AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | Cediranib (AZD2171) |
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# A Phase I, Open Label, Multi-Centre Study to Assess the Safety and Tolerability of Cediranib (RECENTIN™, AZD2171) in Combination with Lomustine Chemotherapy for Patients with Primary Recurrent Malignant Brain Tumours for whom Lomustine would be a Standard Therapy

**Study dates:** First patient enrolled: 14 September 2007
Last patient completed: 10 December 2008

**Phase of development:** Clinical pharmacology (I)

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

## Study centre(s)

This study was conducted at 2 centres in the United States of America and 1 centre in the United Kingdom.

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

**Table S1 Primary and secondary objectives and outcome variables**

| Objective | Outcome variables |
|---|---|
| **Primary** | |
| To assess the safety and tolerability of cediranib in combination with oral lomustine and to confirm a dose for further studies with this combination | Adverse events, vital signs including blood pressure, physical examination, electrocardiogram parameters, clinical chemistry, haematology and urinalysis |
| **Secondary** | |
| To compare the pharmacokinetics of cediranib alone versus when in combination with lomustine as measured by $C_{ss,min}$, $C_{ss,2h}$ and $C_{ss,4h}$. | $C_{ss,min}$, $C_{ss,2h}$ and $C_{ss,4h}$ on Day 22 (cediranib alone) and Day 43 (cediranib plus lomustine). |

$C_{ss,min}$: Minimum steady state plasma concentration; $C_{ss,2h}$: Steady state plasma concentration after 2 hours post dosing; $C_{ss,4h}$: Steady state plasma concentration after 4 hours post dosing.

## Study design

This was a Phase I, open label, multi-centre study designed to assess the safety and tolerability of cediranib in combination with lomustine in patients with primary recurrent malignant brain tumours for whom lomustine would be a standard therapy. In the first cohort, patients received cediranib 30 mg + lomustine 130 mg/m$^2$. Safety data were assessed from the first evaluable 6 patients in a cohort in order to decide if that dose was tolerable. Based on the number of patients with dose limiting toxicities (DLTs), the dose was either considered to be: tolerated (which identified the dose as tolerable); requiring further evaluation (which required further patients to be enrolled at the same dose); or insufficiently well tolerated (in which case lower doses of cediranib were to be tested).

## Target patient population and sample size

Males or non-pregnant females, aged at least 18 years, with a histologically or cytologically confirmed primary recurrent malignant brain tumour for whom lomustine would be standard therapy; a Karnofsky performance status at least 60; life expectancy of at least 12 weeks; no more than 2 previous systemic chemotherapy regimens; no steroid treatment or a stable dose of steroid treatment for at least 5 days before enrolment; at least 3 months from completion of cranial radiation therapy and at least 4 weeks from completion of temozolomide or a non-nitrosourea chemotherapy to starting study treatment.

A sample size of at least 6 evaluable patients at each dose level (cohort), and no more than 20 patients in total, was estimated to obtain adequate safety, tolerability and pharmacokinetic (PK) data, whilst exposing as few patients as possible to the study treatment and procedures.

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

The intended starting dose of cediranib (AZD2171) was 30 mg administered orally, once daily. Lower doses could have been administered to later cohorts, and dose reductions were permitted in individual patients to cediranib 20 mg or 15 mg. Cediranib was administered in the morning and patients were to take their medication at least an hour prior to consumption of a meal or more than 2 hours after a meal had been ingested. Cediranib was supplied as 30 mg, 20 mg or 15 mg tablets; 5 batches of cediranib were used during the study and individual Analytical Development Macclesfield numbers are provided in the main study report.

Lomustine was administered as a single oral dose every 6 weeks for a maximum of 6 cycles. The starting dose of lomustine was 130 mg/m$^2$ in the first cohort, which was permitted to be lowered to 110 mg/m$^2$ following a protocol amendment. At Week 6, lomustine was to be administered at least 60 minutes prior to dosing with cediranib. This was to allow for assessment of the potential effect of lomustine on the PK of cediranib. For all other time points, lomustine could be taken before or after cediranib administration.

Cediranib was manufactured by AstraZeneca and lomustine was supplied locally.

**Duration of treatment**

Up to 6 cycles of lomustine could be administered; each cycle had a duration of 6 weeks. Cediranib treatment could be continued for as long as, in the investigators opinion, the patient was receiving clinical benefit, provided that they did not meet at least 1 of the discontinuation criteria and were free from intolerable toxicity.

**Statistical methods**

Analyses were descriptive only. Tolerability of combination treatment from a cohort was evaluated when all patients had completed the first cycle (6 weeks of combination treatment), or had DLT before 6 weeks. PK parameters were assessed for each patient by visual inspection of their plasma-time profile obtained following repeat dosing. The PK of cediranib alone was based on Day 22 plasma concentration-time data, and the PK of cediranib in combination with lomustine was based on Day 43 data. To assess the effect of lomustine on exposure of cediranib (secondary objective), the log-transformed PK parameters were to be analysed by analysis of variance, fitting patient and PK days (Day 43 or Day 22) as factors, to provide point estimates and corresponding 90% confidence intervals for the ratio of Day 43 versus Day 22. This analysis was not performed due to the limited PK data available.

## Subject population

Eighteen patients were enrolled in this study and 12 patients received study treatment. The first cohort of 6 patients received the starting combination dose of cediranib 30 mg + lomustine 130 mg/m$^2$. Two patients had DLTs (1 patient had common terminology criteria for adverse events [CTCAE] Grade 3 fatigue and CTCAE Grade 3 dehydration and 1 patient had CTCAE Grade 4 hypertension), In addition, 1 patient had maximum CTCAE Grade 3 and 4 patients had maximum CTCAE Grade 4 thrombocytopenia and/or neutropenia. Based on these data, the cediranib 30 mg + lomustine 130 mg/m$^2$ cohort was considered to be insufficiently well tolerated and a second cohort with a lower dose of lomustine was planned. A second cohort of 6 patients received cediranib 30 mg + lomustine 110 mg/m$^2$; only 1 patient in this cohort had a DLT (CTCAE Grade 3 fatigue/hypothyroidism). Therefore, the cediranib 30 mg + lomustine 110 mg/m$^2$ combination dose appeared to be tolerable and no further dose cohorts were recruited.

All 12 patients who received treatment discontinued the study; 4 of whom, were discontinued from the study due to an adverse event (AE) (2 patients in each cohort).

The demographic and baseline characteristics were appropriate for the recurrent glioblastoma population studied. The mean age of the 12 patients studied was 49.8 years (range: 31 years to 74 years). All 12 patients who received treatment in the study were Caucasian. All but 1 of the 12 patients had a Karnofsky performance status of at least 80; the remaining patient in the cediranib 30 mg + 110 mg/m$^2$ cohort had a performance status of 60.

## Summary of pharmacokinetic results (secondary objective)

There were insufficient PK data to perform the planned analysis.

## Summary of safety results (primary objective)

The primary objective of the study was to assess the safety and tolerability of cediranib in combination with oral lomustine and to confirm a dose for further studies with this combination.

Overall, 8 of the 12 patients received a mean daily dose of cediranib of at least 25 mg (range for the 12 patients: 17.1 mg to 30.0 mg). The duration of exposure to cediranib was shorter at 62.0 days (actual exposure) in the cediranib 30 mg + lomustine 130 mg/m$^2$ cohort compared with 152.5 days (actual exposure) in the cediranib 30 mg + lomustine 110 mg/m$^2$ cohort. Similarly, the duration of exposure to lomustine was shorter at 1.8 cycles (actual exposure) in the cediranib 30 mg + lomustine 130 mg/m$^2$ cohort compared with 3.2 cycles (actual exposure) in the cediranib 30 mg + lomustine 110 mg/m$^2$ cohort. Dose reductions and pauses for cediranib were required in both cohorts. In the cediranib 30 mg + lomustine 130 mg/m$^2$ cohort, 4 patients required a pause for cediranib, 1 patient required a pause and a reduction for cediranib and 1 patient did not require any change to the cediranib dose. Three patients in this cohort did not receive more than 1 cycle of lomustine treatment, 1 patient required a pause and reduction to lomustine dosing, 1 patient required a reduction the lomustine dose and 1 patient did not require any change to the lomustine dose. In the cediranib 30 mg + lomustine

110 mg/m$^2$ cohort, 2 patients required a pause for cediranib, 3 patients required a pause and a reduction for cediranib and 1 patient did not require any change to the cediranib dose. Five patients in this cohort required a pause and reduction to lomustine dosing and 1 patient did not require any change to the lomustine dose.

All 12 patients had at least 1 AE and 11 of the 12 patients had a CTCAE Grade 3 or higher AE during the study. Bone marrow suppression such as leukopenia, neutropenia, thrombocytopenia and lymphopenia were observed, which were considered to be mainly due to lomustine treatment. Overall, the most commonly reported AEs were thrombocytopenia, diarrhoea, fatigue, leukopenia and neutropenia. The most commonly reported AEs with a maximum CTCAE Grade of 3 or higher were neutropenia, thrombocytopenia, fatigue and leukopenia. Seven of the 12 patients had at least 1 serious adverse event (SAE) during the study (4 patients and 3 patients in the cediranib 30 mg + lomustine 130 mg/m$^2$ and the cediranib 30 mg + lomustine 110 mg/m$^2$ cohorts, respectively); only thrombocytopenia and neutropenia were reported as SAEs by 2 or more patients. Six of the 12 patients had at least 1 AE that led to discontinuation of study treatment (3 patients in each cohort). Of these 6 patients, 4 patients were reported as having discontinued from the study due to these AEs but for the other 2 patients the main reason for discontinuation from the study was recorded as "condition under investigation worsened". Four of the 12 patients (2 patients in each cohort) died during the course of this study. The primary cause of death for all 4 patients was disease progression, which was expected given the prognosis of the study population. No AEs with an outcome of death were reported during this study.