2. SYNOPSIS

Title of study: A Randomized, Double-blind, Placebo-controlled Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Ascending Doses of MEDI1341 in Healthy Male and Female Volunteers

Investigational product: MEDI1341

Sponsor: AstraZeneca Pharmaceuticals LP

International Coordinating Investigator: PPD, USA, 2 centers

Publications: None

Period of study: 26 October 2017 (date of first informed consent) to 31 March 2021 (date of final poststudy observation).

Phase of development: Clinical Phase 1

Objectives:

The primary objective of the study was to assess the safety and tolerability of single ascending doses of MEDI1341 versus placebo in healthy male and female volunteers.

The secondary objectives of the study were to assess the pharmacokinetics (PK) of MEDI1341 in healthy male and female volunteers; to assess the pharmacodynamics (PD) of MEDI1341 in healthy male and female volunteers; and to assess the immunogenicity of MEDI1341 in healthy male and female volunteers.

Methodology:

This was a randomized, double-blind, placebo-controlled study of single ascending intravenous (IV) doses of MEDI1341 in male and nonfertile female healthy volunteers, aged 18 to 65 years. Within each of the 6 planned cohorts of 8 subjects, 6 subjects were randomized to receive MEDI1341, and 2 subjects were randomized to receive placebo. A Dose Escalation Committee reviewed safety, tolerability, and PK data from each cohort, as well as available pharmacodynamic and antidrug antibody (ADA) data, before progression to the next higher dose cohort occurred.

Number of subjects (planned and analyzed):

It was planned to study a total of 48 subjects in 6 groups of 8 subjects. A total of 49 subjects entered the study. Thirty-eight subjects were included in the PK and safety populations. Forty-nine subjects were included in the PD population.

Diagnosis and main criteria for inclusion:

Healthy male and female subjects of non-childbearing potential aged between 18 and 65 years.

The following are the main inclusion and exclusion criteria for subjects in this study:

- Weigh ≥50 kg and have a body mass index between 18.0 and 32.0 kg/m2, inclusive.

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

Dose levels of MEDI1341 were 70, 210, 400,1200, 2400, and 4500 mg. Doses were administered as an IV infusion via IV bag; batch/lot number CCI .

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

Placebo solution of 0.9% (w/v) sodium chloride administered an IV infusion via IV bag; batch/lot number CCI .

Duration of treatment:

Single IV infusions were administered in each group.

Outcome Measures:

Pharmacokinetics:

Blood and cerebral spinal fluid (CSF) samples were collected for the analysis of serum and CSF concentrations of MEDI1341. Pharmacokinetic parameters included maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the concentration-time curve (AUC) from time 0 to time t_{last}, where t_{last} is the time of the last quantifiable concentration (AUC_{0-t}) and from time 0 extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal elimination half-life ($t_{1/2\lambda z}$), total serum clearance (CL), volume of distribution at steady-state (V_{ss}), and mean residence time (MRT).

Pharmacodynamics:

Blood and CSF samples for the analysis of PD parameters: total α-synuclein in plasma and free α-synuclein in CSF.

Immunogenicity:

Blood samples for the determination of ADAs in serum.

Safety:

Adverse events (AEs), vital signs, clinical laboratory evaluations, electrocardiography, physical and neurological examinations, ophthalmic assessments, injection site reaction assessments, Columbia-Suicide Severity Rating Scale assessments (C-SSRS), Montreal Cognitive Assessment (MoCA) results.

Statistical methods:

All subjects who received at least 1 dose of randomized MEDI1341 or placebo, and for whom any postdose data were available, were included in the safety analysis set. Throughout

the safety results sections, erroneously treated subjects were accounted for in the actual treatment group.

The PK analysis set was based on all subjects for whom PK data were available. The PK analysis set included all evaluable PK data appropriate for the evaluation of interest (eg, with no important protocol deviations or violations thought to significantly affect the PK of the drug) from all subjects who received at least 1 dose of MEDI1341. Subjects who received placebo were not part of the PK analysis set.

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

MEDI1341 concentration data (serum and CSF) were summarized using descriptive statistics by treatment regimen and nominal sampling timepoint, and MEDI1341 serum PK parameters were summarized using descriptive statistics by treatment regimen.

Dose proportionality and linearity were evaluated using a power model. If the assumption of linearity was considered unacceptable in the power model, log-transformed, dose-normalized PK parameters were analyzed using an analysis of variance model. The model included treatment as a fixed effect. Least squares mean for each dose level were calculated. P-values for overall and pairwise treatment comparisons were presented.

Mean absolute and mean and median percentage changes from baseline over time for total α-synuclein (from plasma) were plotted by dose. Mean and median percentage change from baseline in free α-synuclein (from CSF) were also plotted by dose.

Spaghetti plots of free α-synuclein (from CSF) concentrations in individual subjects were produced for each dose studied.

The effect of different doses of MEDI1341 on the percentage change from baseline CSF free α-synuclein concentrations at postdose were also explored graphically.

Percentage changes from baseline in free α-synuclein concentrations (from CSF) were summarized with box and whisker plots by dose and scatter plots against MEDI1341 serum concentrations by dose and study day.

All safety data for the safety population are listed.

Treatment emergent AEs (TEAEs) were summarized by treatment, severity, and relationship to the investigational product. The frequency of TEAEs was summarized by treatment and Medical Dictionary for Regulatory Activities system organ class and preferred term. Summary and frequency TEAE tables were presented for all causalities and for those considered related to the investigational product.

Clinical chemistry and hematology data were summarized by treatment. In addition, all serum biochemistry, hematology, and urinalysis data outside the clinical reference ranges were listed by parameter and treatment.

Vital signs and ECG data were summarized by treatment, together with changes from baseline.

The C-SSRS was listed and summarized by timepoint.

The MoCA results were listed and summarized by timepoint.

The injection site and infusion reaction assessments were listed and summarized by timepoint.

Ophthalmic examinations data were listed. In addition, visual acuity and intraocular pressure were summarized by treatment and timepoint. Furthermore, abnormal findings from the slit-lamp and ophthalmic examinations were summarized by treatment and timepoint in frequency tables.

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Summary - Conclusions:

Subject disposition:

Forty-nine subjects were randomized into 6 groups and dosed with MEDI1341 or given a placebo in accordance with the protocol. Forty-eight subjects completed the study in accordance with the protocol.

Pharmacokinetic results:

Following single IV infusion of 70 mg to 4500 mg MEDI1341, attainment of maximum serum concentrations of MEDI1341 was variable, but generally observed at the end of the 1-hour infusion with median t_{max} values ranging from approximately 1 hour to 17 hours after the start of infusion. There was a particularly wide range of individual subject t_{max} values observed at the 400- and 1200-mg dose levels, reflective of the 1 subject in each of these dose groups who had a notably different shape to their serum MEDI1341 concentration-time profile (extravasation during IV administration was suspected, but no evidence of this occurring). After the end of IV infusion, serum concentrations of MEDI1341 slowly declined, with geometric mean $t_{1/2\lambda z}$ values ranging from 16.6 to 24.3 days and appearing similar across the dose levels. Serum MEDI1341 PK appeared linear for C_{max} over the dose range investigated and for AUCs over the dose range of 70 mg to 2400 mg. With the further increase in dose from 2400 mg to 4500 mg, increases in systemic exposure ($AUC_{0-\infty}$ and AUC_{0-t}) were supra-proportional, with a nearly 3-fold increase in geometric mean $AUC_{0-\infty}$ and AUC_{0-t} for the 1.88-fold increase in dose. Geometric mean CL and V_{ss} appeared generally similar across the dose range of 70 mg to 2400 mg (respective ranges of 0.927 to 1.09 L/day and 13.6 to 18.5 L) but were comparatively lower at the 4500-mg dose level, with geometric mean CL and V_{ss} values of 0.590 L/day and 11.1 L, respectively. Across the entire dose range of 70 to 4500 mg, the geometric mean CL and V_{ss} values were similar to higher than previously reported values for monoclonal antibodies.

Across the MEDI1341 dose levels, geometric mean CSF concentrations were highest on Day 8 compared to Days 15 and 29.

Across all dose levels and timepoints, individual subject CSF MEDI1341 concentrations were <1% of their respective MEDI1341 serum concentrations, indicating minimal blood brain barrier penetration. Across the dose levels, geometric mean CSF/serum MEDI1341 concentration ratios, expressed as percentages, appeared to increase with time, from Day 8 to Day 29. At each timepoint, across the applicable dose ranges, geometric mean CSF/serum MEDI1341 concentration ratios appeared to be similar or slightly decrease with the increase in MEDI1341 dose.

Pharmacodynamic results:

Following single IV infusion of 70 mg to 4500 mg MEDI1341, arithmetic mean percentage change from baseline values for total α-synuclein in plasma generally appeared to increase and then decrease back to baseline over time. The fluctuation in percentage change from baseline appeared possibly MEDI1341 dose-related, with the greatest increases in arithmetic mean percentage change from baseline being 449.5 (169.96)% on Day 8 for the 2400-mg dose and 446.8 (406.28)% on Day 22 for the 4500-mg dose. Comparatively, there was minimal fluctuation in plasma total α-synuclein levels following single IV infusion of placebo, with arithmetic mean percentage change from baseline values ranging from -14.5% to 34.1% across all timepoints. The results for total α-synuclein in plasma should be interpreted with caution as between subject variability was high across all treatments and all timepoints.

Suppression of free α-synuclein in CSF generally appeared to increase in a dose-dependent manner on Days 8 and 15. The greatest suppression of free α-synuclein in CSF was observed at the highest MEDI1341 dose level (4500 mg), with arithmetic mean percentage change from baseline values for CSF free α-synuclein of -47.6% and -53.7% on Days 8 and 15, respectively. There appeared to be a general correlation between increased MEDI1341 serum concentration and greater suppression of free α-synuclein in CSF on Days 8, 15, and 29 following a single IV infusion of 70 to 4500 mg MEDI1341.

Immunogenicity

Borderline ADA positive or positive ADA titer results were generally observed at later post-infusion timepoints (Days 57 and 92) compared to earlier post-infusion timepoints. In the active treatments, the earliest visit where ADA was detected was on Day 57. As the MEDI1341 dose increased, there did not appear to be an increased number of subjects with borderline ADA positive and/or positive ADA titer results, and there was no discernable trend in positive ADA titer values. Borderline ADA positive or positive ADA titer results appeared to have no impact on the PK and PD data.

Safety results:

MEDI1341 was found to have a good safety profile and to be well tolerated following single IV infusions of 70 mg to 4500 mg administered to 36 subjects. Two serious AEs (SAEs) were reported during the study; both SAEs were considered unrelated to MEDI1341. All TEAEs related to MEDI1341 were mild in severity. There were no medically important findings or

trends for changes on any of the other safety endpoints, including safety laboratory tests (hematology, clinical chemistry, and urinalysis), ECGs, vital signs, and physical or neurological examinations. There were no medically important findings or trends for changes with respect to patient-reported visual function or any of the ophthalmic assessments.

Conclusions:

- Single IV doses of MEDI1341 were found to have a good safety profile and to be well tolerated by healthy male and female subjects when administered at dose levels of 70 mg to 4500 mg in this study. The majority of TEAEs reported were mild to moderate in severity and resolved without treatment. There were no severe TEAEs reported during the study.

- There were no treatment or dose-related trends and no clinically significant findings in the clinical laboratory evaluations, vital signs data, 12-lead ECG data, or physical examination findings during the study that would suggest any safety concerns. There were no significant findings in relation to the ophthalmic assessments.

- Following single-dose IV infusions of 70 mg to 4500 mg MEDI1341, attainment of maximum serum concentrations of MEDI1341 was variable, but generally observed at the end of the 1-hour infusion. After the end of IV infusion, serum concentrations of MEDI1341 slowly declined, with geometric mean $t_{1/2\lambda z}$ values ranging from 16.6 to 24.3 days.

- Across the MEDI1341 dose range of 70 mg to 4500 mg, increases in C_{max} were dose proportional. Increases in $AUC_{0-\infty}$ and AUC_{0-t} appeared dose proportional over the dose range of 70 mg to 2400 mg but were supra-proportional with the further increase in dose from 2400 mg to 4500 mg.

- Geometric mean CSF MEDI1341 concentrations were highest on Day 8 compared to Days 15 and 29.

- Across all dose levels and timepoints, geometric mean CSF/serum concentration ratios, expressed as percentages ranged from 0.178% to 0.714%.

- Following single IV infusion of 70 mg to 4500 mg MEDI1341, arithmetic mean percentage change from baseline values for total α-synuclein in plasma generally appeared to increase and then decrease back to baseline over time.

- Suppression of free α-synuclein in CSF generally appeared to increase in a dose-dependent manner on Days 8 and 15. The greatest suppression of free α-synuclein in CSF was observed at the highest MEDI1341 dose level (4500 mg).

- There appeared to be a general correlation between increased MEDI1341 serum concentration and greater suppression of free α-synuclein in CSF on Days 8, 15, and 29 following a single IV infusion of 70 to 4500 mg MEDI1341.

- Borderline ADA positive or positive ADA results were generally observed at later post-infusion timepoints (Days 57 and 92) compared to earlier post-infusion

timepoints. In the active treatments, the earliest visit where ADA was detected was on Day 57. There was no increase in the number of subjects with borderline ADA positive and/or positive ADA results and there was no discernable trend in titer values as the MEDI1341 dose increased. None of the borderline ADA positive or positive ADA results appeared to have impacted PK and PD data. Titer results increased over time, but were not dose-related.