AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00020
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A Phase I, Open Label, Non-randomised Study to Assess the Effect of Ketoconazole on the Pharmacokinetics of Multiple Oral Doses of Cediranib (AZD2171, RECENTIN™), in Patients with Advanced Solid Tumours

Study dates: First patient enrolled: 25 August 2008
Last patient enrolled: 24 March 2009

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 was a clinical pharmacology (I) study conducted at 3 centres in Canada and 2 centres in Denmark.

Publications

None at the time of writing this report.

Objectives

Primary objectives

The primary objective of the study was to assess the effect of ketoconazole on the steady-state pharmacokinetics of cediranib in patients with advanced solid tumours.

Secondary objectives

The secondary objectives of the study were to assess the safety and tolerability of cediranib in the presence of ketoconazole.

Exploratory objectives

The exploratory objectives of the study were:

- Assessment of dose delays and/or dose reductions of cediranib during concomitant administration of ketoconazole
- To determine the minimum plasma (trough) drug concentration (C_{min}) of ketoconazole, after repetitive dosing but before steady state, when co-administered with cediranib.

Study design

Phase I, non-randomised, fixed-sequence, open-label study to assess the effect of ketoconazole on the pharmacokinetics of cediranib in patients with advanced solid tumours.

Patients were to receive a once-daily dose of cediranib 20 mg alone for 7 consecutive days. This was followed by continued once-daily cediranib 20 mg dosing and in addition a once-daily dose of ketoconazole 400 mg for 3 days. Full PK sampling profiles were planned for Day 7 and Day 10. Patients were then eligible to receive cediranib monotherapy for the remainder of their duration in the study with the option to dose escalate from Day 24 onwards following consultation and recommendation from their study doctor. Treatment with cediranib was continued for an indefinite period, until a criterion for discontinuation was met (ie, disease progression, toxicity, death, consent withdrawal or another discontinuation criterion).

To be evaluable for the statistical analysis, patients needed to receive at least 7 consecutive days dosing with cediranib 20 mg followed by 3 consecutive days of dosing with ketoconazole 400 mg plus cediranib 20 mg (ie, have no pauses or reductions) and have

evaluable paired pharmacokinetic data for the AUC_{ss} and/or $C_{ss,max}$ parameters (Day 7 and Day 10 parameters).

A formal interim analysis was incorporated into the study so that if it was possible to either declare no effect of ketoconazole on cediranib pharmacokinetics or to establish a low probability of concluding no effect even if the study was to continue to the final analysis, then recruitment into the study could be stopped at this stage.

A decision to stop the study based on interim results would result in all patients already recruited being eligible to continue dosing with cediranib (if in the opinion of the investigator they were receiving benefit) but no further patients would be recruited.

Target patient population and sample size

Males and female patients aged 18 years or older with histological or cytological confirmation of advanced solid tumour (with the exception of prostate cancer) refractory to standard therapies or for which no standard therapy exists. WHO performance status 0–2; life expectancy ≥8 weeks.

Planned enrolment was for up to approximately 60 patients to be dosed to provide approximately 46 patients with evaluable paired PK data for the primary analysis. A formal interim analysis was scheduled for when approximately 30 patients were dosed to provide evaluable paired data for approximately 23 patients. Recruitment into the study was to continue during the interim analysis but could be stopped following review of the interim analysis results.

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

Cediranib doses were administered as 15 mg, 20 mg or 30 mg tablets and were to be taken orally at least 1h before or at least 2 h after a meal. Analytical Development Macclesfield (ADM) numbers are provided in the main study report. Ketoconazole was administered as a standard regimen (2 x 200 mg tablets, once daily).

Duration of treatment

Cediranib 20 mg was administered once daily from Days 1 to 23. Cediranib was dosed for a minimum of 7 consecutive days prior to administration of ketoconazole to achieve steady-state. Patients received ketoconazole 400 mg once daily for 3 days from Days 8 to 10.

Any patient who was unable to tolerate cediranib 20 mg alone for 7 consecutive days (ie, required dose reductions or dose pauses) was not to receive concomitant ketoconazole and the Day 10 PK sampling was not completed. These patients had the option to dose-reduce to cediranib 15 mg with the option of remaining on this dose if the investigator was of the opinion that the patient may derive benefit from therapy.

From Day 24, if cediranib 20 mg had been well tolerated and the treating investigator felt a higher dose level would be beneficial, patients had the option to remain on cediranib 20 mg or

dose escalate to cediranib 30 mg. If cediranib 30 mg was tolerated for at least 14 days, patients became eligible to receive cediranib 45 mg per day, at the discretion of the treating investigator. There was a minimum window of 14 days and a maximum window of 28 days between each dose escalation.

Criteria for evaluation - pharmacokinetics (main variables)

The primary PK outcome variables were AUC_{ss} and $C_{ss,max}$ of cediranib in the presence and absence of ketoconazole. The secondary PK outcome variables were $C_{ss,min}$ and t_{max} of cediranib in the presence and absence of ketoconazole.

Criteria for evaluation - safety (main variables)

The main variables used to evaluate safety were AEs, clinical chemistry, haematology, urinalysis, LFTs, vital signs including BP, physical examination and ECG.

Statistical methods

Primary endpoint

Statistical analyses of each of the primary variables AUC_{ss} and $C_{ss,max}$ consisted of paired t-tests for each PK parameter of cediranib in combination with ketoconazole against cediranib alone (ie, Day 10 vs. Day 7 AUC_{ss} and Day 10 vs. Day 7 $C_{ss,max}$). Based on previous experience, these data were logarithmically transformed prior to analysis. The results are reported as 94% CIs about the ratio of geometric means of cediranib in combination with ketoconazole to cediranib alone for each parameter separately. Values of the ratio >1 indicate increases in exposure of cediranib due to concomitant administration with ketoconazole. Given the implementation of an interim analysis, 94% CIs were used at both the interim and final analysis to ensure preservation of the overall type I error in the trial (using a Pocock alpha spending function). A maximum of 2 formal analyses of the PK data were to be performed. The first formal statistical analysis was planned with paired PK data from approximately 23 patients for each of AUC_{ss} and $C_{ss,max}$. If the 94% CI for the ratio of geometric means fell within the 0.8 to 1.25 equivalence boundaries for each of the PK parameters AUC_{ss} and $C_{ss,max}$, recruitment to the study was to stopped. If the study was to continue following the interim analysis, the final analysis was to be implemented when approximately 46 patients (including the original 23 patients) had provided evaluable paired PK data.

Subject population

In total, 51 patients were enrolled (ie, provided informed consent) of which 46 entered the study. The interim analysis was performed after 30 patients were dosed which resulted in 25 patients being evaluable for the $C_{ss,max}$ statistical analysis, and 23 for the AUC_{ss} statistical analysis. For the final analysis a total of 46 patients received study treatment of which 38 were evaluable for the $C_{ss,max}$ statistical analysis, and 36 for the AUC_{ss} statistical analysis. The final analysis was performed once all 46 patients had completed Day 24 of the study. The data cut-off for this CSR was 22nd April 2009 at which time 14 (30.4%) patients had

withdrawn due to adverse events (AE), 14 (30.4%) patients had withdrawn due to the condition under investigation worsening and 18 (39.1%) patients were ongoing.

Demographic baseline characteristics were representative of the intended population. The majority of patients were white (91.3%) and female (73.9%). Adenocarcinoma (58.7%) was the most common histology type and the most common tumour was colorectal (43.5%). The WHO performance status for the total population was: 0 (41.3%), 1 (54.3%) and 2 (4.3%).

Summary of pharmacokinetic results

Interim pharmacokinetic analyses

There were 25 patients with evaluable paired $C_{ss,max}$ data and 23 patients with evaluable paired AUC_{ss} data included in the interim statistical analysis. Comparison of the Day 7 and Day 10 data within each individual indicated that for the majority of patients the $C_{ss,max}$ and AUC_{ss} were higher when cediranib was administered in the presence of ketoconazole, compared to when cediranib was administered alone.

The gmean ratio for AUC_{ss} and $C_{ss,max}$ were above 1 and the 94% CIs were not within the pre-specified equivalence boundaries. In particular, the lower limit of the 94% CI was clearly above 1 indicating a statistically significant effect in the presence of ketoconazole.

Given the results observed at the interim analysis, there was a low probability of declaring that co-administration of ketoconazole would have no effect on the PK parameters of cediranib at final analysis if the study continued to recruit the planned 46 evaluable patients. For the AUC parameter there was ~5% chance that the 94% CI would be within the 0.8–1.25 boundaries at the final analysis and for the C_{max} parameter there was less than a 1% chance. Therefore, in line with the protocol, recruitment was stopped at this stage. Patients who were already receiving study medication once the decision to stop the study had been made continued to receive cediranib as per protocol. As patients had been recruited whilst the interim data was being analysed, there was a need to perform an updated PK analysis of all patients recruited in the study.

Final pharmacokinetic analyses

The final PK analysis comprised 38 patients with evaluable paired $C_{ss,max}$ data and 36 patients with evaluable paired AUC_{ss} data. The results of the statistical analysis were consistent with the results from the interim analysis. The gmean AUC_{ss} and $C_{ss,max}$ for cediranib 20 mg increased by 21% (94% CI = 9–35%) and 26% (94% CI = 10–43%) respectively in the presence of ketoconazole 400 mg. The gmean ratio for AUC_{ss} and $C_{ss,max}$ were above 1 and the 94% CIs were not within the pre-specified equivalence boundaries. In particular, the lower limit of the 94% CI was clearly above 1, indicating a statistically significant effect in the presence of ketoconazole.

The change in gmean ratio values were modest and there was correspondingly a range of individual values. In total, 40–45% of patients showed a decrease or small increases (≤25%) in AUC_{ss} and $C_{ss,max}$.

For AUC_{ss}, the maximum ratio observed was 2.26 (126% increase) and the remaining patients all had a ratio below 2 (ie < 100% increase). Eight patients had increases less than 25% and 8 patients had decreases in AUC_{ss} in the presence of ketoconazole.

For $C_{ss,max}$, 22 of the 38 evaluable patients had a ratio >1.25 (maximum ratio 2.32, 132% increase). Four patients had increases less than 25%, and 12 patients had decreases in $C_{ss,max}$ in the presence of ketoconazole.

The average increases in AUC_{ss} and $C_{ss,max}$ observed would equate to approximately a 5 mg increase on a cediranib 20 mg dose. Given the known PK variability (Study D8480C00001), these rises were not considered clinically meaningful.

Summary of safety results

In total, 22 out of the 46 patients dose-escalated to cediranib 30 mg. Of these, 6 increased their dose again to cediranib 45 mg. Although 16 patients required a dose reduction at some point during the study, only 6 of these dose reduced from cediranib 20 mg to 15 mg.

All patients reported at least one AE. The overall AE profile was consistent with the general cediranib safety profile with diarrhoea (37 [80.4%]), fatigue (33 [71.7%]), hypertension (32 [69.6%]), dysphonia (26 [56.5%]), nausea (23 [50.0%]) and anorexia (20 [43.5%]) the most frequently reported AEs. Toxicities were managed successfully through dose modifications and standard medical practice.

The most common AEs by worst CTCAE Grade were fatigue (Grade 3: 5 [10.9%]; Grade 4: 2 [4.3%]), alanine aminotransferase increased (Grade 3: 7 [15.2%]) and diarrhoea (Grade 3: 6 [13.0%]).

Two patients, both receiving cediranib 20 mg, had died before the time of data cut-off for the CSR. One of these patients had an AE with outcome of death (Haemopericardium), the other patient died due to disease progression. In total, 11 (23.9%) patients reported serious AEs and only subileus (2 [4.3%]) occurred in more than 1 patient. Adverse events leading to discontinuation of study treatment (DAE) were reported in 15 (32.6%) of all study patients. The most common DAEs were fatigue (4 [8.7%]) and alanine aminotransferase increased (3 [6.5%]).

Trends in lab data were consistent with those seen in previous cediranib studies. Addition of ketoconazole did not appear to significantly affect the average ALT or AST profile, the majority of abnormalities in liver transaminases were Grade 1 changes from baseline. There were no clinically significant changes in ECG and increases in systolic and diastolic blood pressure were similar to previous cediranib studies.