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Title:	Meta-Analysis Plan for 200276, Liver analysis with pazopanib (GW786034) treatment in renal cell carcinoma, soft tissue sarcoma and ovarian

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Description:

Drug-induced liver test abnormalities and liver dysfunction are amongst the most common side effects observed for pazopanib. This meta-analysis will evaluate the incidence, course, outcome and pattern of pazopanib-induced liver events in order to provide further guidance to treating physicians and patients. Data from nine phase II and III studies in the RCC, STS and ovarian indications form the basis of this analysis.

Subject: Safety: liver dysfunction

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ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
DILI	Drug induced liver injury
PDGFR	Platelet-derived growth factor receptor
RCC	Renal cell carcinoma
STS	Soft tissue sarcoma
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor

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1. INTRODUCTION

Pazopanib is a multi-target receptor tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR) -1, -2 and -3, platelet-derived growth factor receptors (PDGFR) –α and -β, and stem cell factor receptor (c-kit).

Liver chemistry abnormalities were identified early in the pazopanib clinical development program and have been extensively evaluated. Prescribing information and study protocols include guidelines for monitoring liver chemistries and withdrawing treatment when there are severe changes in liver chemistry abnormalities. Information on liver events is also included in the patient information leaflet.

All study protocols included guidelines for the management of treatment emergent hepatoxicity. The protocol guidelines required monitoring hepatic enzymes, dose modifications, and stopping criteria. The current study guidelines are briefly described here:

- No dose interruption required for ALT/AST elevations ≤8xULN and without concomitant bilirubin elevations.
- Pazopanib dose interruption required at first ALT elevation >8xULN. Re-challenge allowed if the elevation recovers to Grade 1 (>ULN to ≤2.5xULN), total bilirubin <1.5xULN, no hypersensitivity, and benefitting from therapy. Dose reduction is not mandatory and is at the discretion of investigator.
- Pazopanib must be discontinued on recurrence of ALT elevation >3xULN.
- Pazopanib stopping criteria included discontinue pazopanib if elevation of ALT>3xULN with concomitant elevation in bilirubin (defined as total bilirubin ≥1.5xULN) or hypersensitivity.

Guidelines evolved as the pazopanib program progressed and more was understood about pazopanib induced hepatotoxicity. Therefore, protocols initiated prior to 2007 initially recommended interruption at lower elevations of ALT/AST >2.5xULN and re-challenge with pazopanib with a specified dose reduction to 400 mg. These guidelines were included in studies VEG20002, VEG102616, VEG101592 and VEG107769.

2. OBJECTIVE(S) AND ENDPOINT(S)

2.1. Objective(s)

- To characterise pazopanib-induced liver toxicity.
- To explore potential predictive and/or prognostic factors for pazopanib-induced liver events and explore risk factors for rechallenge failure.
- To evaluate correlations between pazopanib-induced liver events and other pazopanib-related toxicities.
- To provide evidence-based patient management guidelines for treating physicians.

2.2. Endpoint(s)

- Summary of the all treated population: summaries of baseline and demographic characteristics, plus a summary of duration of exposure.

- Characterisation of the incidence, time course and outcome of on-therapy liver laboratory abnormalities (defined as ALT > 3xULN): summaries include total number of subjects with elevations, time to onset of the first elevation, duration of first elevation and outcome of the first elevation.

- Characterisation of ALT elevations with clinical symptoms: summaries of specified AEs occurring concurrent with ALT elevations.

- Characterisation of the pattern of liver laboratory abnormalities: the number of subjects with heptaocellular, mixed and cholestatic liver events.

- Clinical adjudication and characterisation of cases with concurrent ALT > 3xULN and total bilirubin ≥ 2xULN to identify those meeting Hy's Law and cases of ALT > 20xULN: summaries of the number and outcome of these cases.

- Multivariate analysis for predictive and prognostic factors associated with ALT elevations > 3, > 5 and > 8xULN.

3. DATA SOURCES/STUDIES INCLUDED

The following phase II and III studies provide 2080 pazopanib treated subjects and will serve as the basis of the meta-analysis:

- **VEG102616**, a phase II single arm study in subjects with locally-recurrent or metastatic clear-cell renal cell carcinoma (Total N=225). A data cut off of 9th January 2009 will be used for purposes of these analyses.
- **VEG105192**, a phase III study in subjects with locally recurrent or metastatic renal cell carcinoma; pazopanib versus placebo (N=435, pazopanib treated n = 290). A data cut off of 15th March 2010 will be used for purposes of these analyses.
- **VEG107769**, an open-label extension study in subjects with advanced RCC who have previously been enrolled in study VEG105192 and have documented disease progression after receiving placebo treatment (N=80). A data cut off of 15th March 2010 will be used for purposes of these analyses.
- **VEG108844**, a phase III study in subjects with locally recurrent or metastatic renal cell carcinoma; pazopanib versus sunitinb (N=927) and **VEG113078**, a sub study to VEG108844 in Asian subjects (N=183). The total pazopanib treated n is 554. A data cut off of 21st May 2012 will be used for purposes of these analyses.

- **VEG20002**, a phase II single arm study in subjects with relapsed or refractory soft tissue sarcoma (N=142). A data cut off of 29th October 2010 will be used for purposes of these analyses.
- **VEG110727**, a phase III study in subjects with soft tissue sarcoma whose disease has progressed during or following prior therapy; pazopanib versus placebo (N=369, pazopanib treated n = 240). A data cut off of 22nd November 2010 will be used for purposes of these analyses.
- **VEG110655**, a phase III study in women with ovarian, fallopian tube or primary peritoneal cancer whose disease had not progressed after completing standard debulking surgery and first-line chemotherapy; pazopanib versus placebo (N=940) and **VEG114012**, a sub study to VEG110655 in Asian subjects (N=145). The total pazopanib treated n is 549, which includes 6 subjects randomised to the placebo arm who took pazopanib in error. Data cut offs of 8th July 2012 for VEG110655 and 12th October 2012 for VEG114012 will be used for the purposes of these analyses.

4. PLANNED ANALYSES

The remainder of this analysis plan will detail analyses of integrated liver safety summaries for the nine studies.

5. ANALYSIS POPULATIONS

The integrated safety summaries described in this analysis plan will use the all treated population which consists of all subjects who received at least one dose of pazopanib. This will use the safety/all treated populations defined in each of the individual studies.

6. TREATMENT COMPARISONS

No treatment comparisons are planned as only pazopanib treated subjects will be analysed.

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES

7.1. Multicentre Studies

As subject accrual was spread thinly across centres, summaries of data by centre will not be informative; therefore, centre will not be considered as a covariate in any of the summaries or analyses. Data from all participating centres will be pooled prior to analysis.

7.2. Multiple Comparisons and Multiplicity

No adjustments for multiplicity are planned.

8. DATA HANDLING CONVENTIONS

8.1. Premature Withdrawal and Missing Data

In seven of the nine studies, subjects were treated until disease progression and in the remaining two ovarian studies (VEG110655 and VEG114012); subjects were treated for up to 24 months. Subjects may have also withdrawn from study treatment for other reasons prior to disease progression such as unacceptable toxicity or withdrawal of consent. All data for patients who withdrew from the study will be included in analyses up to the time of withdrawal.

As the period of treatment depends on efficacy and toxicity, the duration of follow-up will vary between subjects. Consequently, subjects with shorter follow-up are not considered to have missing data.

8.2. Derived and Transformed Data

Detailed data specifications for derived variables are available in the individual study reporting and analysis plans. Datasets from the three existing integrated reporting efforts (for RCC, STS and ovarian) will be integrated together.

A new A&R dataset called LABANAL will be created for the integrated data using the integrated lab dataset. LABANAL will have one record per subject and subjects will be uniquely identified by the variable USUBJID.

The variables and algorithms to be used in these datasets will be described in a separate document.

8.3. Assessment Windows

The windows of interest are defined below:

Pre-therapy is defined as the time prior to the first date a subject received study medication.

On-therapy is defined as the time from the first dose date to 28 days post the last dose of pazopanib.

Post-therapy is defined as any time after the on-therapy period.

8.4. Subgroup and Covariate Definitions

No subgroup analyses are planned.

9. ANALYSES

Data will be summarised by indication (RCC, STS and ovarian) and also by the peak ALT level during the first ALT elevation >3xULN (>3-5xULN, >5-8xULN, >8-20xULN and >20xULN). This is defined as the peak ALT value from the initial elevation >3xULN until recovery. Recovery is defined as ALT returning to 2.5xULN or below for two

consecutive tests or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available. Recovery also includes those cases where dose was interrupted after an ALT>3xULN event, then ALT returned to 2.5xULN or below with only one test and subject was re-challenged before their next ALT test.

The all treated population will be used for the analyses.

9.1. Summary of the all treated population

The following summaries will be provided for the overall all treated population and by indication (RCC, STS and ovarian).

- Baseline demographics, including age, sex and race.
- Baseline characteristics, including performance status, number of metastatic sites, location of disease, paracetamol use and liver laboratory values.
- Concomitant paracetamol use at the time of the first ALT elevation >3xULN, where concomitant use is defined as on the day or in the two weeks prior to the elevation.
- Duration of exposure.

9.2. Characterisation of the incidence, time course and outcome of on-therapy liver laboratory abnormalities

In the studies that form this meta-analysis, routine liver chemistry tests included ALT, AST, total bilirubin and ALP. Bilirubin fractionation was required when total bilirubin was >1.5 xULN and gamma-GT was only included in a few studies as part of the liver chemistry panel. Generally, ALT is considered a somewhat more liver-specific aminotransferase enzyme than AST [Green RM, Flamm S., Gastroenterology 2002]. For this reason, ALT elevations are the primary focus of this meta-analysis.

- The total incidence of ALT, AST, ALP and total bilirubin elevations, as well as concurrent ALT and total bilirubin elevations will be summarised, where concurrent is defined as the total bilirubin elevation on the same day or up to 28 days after the ALT elevation. The summary will be split by indication and categorised by peak ALT (>3-5xULN, >5-8xULN, >8-20xULN and >20xULN). This table looks at the peak ALT whilst on study treatment rather than the peak within the first elevation.

The first ALT elevation > 3xULN (defined as an event below) will be summarised as follows:

- Number of subjects with an ALT elevation > 3xULN and number of subjects with concurrent ALT and total bilirubin elevations.
- Summary statistics for the time from first dose of pazopanib to onset of the first event.

Stacked bar charts will also be produced for the time to onset, with the ALT elevations > 3-8xULN and > 8xULN displayed in different colours/patterns. The subjects will be grouped according to their peak ALT within the first ALT elevation.

Separate charts will be provided for the RCC, STS and ovarian indications due to different liver monitoring schedules within the studies. The RCC studies all have different liver monitoring schedules, so data will be presented separately for VEG102616, VEG105192/VEG107769 and VEG108844/VEG113078. This will give a total of 5 separate figures. An overall figure will also be produced.

The x axis will display the study week and this will be grouped into 1 week periods as follows; 1-10 days, 11-17 days, 18-24 days, etc. The y axis will display the percentage of events that occurred and the denominator for the percentages will be the total number of subjects with at least one post-baseline ALT assessment.

- A table summarising the number of events occurring in the first week of the study (days 1-10) will be produced for studies that had ALT assessments during the first week (VEG102616, VEG105192, VEG107769, VEG20002 and VEG110727).

- A table summarising the number of events occurring in the second week of the study (days 11-17) will be produced for studies that had ALT assessments during the second week (VEG108844 and VEG113078).

- A shift table of the onset and the peak ALT categories (>3-5xULN, >5-8xULN, >8-20xULN and >20xULN). The peak ALT within the first elevation will be used i.e. the highest ALT/ULN before recovery (defined in section 9).

  This will provide information on how many events reached their peak at the onset of the event and may allow us to re-evaluate the current assessment schedule if it is seen that most cases have reached peak at the onset of the event.

- A summary of the time from last dose of pazopanib prior to the onset of the first event. Only on-therapy events will be considered i.e. only events up to and including the 28 days after the last dose of pazopanib.

  This will provide information on how many events start after dose interruption or discontinuation. A clinical evaluation will be performed to determine whether these elevations after dose interruption or discontinuation are likely to be due to pazopanib or whether they are due to other contributing factors. A listing will be provided to accompany this table.

- The outcome of the first event will be summarised for the number (%) of subjects who recovered, did not recover or had no follow-up, where no follow-up is defined as no ALT data after the ALT elevation. Subjects who do not meet the definition for recovery or no follow-up are classed as not recovered.

Recovery will be further broken down into those that recovered with dose interruptions, those that recovered without dose interruptions and those that had adaptation. Adaptation is a subgroup of those who recovered without dose interruption and is defined as an ALT > 3xULN followed by baseline grade or below (and must be ≤2.5xULN) without any dose interruption between the ALT elevation and normalisation.

- Summary statistics for the time from onset of the first event to recovery or adaptation. Recovery time will be further broken down into those that recovered with dose interruptions, those that recovered without dose interruptions and those that had adaptation.

  Bar charts will also be produced for the time to recovery. Separate charts will be provided for the peak ALT during the first ALT elevation (>3-5xULN, >5-8xULN, >8-20xULN and >20xULN).

  The x axis will display the time to recovery and the y axis will display the percentage of events that occurred and the denominator for the percentages will be the total number of subjects who recovered.

- Summary statistics for the duration of re-treatment for subjects who recovered from their first event. This will be calculated from the date of re-treatment for those who interrupted treatment and from the date of recovery for those that didn't. Duration will be further broken down into those that recovered with dose interruptions, those that recovered without dose interruptions and those that had adaptation.

- The outcome of the re-challenge will be summarised for the number (%) of subjects who had a recurrent ALT elevation >3xULN (positive re-challenge), number of subjects who did not have a recurrent ALT elevation >3xULN (negative re-challenge) and number of subjects with no follow-up, which is defined as no ALT data after the re-challenge.

- A bar chart will be produced for the time to recurrence. The x axis will display the time to recurrence and this will be grouped into 2 week periods. The y axis will display the percentage of events that occurred and the denominator for the percentages will be the total number of subjects who had recurrence.

All of the above summaries (except the figures) will be split by peak ALT during the first ALT elevation (>3-5xULN, >5-8xULN, >8-20xULN and >20xULN). A total column summarising all ALT elevations >3xULN will also be provided.

- Baseline characteristics (age, gender and race) and characteristics of the first ALT elevation (grade of first event, onset time and time to recovery) will be summarised for subjects who are re-challenged. Age, onset time and time to recovery will be summarised using summary statistics and the remaining characteristics will be summarised by frequency count.

This summary will be split into those who had a successful re-challenge (i.e. no recurrent elevation) and those who had a recurrent ALT elevation.

- The correlation between the first ALT elevation > 3xULN and hypertension or paracetamol use within the first 12 weeks will be analysed (separately). Two 2x2 tables will be produced (one for hypertension and one for paracetamol use) and chi-squared tests will be performed.

9.3. Characterisation of events with clinical symptoms

The following adverse events will be evaluated to determine whether the event has clinical symptoms: nausea, vomiting, abdominal pain, abdominal pain upper, decreased appetite/anorexia, jaundice, rash (all terms including rash will be included), pruritis and pyrexia.

- The number (%) of subjects with each AE occurring within weeks 2 to 12 (i.e. day 14 to day 84) will be summarised, split by whether they had an ALT elevation >3xULN or no during this period.

- The number (%) of subjects with each AE occurring concurrent with the event will be summarised, split by peak ALT during the first elevation (>3-5xULN, >5-8xULN, >8-20xULN and >20xULN). A concurrent AE is defined as an AE occurring from one week prior to the date of the first ALT elevation > 3xULN until one week after recovery from that elevation. If a subject has more than one elevation > 3xULN then only the first elevation will be used.

9.4. Characterisation of the pattern of liver laboratory abnormalities

The first occurrence of an on-therapy ALT elevation >3xULN will be categorised into one of the three patterns of drug-induced liver injury (DILI); hepatocellular, mixed and cholestatic liver events.

The pattern of liver injury is determined using the R value where:

R = (ALT/ULN)/(ALP/ULN)

- Hepatocellular pattern of DILI if $R \geq 5$

- Mixed pattern of DILI if $R > 2$ and < 5

- Cholestatic pattern of DILI if $R \leq 2$.

R will be calculated using the peak ALT/ULN value and the ALP value from the same date. If ALP is missing for the peak ALT/ULN the highest ALT/ULN with a non-missing ALP will be used.

- The number (%) of the events with each pattern will be summarised based on the peak ALT during the first ALT elevation >3xULN (3-5xULN, >5-8xULN, >8-20xULN and >20xULN).

9.5. Clinical adjudication and characterisation of cases meeting Hy's Law and ALT > 20xULN

All subjects with concurrent ALT>3xULN and total bilirubin ≥2xULN will be clinically adjudicated by an external hepatologist Dr. Neil Kaplowitz and an external medical oncologist Dr. Thomas Powles based on clinical information provided by the GSK clinical team for each case. GSK will provide patient narratives which will include baseline medical conditions, liver chemistry profile, special liver labs (if available) concomitant medications, course of the liver events, clinical signs and symptoms and PGx analysis for UGT1A1 profile.

- Each case will be adjudicated by the external hepatologist and medical oncologist to determine whether the case is likely to be a drug induced liver toxicity caused by pazopanib and then to determine the likelihood of the case meeting the clinical criteria of Hy's law. The clinical outcome will be summarised.

- All ALT >20xULN cases will also be clinically evaluated by a GSK physician to determine whether the case is likely to be a drug induced liver toxicity caused by pazopanib. The clinical outcome will be summarised.

A spreadsheet with the subject number, study ID and the outcome will be provided (by Drs. Kaplowitz and Powles) to the GSK team. This will then be incorporated into the relevant dataset and this information used to summarise the data

9.6. Multivariate analysis for predictive and prognostic factors associated with ALT elevations > 3, > 5 and > 8xULN

- Three logistic regression analyses will be performed. One for the subset of subjects with ALT > 3xULN, one for the subset of subjects with ALT > 5xULN and one for the subset of subjects with ALT > 8xULN. Only the first elevation will be included in the analyses. The following covariates will be entered into the models and selected using stepwise variable selection with entry and exit significance levels of 0.05:

  - Gender (Male/Female)

  - Age (<60/ ≥60)

  - Race (White/Asian/Other) Note: White will be the reference group.

  - Baseline ALT (≤ULN/>ULN)

  - Baseline liver metastasises (Yes/No)

  - Prior anti-cancer therapy (Yes/No)

- Baseline paracetamol use (Yes/No)
- Indication (RCC/STS/ovarian)
- Baseline performance status (WHO 0 or ECOG 0 or KPS 100-90/WHO 1-2 or ECOG 1-2 or KPS < 90)
-

Odds ratios and 95% confidence intervals will be presented for all terms remaining in the models.

Further exploratory analyses may be conducted.

10. REFERENCES

Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology 2002;123(4):1367-84

11. ATTACHMENTS

11.1. List of Trials

VEG102616

VEG105192

VEG107769

VEG108844

VEG113078

VEG20002

VEG110727

VEG110655

VEG114012

11.2. Table of contents for Data Display Specifications

11.3. Data Display Specifications