Synopsis

Study Number: 200277

Title: Meta-Analysis for liver analyses with GW786034 (pazopanib) treatment in advanced/metastatic renal cell carcinoma and soft tissue sarcoma to support a regulatory post marketing requirement

Publication(s): None at the time of this report

Study Period: 13 MAR-2013 - 5-APR-2013

Phase of Development: Phase II/III Meta-Analysis

Objectives: The primary objective was to characterize the liver safety profile of pazopanib in subjects with locally recurrent and/or metastatic renal cell carcinoma or advanced or recurrent soft tissue sarcoma. The endpoint was to examine the safety of dose modification of pazopanib and patient re-challenge with pazopanib following hepatotoxicity.

Methodology: The Meta-Analysis included 1531 pazopanib-treated subjects from ongoing or completed trials. This analysis evaluated pazopanib-treated subjects from 5 renal cell carcinoma and 2 soft tissue sarcoma studies.

Study ID	Study Title
VEG102616	Phase II, randomized, global multicenter; assess safety and efficacy in subjects with locally recurrent or metastatic RCC
VEG108844	Phase III, randomized, open-label, global multi-center to assess safety and efficacy in subjects with locally recurrent or metastatic RCC
VEG113078	Phase III, randomized, open-label, global multi-center to assess safety and efficacy in Asian subjects with locally recurrent or metastatic RCC (sub-study to VEG108844)
VEG105192	Phase III, randomized, double-blind, placebo-controlled, global, multi-center to assess safety and efficacy of pazopanib versus placebo in subjects with locally recurrent or metastatic RCC
VEG107769	Extension study, open-label, to assess the safety and efficacy of pazopanib in subjects with advanced RCC who have previously been enrolled in study VEG105192 and have documented disease progression after receiving placebo treatment
VEG20002	Phase II single arm study to evaluate safety and efficacy of pazopanib in subjects with relapsed or refractory soft tissue sarcoma
VEG110727	Phase III randomized; double blind, multicenter; to assess safety and efficacy of pazopanib versus placebo in subjects with soft tissue sarcoma whose disease has progressed during or following prior therapy

Number of subjects: Planned for at least1500 pazopanib-treated subjects; Actual analysis included 1531 pazopanib-treated subjects, 1149 subjects from RCC studies and 382 subjects from STS studies.

Treatment administration: All subjects were administered pazopanib 800 mg as starting dose.

Statistical methods:

The Meta-Analysis integrated data by indication (STS, RCC). Safety Populations (all-treated population) from individual studies were the primary datasets used for the analyses. The safety population was defined as all subjects who received at least one dose of study medication and was based on actual treatment received for each study. In addition to the integrated data, individual study reports were reviewed for additional clinical information on subjects to assess recovery status after ALT elevations. The focus of this analysis is on liver chemistry data rather than hepatic adverse event data to have the most comprehensive evaluation of hepatotoxicity because not all elevations in liver chemistries are reported as adverse events.

The outcome of re-challenge summarizes subsequent ALT elevations following re-treatment after interruption due to an ALT elevation. Subjects were considered to have met re-challenge criteria when pazopanib was re-started following an interruption after an ALT elevation >3xULN. Additional analyses of the incidence of liver chemistry abnormalities and recovery and adaptation from ALT elevations are also included to provide context. Recovery is defined as ALT Grade 1 or below for 2 consecutive visits or Grade 1 or below for one visit if subject discontinued and no subsequent ALT data are available.

Safety Summary:

Incidence of hepatic laboratory: ALT elevations >3xULN occurred in 21%; ALT >5xULN in 12%; ALT >8xULN in 7%, and ALT >20xULN in 2% of all pazopanib-treated patients from studies included in this analysis.

Concomitant elevation of ALT>3xULN and bilirubin >2xULN and alkaline phosphatase (ALP) <3xULN (or ALP missing) (Hy's Law by laboratory criteria) predicts potentially severe drug induced liver injury. Two percent of patients in the RCC studies and 1% in the STS studies met Hy's Law by laboratory criteria.

Re-Challenge: Re-Challenge was defined for a subject with an ALT >3xULN elevation, whose study treatment was interrupted/delayed and subsequently has an ALT value of Grade 1 or below on or prior to re-starting study treatment.

Most of the subjects who were re-challenged had no recurrence of an ALT elevation >3xULN (RCC 58%, STS 63%). Recurrent ALT elevation >3xULN occurred in 28 subjects (39%) re-challenged in RCC and 6 subjects (38%) in STS.

Recovery was documented in most subjects who had elevations after re-challenge (22 of 28 subjects in RCC and 6 of 6 subjects in STS).

Adaptation: Adaptation was defined as an ALT>3XULN followed by a return to baseline grade or below without any dose interruption between the ALT elevation and normalization.

Most subjects who adapted had a peak ALT elevation >3xULN and ≤5xULN (RCC 60%, STS 80%). The majority of subjects (RCC 94 %, STS 100%) who met the definition of adaptation remained on the same dose of study treatment as prior to the elevation.

Dose Modifications: Dose reductions were used in some subjects with ALT elevations for subjects who met re-challenge and adaptation criteria. Dose reductions were not mandated for those subjects who met criteria for continuing pazopanib treatment (i.e., ALT >3xULN and < 8xULN), but were used by some investigators.

In RCC, of those subjects who met adaptation criteria, 5/86 (6%) had a dose reduction. Of the subjects who were re-challenged, 58/72 (81%) had a dose reduction at the time of re-challenge.

In STS, of those subjects who met adaptation criteria, no subject had a dose reduction. Of those subjects who were re-challenged, 13/16 (81%) had a dose reduction at the time of re-challenge.

Recovery: Recovery from an ALT elevation was defined as an ALT staying at grade 1 or below for two consecutive visits or dropping to grade 1 or below once after discontinuation of pazopanib with no further ALT data available.

The majority of subjects (85%) with reported ALT elevations >3xULN (with baseline ALT < 3xULN or missing) recovered.

Conclusions:

- The incidence and outcome of liver chemistry abnormalities described in this report are consistent with the current prescribing information, (Votrient US Prescribing Information, 2013).
- Most of the subjects who were re-challenged did not have recurrence of ALT elevation and those who had a repeat elevation recovered after discontinuing pazopanib.
- Dose modifications were used successfully in some subjects by investigators in the management of liver chemistry abnormalities.
- Most subjects who met criteria for adaptation were able to continue pazopanib with or without dose modifications to manage the ALT elevation.
- The majority of liver chemistry abnormalities were reversible.
- Based on these pooled data, the current management of subjects with liver chemistry abnormalities while on pazopanib with dose modification and re-challenge is safe.

Effective Date: 13-JUN-2013