AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Lesogaberan (AZD3355)
Study Code	D9120C00022
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A Phase I, Open label, Non-randomized, Parallel Group, Pharmacokinetic Study in Subjects with Normal Renal Function, Moderate or Severe Renal Impairment Receiving a Single Dose of Oral 130 (65+65) mg Lesogaberan (AZD3355)

Study dates: First subject enrolled: 6 May 2009
Last subject last visit: 16 February 2010

Phase of development: Clinical pharmacology (I)

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

Study centres

The study was conducted by Quintiles AB at 3 centres in Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective of this study was to assess the pharmacokinetics following a single dose of 130 (65+65) mg lesogaberan (AZD3355) orally in patients with moderate or severe renal impairment[b] compared to healthy volunteers with normal renal function.	Pharmacokinetic parameters for lesogaberan: AUC_{0-t}, AUC, C_{max}, CL/F, $t_{1/2}$, t_{max}, A_e and CL_R (definitions see below)[a] were calculated based on plasma concentrations from pre-dose to 72 h post dose and urine concentrations from 0 to 48 h post dose	Pharmacokinetic
Secondary	**Secondary**	
The secondary objective of this study was to assess the safety and tolerability following a single dose of 130 (65+65) mg lesogaberan (AZD3355) orally in patients with moderate or severe renal impairment[b] compared to healthy volunteers with normal renal function.	Adverse events, laboratory safety assessments , physical examination, electrocardiogram and vital signs (blood pressure and pulse)	Safety
Exploratory	**Exploratory**	
The exploratory objective was to assess the pharmacokinetics of the lesogaberan (AZD3355) metabolite(s) following a single dose of lesogaberan in patients with moderate or severe renal impairment[b] compared to healthy volunteers with normal renal function.	Plasma concentrations of metabolites measured from pre-dose to 72 h post dose Urine concentrations of metabolites from 0 to 48 h post dose Pharmacokinetic parameters to be decided[c]	Pharmacokinetic

[a] Definitions of pharmacokinetic parameters:

- AUC_{0-t} the area under the plasma concentration *vs* time curve, between time zero and the last quantifiable plasma concentration (C_{last}) calculated by the linear/log trapezoidal method
- AUC the total area under the plasma concentration *vs* time curve, calculated by $AUC_{0-t} + AUC_{t-\infty}$, where $AUC_{t-\infty}$ is the residual area under the plasma concentration *vs* time curve, extrapolated by C_{last}/λ_z (λ_z is the elimination rate constant estimated from individual linear regression of the terminal part of the log concentration *vs* time curve)
- C_{max} the observed maximum plasma concentration
- CL/F oral plasma clearance, calculated by Dose/AUC
- $t_{1/2}$ terminal half-life, calculated by $\ln 2/\lambda_z$.
- t_{max} time to reach C_{max}
- A_e the amount of drug excreted unchanged into urine
- CL_R renal clearance, calculated by A_e (0-48 hours) /AUC (0-48 hours)

[b] Renal function was estimated using the Modification of Diet in Renal Disease (MDRD) Study Equation, as well as using the Cockcroft-Gault (C-G) formula planned in the CSP. The MDRD results were used to group subjects into renal function groups for inclusion in the study. It was decided after database lock to report the results from the C-G as well as the MDRD equation for each subject and to include further PK and safety analyses based on C-G assessment. The main analysis was however based on the MDRD grouping, since the number of subjects per renal group and age, weight and sex matching of the groups were ensured for the MDRD assessment.

The MDRD formula used was:

For males = $175 \times (\text{Serum-Creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203}$

For females = MDRD for males x 0.742

For African American = MDRD for males (or females) x 1.212

[c] The results from exploratory analysis of metabolites will be reported separately from the clinical study report.

Study design

This was a Phase I, open label, non-randomized, parallel group, pharmacokinetic (PK) study in healthy volunteers with normal renal function, and patients with moderate and severe renal impairment. Each subject received a single dose of oral lesogaberan modified release 1 h, capsule, 130 mg (given as two 65 mg capsules). This formulation releases about 80% of the dose in 1 hour.

Target subject population and sample size

It was planned to include approximately 8 subjects from each of the following groups based on MDRD assessments of renal function:

- Healthy volunteers with normal renal function (CL_{cr} >80 mL/min)
- Patients with moderate renal impairment (CL_{cr} 30 to 49 mL/min)
- Patients with severe renal impairment (CL_{cr} <30 mL/min)

The actual number of subjects analysed based on MDRD was: 8 subjects with normal renal function, 7 subjects with moderate renal impairment, and 8 subjects with severe renal impairment.

The actual number of subjects analysed based on C-G assessment of renal function was: 8 subjects with normal renal function, 6 subjects with mild renal impairment, 6 subjects with moderate renal impairment and 3 subjects with severe renal impairment.

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

Lesogaberan (AZD3355) modified release 1 h, capsule, 130 mg (given as two 65 mg capsules). Batch no. H2021-01-01-01

Duration of treatment

Single dose

Statistical methods

The differences in means between moderate impairment - normal and severe impairment - normal renal function groups with corresponding 2-sided 90% confidence intervals (CIs) were estimated for log(AUC) and log(C_{max}) of lesogaberan using an analysis of variance. The differences were subsequently back-transformed to the original scale to be expressed as ratios of renal function groups. This analysis was performed on renal function groups based on MDRD assessment. Additionally, it was decided after database lock not only to report the

results from both the Cockcroft-Gault and MDRD equation for each subject, but also to include this and further PK and safety analyses based on C-G assessment. Since the grouping based on C-G also included a mild impairment group, a statistical analysis was also performed comparing C-G mild impairment to C-G normal renal function.

Subject population

In total, 23 subjects were included at 3 centres. All subjects completed the study.

The number of subjects and the number of males and females were comparable between the MDRD renal function groups. At least 2 males and 2 females were included in each group and the ranges of age and weight were matched between the groups as defined in the clinical study protocol. The mean ages were higher in the moderate and severe impairment MDRD groups than in the normal group (51.1, 55.8 and 33.6 years respectively) and mean weight and body mass index were slightly higher in the same groups.

When renal function groups were based on C-G assessment, the number of subjects differed between the groups: ranging from 3 subjects in the severe renal impairment group to 8 subjects with normal renal function.

Summary of pharmacokinetic results

Based on MDRD groups (3 groups; moderate and severe renal impairment and normal renal function)

There was no statistically significant difference in plasma exposure (AUC and C_{max}) of lesogaberan between the moderate or severe renal impairment groups and the normal renal function group. The estimated geometric mean ratios for renal impairment *vs* normal renal function (90% CI) of AUC and C_{max} were 1.20 (0.92 to 1.55) and 1.22 (0.94 to 1.58), respectively, for moderate renal impairment and 1.18 (0.92 to 1.52) and 1.13 (0.88 to 1.45), respectively, for severe renal impairment.

Time to C_{max} (median; range) was the same for the groups with moderate or severe renal impairment (2.00; 1.50 to 2.50 h) and similar to the group with normal renal function (2.02; 1.52 to 2.50 h).

Oral plasma clearance (geometric mean; range) of lesogaberan in the moderate (25.0; 15.1 to 37.9 L/h) and severe (25.3; 18.4 to 40.1 L/h) renal impairment groups were comparable to that in the normal renal function group (29.9; 19.7 to 42.4 L/h). Terminal plasma half-life (geometric mean; range) of lesogaberan in the moderate (13.7; 11.0 to 17.2 h) and severe (13.7; 10.6 to 18.6 h) renal impairment groups were slightly longer than in the normal renal function group (10.7; 8.09 to 13.0 h).

Renal clearance of lesogaberan decreased with decreased renal function, from a geometric mean (range) of 5.27 (3.95 to 7.31) L/h in the normal renal function group to 0.913 (0.360 to 1.43) L/h in the severe renal impairment group. There was however no clear relationship between the extent of plasma exposure (AUC) and renal clearance of lesogaberan.

Based on C-G groups (4 groups; mild, moderate and severe renal impairment and normal renal function)

The PK results based on renal function grouping by C-G, which included a mild renal impairment group in addition to the moderate and severe (only 3 subjects) renal impairment groups, were in agreement with the PK results based on renal function grouping by MDRD.

Summary of safety results

Few adverse events (AEs) (16 events in 10 subjects) occurred in the study and all were of mild or moderate intensity. There were no serious adverse events (SAEs), no other significant AEs and no discontinuations due to AEs. AEs were most commonly reported in 'nervous system disorders' (4 subjects), 'musculoskeletal and connective tissue disorders' (3 subjects) and 'gastrointestinal disorders' (3 subjects).

There were no clinically significant safety findings based on laboratory safety assessments, vital signs, electrocardiograms or physical examination.