 (11.1%) subjects dosed with MEDI1341 developed treatment-emergent ADA. No impact of ADA on PK, pharmacodynamics, or safety was identified.
- Following IV infusions of CCI MEDI1341 on Days 1 and 57, maximum serum concentrations of MEDI1341 were achieved at the end of the 1-hour infusion.
- Following IV infusions of CCI MEDI1341 on Day 57, the geometric mean $t_{1/2\lambda z}$, median t_{last}, CL, V_d, and R_o appeared to be comparable between the 2 MEDI1341 groups.
- Dose proportionality was observed for $AUC_{0-\tau}$ and C_{max}.
- For both the MEDI1341 groups CCI, geometric mean CSF concentrations were 0.187% to 0.608% of their respective serum concentrations and appeared to increase with time from Day 61 to 85. The geometric mean CSF/serum concentration ratios appeared to be comparable between the 2 MEDI1341 dose levels.
- Following the IV infusion of MEDI1341, total α-synuclein in plasma increased for the MEDI1341 CCI groups and the levels started to fall 7 days and 14 days, respectively, on both Day 1 and 57.
- A dose-dependent suppression of free α-synuclein in CSF was observed. Suppression of free α-synuclein in CSF was found to be higher at the CCI dose level than at the CCI dose level. The median (minimum, maximum) percentage change of free α-synuclein in CSF from baseline was -59.0% (-80.3%, -37.6%) at Day 85 at the CCI dose level.