AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3241
Study Code	D0490C00004
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A Phase IIA, Multi-centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Effect of 8 Weeks Treatment with Oral AZD3241 on Microglia Activation, as Measured by Positron Emission Tomography (PET), in Patients with Parkinson's Disease

Study dates:	First subject enrolled: 17 April 2012 Last subject last visit: 9 January 2013
Phase of development:	Therapeutic exploratory (IIA)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Note: This study included patients with Parkinson's disease and will be referred to as subject(s) throughout this document.

Study centres

The study was a multi-centre study conducted at 1 centre in Finland and 4 centres in Sweden.

Publications

None at the time of writing this Clinical Study Report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacodynamic	Evaluate the effect of 8 weeks treatment with AZD3241 on microglia activation as measured by [^{11}C]PBR28 binding to TSPO	Total distribution volume (V_T)
Secondary	Safety	Evaluate safety and tolerability of AZD3241 in subjects with Parkinson's disease	Adverse events, vital signs measurements including body temperature, physical examinations including weight, paper ECGs, Columbia-Suicide Severity Rating Scale assessments and clinical laboratory evaluations
Secondary	Pharmacodynamic	Evaluate the pharmacodynamic effect of AZD3241 by assessment of plasma activity of MPO	Activity per concentration of MPO protein at each time point and corresponding difference, percent of, and percent from baseline activity
Secondary	Pharmacokinetic	Explore the pharmacokinetics of AZD3241 in Parkinson's disease	A separate PK analysis will be performed by AstraZeneca using a population PK model. Maximum observed concentration across visits was summarized to compare AZD3241 exposure to previous studies and to assess exposure in subjects who missed doses of AZD3241.
Exploratory	UPDRS	Explore the effect of 8 weeks treatment with AZD3241 on signs and symptoms as measured by Unified Parkinson's Disease Rating Scale in subjects with Parkinson's disease	Change from baseline of the total score for each part in Week 8 or EoT Visit (last non-missing post-baseline value) derived total score for each Part (I – III)[a]

Objective			Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Pharmacodynamic[b]	Explore the effect of AZD3241 on new potential pharmacodynamic biomarkers	Not applicable
Exploratory	Pharmacodynamic[b]	Explore potential disease biomarkers for Parkinson's disease subject characterisation	Not applicable
Exploratory	Pharmacogenetic[b]	Collect and store DNA to identify/explore genetic variations that may affect the pharmacokinetics, pharmacodynamics, safety and/or tolerability related to AZD3241 treatment or the target (MPO and TSPO). In addition, susceptibility genes and genes related to underlying disease may be explored in DNA samples taken from consenting subjects	Single nucleotide polymorphism for TSPO

[11C]PBR28 N-(2-methoxybenzyl)-*N*-(4-phenoxypyridin-3-yl)acetamide; EoT End of treatment; TSPO Translocator protein; ECG Electrocardiogram; BP Blood pressure; MPO Myeloperoxidase; UPDRS Unified Parkinson's Disease Rating Scale; DNA deoxyribonucleic acid; V_T Total distribution volume
[a]Data from exploratory analysis are not reported in this CSR except for the effect of 8 weeks treatment with AZD3241 on the signs and symptoms as measured by the UPDRS in subjects with Parkinson's disease which was available at the time the CSR was prepared
[b]Results from any genetic research, PK/PD relationship assessment and disease biomarker analysis, if performed, will be reported separately from this CSR.

Study design

This was a randomised, double-blind and placebo-controlled study to evaluate the effect of AZD3241 on microglia activation as measured by [^{11}C]PBR28 binding to TSPO.

A total of 24 subjects were randomised in 3:1 ratio to one of 2 parallel groups (AZD3241 600 mg twice daily [bd] or placebo) and were treated for approximately 8 weeks. AZD3241 dosage was titrated, starting with 50 mg bd on Day 1, 100 mg bd on Day 2, 200 mg bd on Day 3, 300 mg bd on Day 4, 400 mg bd on Day 5 and 600 mg twice daily from Day 6 and throughout the duration of the treatment (Day 56±3 days).

The study consisted of 12 visits, of which some occurred on the same day. The subject visited the study centre at the following time points, Enrolment Visit (14 to 28 days prior to randomisation), Randomisation Visit (Day 1), Week 1, Week 2, Week 4, End of Treatment Visit (Week 8) and at the study follow-up visit (Week 10). The study centre staff contacted subjects by telephone on Day 4 and during weeks with no planned visits (Week 3, 5, 6 and 7) and reminded the subjects about the importance of compliance and asked the subjects the standard open question used to capture adverse events. If a subject reported a worsening in condition to the study centre, an additional centre visit was scheduled.

Subjects were referred to the Positron Emission Tomography (PET) centre, one in each participating country, for the PET measurements and therefore these measurements occurred on days other than the main visits and were regarded as separate visits. The first PET measurement, including [^{18}F]FE-PE2I and [^{11}C]PBR28 (PET-TSPO) measurement, took place prior to the actual randomisation visit and was used both as criteria for inclusion ([^{18}F]FE-PE2I and [^{11}C]PBR28) as well as constituted the baseline assessment for PET ([^{11}C]PBR28). The second and third PET-TSPO measurement ([^{11}C]PBR28) took place 2 to 4 weeks and 7 to 8 weeks after randomisation, respectively.

Magnetic Resonance Imaging (MRI) examination was included as part of the Screening procedure. Subjects were referred to a MRI centre for the same.

At randomisation, the subject was confined to the study centre for at least 6 hours after intake of first dose of the investigational product.

To facilitate participation in the study examinations for the subject, he/she was offered an overnight stay in the hospital, eg, in conjunction with PET measurements. If additional clinical evaluation was deemed necessary by the Investigator, unscheduled visits occurred.

If possible, subjects who discontinued the investigational product were seen by an Investigator and underwent a final PET-TSPO measurement (only applicable if within 2 to 3 days after last dose of the investigational product) and the assessments and procedures scheduled for Visit 12 (Follow-up Visit).

Target subject population and sample size

This study was conducted in male and/or female subjects of non-childbearing potential aged 45 to 75 years (inclusive), with a clinical diagnosis meeting the criteria of "diagnosis of idiopathic Parkinson's disease" according to the modified United Kingdom Parkinson's Disease Society Brain Bank criteria and a Modified Hoehn and Yahr stage of 1 to 2, de novo or on stable treatment.

Investigational product and comparator: dosage, mode of administration and batch numbers

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD3241	ER tablet 25 mg	AstraZeneca	12-001916AZ
AZD3241	ER tablet 100 mg	AstraZeneca	12-001845AZ
Placebo for AZD3241 25 mg	Tablet	AstraZeneca	12-001916AZ
Placebo for AZD3241 100 mg	Tablet	AstraZeneca	12-001845AZ

ER extended release

Duration of treatment

The total duration of the study from the time of enrolment to Follow-up Visit was a maximum of 120 days. The total duration of treatment was approximately 56 days.

Statistical methods

PET

The primary aim of PET data set statistical analysis was to estimate the relative change in [^{11}C]PBR28 binding to TSPO brain regions in relation to baseline. The primary analysis was comparison of V_T at 4 and 8 weeks of treatment versus baseline within treatment arm, and secondary analysis was comparison of V_T changes in AZD3241 group versus placebo group. For each brain region, descriptive statistics (mean and SD) were presented for observed total distribution volume V_T of [^{11}C]PBR28, change from baseline and percent change from baseline at baseline, Week 4 and Week 8 assessments. In addition, effect size for each treatment was also presented as absolute value of mean change from baseline divided by SD.

The primary analysis was carried out separately for each assessment visit using an analysis of variance (ANOVA) model on change from baseline in V_T of [^{11}C]PBR28 with a fixed for treatment for each brain region. From this model, the point estimate for change from baseline along the corresponding 95% confidence interval (CI) and the p-value for testing change from baseline equal to zero were provided for each treatment group. The least squares (LS) mean estimate for the difference between AZD3241 and placebo along with corresponding 95% CI and the p-value for testing the difference equal to zero were provided. In addition, the effect size computed as absolute value of the difference in AZD3241 and placebo LS means divided by square root of mean squared error (MSE) from the ANOVA model was also provided.

As an exploratory analysis, total distribution volume V_T of [^{11}C]PBR28 was also analysed using a repeated measures analysis of covariance (ANCOVA) model with terms for treatment, visit, treatment by visit interaction, genotype and baseline as a covariate under compound symmetry (CS) covariance structure for 5 selected brain regions (striatum, caudate, putamen, substantia nigra and gray matter). For this model, LS means along with 95% CIs were estimated for each treatment at each assessment visit and overall for each brain region. Least squares means along with the corresponding 95% CIs for the treatment difference (AZD3241 minus placebo) and the p-value for treatment comparison were also estimated at each assessment visit and overall for each brain region.

Safety

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities. Adverse events were summarised for each treatment group by system organ class and preferred term. Medications were classified according to the AstraZeneca Drug Dictionary. Tabulations and listings of data for vital signs, weight, clinical laboratory tests, electrocardiograms, and physical examinations were presented. For clinical laboratory tests, vital signs and electrocardiograms, listings of values for each subject were presented with abnormal or out-of-range values flagged. The number and percent of subjects who met any of

the potentially clinically significant criteria for vital signs at any post-dose assessment were tabulated by treatment. Potentially clinically important vital signs for individual subjects were listed.

Exploratory

Unified Parkinson's Disease Rating Scale endpoints were analysed for exploratory purposes. For each UPDRS endpoint, the observed and change from baseline in Week 8 or EoT Visit values were summarised descriptively (n, mean, SD, median, minimum and maximum) by treatment based on the available data, ie, subjects missing either baseline or post-baseline value were excluded from the analysis. For each total score in Part I, II and III, change from baseline in Week 8 or EoT Visit score was analysed using an ANOVA model with fixed effect for treatment and respective baseline score as a covariate. Least squares means and corresponding 95% CIs were provided for each treatment group and for the difference (AZD3241 minus placebo) between the 2 treatment groups. The p-value for treatment comparison was also provided. The Part IV data were provided in the listings

Pharmacodynamic

Plasma MPO activity was reported as activity per concentration of MPO protein at each time point. All summaries and analyses were conducted using the average of the 3 MPO activity values derived at each subsequent on-treatment visit and the single assessment at follow-up. Plasma MPO activity and change from baseline results were summarised for each treatment. In addition, descriptive statistics for percent reported baseline MPO activity (MPO% calculated as 100*[post-baseline MPO value divided by baseline MPO value]) and percent change from baseline (calculated as [post-baseline MPO% minus 100%]) were presented.

An exploratory repeated measures ANCOVA model was fitted to the change from baseline in activity-to-protein ratio with terms for treatment, visit, treatment by visit interaction and respective baseline score as a covariate under UN covariance structure. In addition to analysing change from baseline, the percentage change from baseline was also analysed using a similar statistical model. Baseline was the average of all measurements prior to first dose of IP. Least squares means along with 95% CIs were estimated for each treatment at each assessment visit and overall. Least squares means along with the corresponding 95% CIs for the treatment difference (AZD3241 minus placebo) and the p-value for treatment comparison were also estimated at each assessment visit and overall.

Pharmacokinetic

The PK sample collection schedule was designed to support a PK analysis using a population PK model. This analysis will be performed by AstraZeneca and presented in a separate report. The maximum observed concentration and the time of this observation were summarised by visit for this report. The geometric mean of the maximum observed concentration was also presented graphically by visit.

Subject population

In total, 24 male and female subjects of non-childbearing potential with Parkinson's disease were enrolled and randomised to either AZD3241 or placebo at 5 study centres. Of these 22 subjects completed treatment with the IP (either AZD3241 or placebo). For 2 subjects in the AZD3241 group (E0005004 and E0005006), Visit 11 (EoT Visit) was incorrectly scheduled earlier and did not follow the protocol defined timelines (at least Day 53). EoT Visit for subject E0005004 was on Day 52 and for subject E0005006 it was on Day 51.

Summary of PET results

The primary variable used to examine drug effect on microglia was total distribution volume, V_T of [^{11}C]PBR28 binding to TSPO in the brain.

The primary statistical analysis (comparison to baseline within treatment group) showed that AZD3241 at doses of 600 mg bd significantly reduced V_T compared to baseline in the nigrostriatal regions, thalamus, cerebellum, limbic and temporal cortex at both Week 4 and Week 8 assessments ($p<0.05$). The size of mean reduction in V_T across these brain regions was in the range of 14 to 17% and 13 to 16% at Week 4 and Week 8, respectively. The effect size was in the range of 0.5 to 0.6. In the placebo group, there was no significant change in V_T compared to baseline. The size of mean changes in V_T across the brain regions was in the range of -4 to 1 % and 3 to 6 % at Week 4 and Week 8 assessments, respectively.

Secondary statistical analysis (comparison between treatment groups) showed no statistically significant difference in V_T changes between AZD3241 and placebo at either assessment time. The reason for this could be that the sample size determination was done assuming a 60% reduction but reductions observed in this study were much smaller than 60%. Thus, the sample size for the placebo group may be underpowered.

The study results show that AZD3241 administered to subjects with Parkinson's disease at the dose of 600 mg bd for 8 weeks significantly reduces [^{11}C]PBR28 binding to TSPO in the brain as compared to baseline.

Summary of pharmacokinetic results

In this study in subjects with Parkinson's disease, the median time of the maximum observed concentration ranged from approximately 2 to 4 hours across the study visits. This was similar to the median time to maximum concentration (t_{max}) observed in a multiple dose study conducted in healthy volunteers (Study D0490C00002). In healthy volunteers following 10 days of dosing, median t_{max} ranged from approximately 2.5 to 4 hours.

For PK analysis, 3 blood samples were taken during each of the visits (therefore, a total of 12 samples). One was taken at arrival at the study centre, one in the middle and one was taken at the end of the visit. At one of the visits other than the Randomisation Visit and preferably at Visit 9 (Week 4), the first sample was taken pre-dose. The exact time of dose prior to PK sampling (at home [evening or morning] or in the centre) and PK sampling was recorded. In this study, the geometric mean of the maximum observed concentration following a 600 mg

dose of AZD3241 bd for 4 to 8 weeks was approximately 3.5 µmol/L and 4 µmol/L, respectively. By comparison, in Study D0490C00002, the geometric mean C_{max} value for the 300 mg and 600 mg dose of AZD3241 bd for 10 days was approximately 2 µmol/L and 5.5 µmol/L, respectively. In this study, considering the limited sampling, AZD3241 exposure in subjects with Parkinson's disease was comparable to exposure observed in healthy volunteers.

Summary of pharmacodynamic results

Least squares (LS) mean MPO activity (U/ng) values in the AZD3241 group following multiple dosing were approximately 70% to 75% of baseline. By comparison, LS mean MPO activity (U/ng) values in placebo treated subjects remained at near basal levels throughout the study. Least squares mean MPO activity (U/ng) values in the AZD3241 group was approximately 25% to 30% lower than values in the placebo group. The difference between treatments was statistically significant at each time point ($p<0.05$).

Summary of UPDRS results

There were no statistically significant differences in the change from baseline between the placebo group and the AZD3241 group in the UPDRS Part I, Part II and Part III scores, nor were there clinically meaningful numerical trends. The UPDRS Motor Score (UPDRS Part III) showed a decrease over time in both the both AZD3241 and placebo groups, with no apparently meaningful difference between groups (mean [SD] Motor Score decreasing from 18.3 [6.2] at baseline to 14.7 [5.3] at Week 8 in the AZD3241 group, and from 16.2 [6.4] at baseline to 13.8 [6.5] at Week 8 in the placebo group).

Summary of safety results

- AZD3241 was found to be well-tolerated and safe with no deaths, serious adverse events, or discontinuation due to AEs reported in the study
- A total of 13 (72.2%) subjects in the AZD3241 group and 3 (50.0%) subjects in the placebo group reported at least 1 AE
- Overall, the most frequently reported AEs were fatigue, nasopharyngitis, headache (overall: 4 [16.7%] subjects each) and insomnia (overall: 3 [12.5%] subjects)
- Headache, nausea and insomnia were reported only by subjects in the AZD3241 group. None of the subjects in the placebo group reported these AEs
- Most of the AEs reported were considered by the Investigator to be of moderate or mild intensity except for one subject (E0004004) in the placebo group who reported an AE of fatigue which was of severe intensity
- A total of 9 (37.5%) subjects had AEs which were considered to be causally related to the IP by the Investigator. Of these, 6 subjects (33.3%) belonged to the AZD3241 group and 3 subjects (50%) to the placebo group

- Time activity curves for plasma uric acid concentrations during the study in the AZD3241 group showed a greater decrease compared to the placebo group during the period of IP administration. The mean plasma uric acid concentrations returned to baseline values by the time of the Follow-up Visit (Day 70) in both the groups. An effect of AZD3241 on uric acid levels cannot be excluded

- On Day 56 (EoT Visit), an increase from baseline in mean thyroid stimulating hormone (TSH) level was observed in both the AZD3241 group and the placebo group; however the increase of the same was higher in the AZD3241 group compared to the placebo group. An effect of AZD3241 on thyroid function cannot be excluded

- Overall the data showed no clinically important effects of AZD 3241 on vital signs during this study

- No subject showed any clinically important change in the 12 lead ECG during this study as assessed by the Investigator.

Overall Summary

- Administration of AZD3241 to subjects with Parkinson's disease at the dose of 600 mg bd for 8 weeks reduces [^{11}C]PBR28 binding to TSPO compared to baseline across all brain regions. Statistically significant reduction was reached in the nigrostriatal regions, thalamus, cerebellum, limbic and temporal cortex, at both Week 4 and Week 8 assessments

- A statistically significant reduction in MPO activity was observed in subjects with Parkinson's disease following 600 mg bd AZD3241 compared to placebo

- AZD3241 was found to be safe and well tolerated in subjects with Parkinson's disease

- The present study showed an effect of AZD3241 on TSPO, suggesting that the potential mechanism of action of the myeloperoxidase inhibitor AZD3241 involves a reduction of brain microglia activity.