In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

Division: Worldwide Development
Information Type: Clinical Study Report
Control: Not Applicable

Title:	Meta-Analysis of Liver Chemistry Abnormalities with GW786034 (Pazopanib) Treatment in Advanced/Metastatic Renal Cell Carcinoma, Soft Tissue Sarcoma and Ovarian Cancer

Additional Study Design Information: This meta-analysis evaluated the incidence, time course, outcome, re-challenge and pattern of pazopanib-induced liver events, as well as potential predictive factors, in order to provide further guidance to treating physicians and patients. Data from nine Phase II and III GSK-sponsored studies in the advanced RCC, STS and ovarian indications form the basis of this analysis.

Phase: Meta-Analysis

Compound Number: GW786034

Effective Date: 30-JUL-2014

Subject: Meta-analysis, liver chemistry abnormality, drug-induced liver injury, pazopanib, renal cell carcinoma, soft tissue sarcoma, ovarian cancer

Author(s): [redacted]

Initiation Date: 02-OCT-2013

Completion Date: 05-DEC-2013

Sponsor Signatory: [redacted]
(and Medical Officer) MDC Oncology
GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents. This study complies with US 21 CFR 312.120, as described in the Ethics and Good Clinical Practice section.

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ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
DILI	Drug-induced liver injury
DILIN	DILI Network
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
KPS	Karnofsky performance score
RCC	Renal cell carcinoma
SAE	Serious Adverse Event
STS	Soft tissue sarcoma
UGT1A1	Uridine 5'-diphospho-glucuronosyltransferase 1 family, polypeptide A1
ULN	Upper limit of normal
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
VOTRIENT	None

ETHICS AND GOOD CLINICAL PRACTICE

The study protocols, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable country-specific requirements, including US 21 Code of Federal Regulations (CFR) 312.3(b) for constitution of independent ethics committees. Ethics committee or institutional review board approvals are maintained in the Sponsor's study files.

These studies were conducted in accordance with ICH GCP and all applicable subject privacy requirements, and, the ethical principles that are outlined in the Declaration of Helsinki 2008. These studies were monitored in accordance with ICH E6, Section 5.18.

Investigators were trained to conduct the studies in accordance with GCPs and the study protocols as defined in ICH E3, Section 9.6. Written commitments were obtained from investigators to comply with GCP and to conduct the studies in accordance with the protocols.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The investigator agreed to provide the subject as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion. Case report forms were provided for each subject's data to be recorded.

Synopsis

Study Number: 200276

Title: Meta-Analysis of Liver Chemistry Abnormalities with GW786034 (Pazopanib) Treatment in Advanced/Metastatic Renal Cell Carcinoma, Soft Tissue Sarcoma and Ovarian Cancer

Investigator(s): Multi-center meta-analysis

Study center(s): Study centers were per the individual studies selected for the meta-analysis.

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

Study Period: The study periods were per the individual studies of the meta-analysis. Data cut-off dates for the individual studies were between 9 JAN 2009 and 12 OCT 2012.

Phase of Development: II, III

Objectives:

- Characterized pazopanib-induced liver toxicity.
- Explored potential predictive and/or prognostic factors for pazopanib-induced liver events and explored risk factors for re-challenge failure.
- Evaluated correlations between pazopanib-induced liver events and other pazopanib-related toxicities.
- Provided evidence-based patient management guidelines for treating physicians.

Methodology:

Liver Chemistry Monitoring

Most studies (VEG105192, VEG107769, VEG108844, VEG113078, VEG110655, VEG114012, VEG110727) had entry criteria of alanine aminotransferase(ALT)/ aspartate aminotransferaseAST) of ≤2.5x upper limit of normal (ULN) and total bilirubin of ≤1.5xULN. Routine liver chemistry panels included ALT, AST, alkaline phosphataseALP) and total bilirubin with bilirubin fractionation required when total bilirubin was >1.5xULN or >2xULN. Post-baseline liver chemistry tests were generally performed every 3 or 4 weeks. Earlier studies included Day 8 testing.

All study protocols included guidelines for the management of treatment emergent hepatotoxicity. The protocol guidelines required monitoring hepatic enzymes, dose modifications, and stopping criteria. Guidelines evolved as the pazopanib program progressed and more was understood about pazopanib induced hepatotoxicity. 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, VEG105192 and VEG107769.

Revised guidelines implemented in 2007 for ongoing and new studies (VEG108844/VEG113078, VEG110727, VEG110655, and VEG114012) are briefly described here:

- No dose interruption was required for ALT elevations ≤8xULN without concomitant bilirubin elevations.
- Pazopanib dose interruption was required at first ALT elevation >8xULN without concomitant bilirubin elevations. Re-challenge was allowed if ALT reduced to Grade 1 (>ULN to ≤2.5xULN), total bilirubin <1.5xULN, no hypersensitivity, and the subject was benefitting from therapy. Dose reduction was not mandatory and was at the discretion of investigator.
- Pazopanib discontinuation was required on recurrence of ALT elevation >3xULN.
- Pazopanib stopping criteria included discontinuation of pazopanib if elevation of ALT>3xULN with concomitant elevation in bilirubin (defined as total bilirubin ≥1.5xULN) or with hypersensitivity symptoms (e.g., fever, rash).

For concurrent ALT >3xULN and total bilirubin ≥2xULN with >35% direct bilirubin or with hypersensitivity (i.e. possible laboratory defined Hy's law cases), dosing was permanently discontinued and subjects were further evaluated to exclude other causes.

Clinical review and adjudication for potential Hy's law and cases with no recovery

Cases meeting laboratory criteria for Hy's law were clinically evaluated by an expert hepatologist, Dr. [redacted] Data reviewed were based on available clinical, laboratory, and Uridine 5'-diphospho-glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) genotyping data. The liver chemistry abnormalities were first adjudicated for potential association with pazopanib-induced liver injury based on the causality criteria by drug-induced liver injury Network (DILIN). Cases with liver injury possibly, probably, or likely associated with pazopanib treatment were further evaluated for confirmation of Hy's law. Additional clinical evaluation from the perspective of a medical oncologist who treats advanced cancer subjects was obtained from Dr. [redacted].

Cases with no laboratory data documenting ALT recovery were clinically reviewed to determine reasons for no recovery, such as death or lost/inadequate follow-up. Subjects who died of liver failure or with liver chemistry abnormalities at the time of death were clinically adjudicated by Dr. [redacted] and Dr. [redacted] (hepatologist) for potential association with pazopanib-induced liver injury.

Number of subjects:

The meta-analysis analyzed data from 2080 pazopanib treated subjects from 9 studies (Table 1). Nine Phase II and Phase III prospective studies sponsored by GlaxoSmithKline (GSK) that evaluated efficacy and safety of pazopanib monotherapy

800 mg once daily dose in advanced cancer subjects were included: 5 RCC studies, 2 STS studies and 2 Ovarian studies. In all these studies, subjects were treated continuously until disease progression, death, unacceptable toxicity or withdrawal of consent with exception of the Ovarian studies VEG110655 and VEG114012, in which the maximum treatment was 2 years. Data from all subjects treated with at least one dose of pazopanib (N = 2080) was integrated and used for this meta-analysis.

Table 1 Summary of Phase II and Phase III Studies Included in the Liver Toxicity Meta-analysis

Study ID	Phase	Design	Subject population	Subjects Enrolled[a], n	GSK Document Number
VEG102616	II	Single-arm, open-label	Locally recurrent or metastatic RCC	Pazopanib, 225	RM2007/00899/02
VEG105192	III	Randomized, double-blind, placebo-controlled	Locally advanced or metastatic RCC	Pazopanib, 290 Placebo, 145	UM2008/0012/00
VEG107769	III	Single-arm, open-label extension study to VEG105192	Locally advanced or metastatic RCC	Pazopanib, 80	UM2008/00010/00
VEG108844/ VEG113078	III	Randomized, open-label, pazopanib vs. sunitinib. VEG113078 is a substudy of VEG108844 in Asian population	Locally advanced or metastatic RCC	Pazopanib, 557 Sunitinib, 553	2012N141517_01 2012N151606_00
VEG20002	II	Single-arm, open-label	Relapsed or refractory STS	Pazopanib, 142	RM2008/00278/00
VEG110727	III	Randomized, double-blind, placebo-controlled	Advanced STS progressed from prior treatment	Pazopanib, 246 Placebo, 123	2010N109979_01
VEG110655	III	Randomized, double-blind, placebo-controlled	Women with ovarian, fallopian tube or primary peritoneal cancer whose disease had not progressed after completing standard debulking surgery and first-line chemotherapy	Pazopanib, 472 Placebo, 468	2013N158256_00
VEG114012	II	Randomized, double-blind, placebo-controlled	Same as Study VEG110655	Pazopanib, 73 Placebo, 72	2012N151679_00

Abbreviation: RCC = renal cell carcinoma; STS = soft tissue sarcoma; GSK = GlaxoSmithKline

a. In some studies, a small number of enrolled subjects never receive study treatment (pazopanib or the comparator).

Diagnosis and main criteria for inclusion:

Key inclusion and exclusion criteria were per the individual studies of the meta-analysis.

Treatment administration:

Subjects in each study of the meta-analysis were treated with 800 mg once daily of pazopanib. Batch numbers were per the individual studies of the meta-analysis.

Criteria for evaluation:

- 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 including identification of 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.

Statistical methods:

The safety population was the all treated population, which consisted of all subjects who received at least one dose of pazopanib. The meta-analysis used the safety/all treated populations defined in each of the individual studies.

Characterization of liver chemistry abnormalities

All analyses were performed as per the Meta-Analysis Plan. Incidence of ALT, AST, total bilirubin, and ALP elevations was based on peak values calculated as a multiple of ULN. Transaminases >3xULN were considered events of significance and were further categorized based on peak values of >3-5xULN, >5-8xULN, >8-20xULN, and >20xULN. Because ALT was considered hepatic specific, ALT was used instead of AST for characterization of the liver events. Subjects with baseline ALT >2.5xULN were excluded. Concurrent ALT >3xULN and total bilirubin ≥2xULN was defined as total bilirubin ≥2xULN occurring at or within 28 days of ALT >3xULN.

Time course of the first ALT >3xULN events was characterized for time to onset, defined as time from first dose of pazopanib to onset of the event, and for time from onset to

recovery, defined as time from event onset until ALT returned 2.5xULN or below for two consecutive visits or to 2.5xULN or below once after study treatment discontinuation with no further data available. The mean and median (with 5th and 95th percentile) times to onset and recovery were calculated.

Outcome of the first ALT >3xULN events was categorized as recovery, defined as ALT returned to ≤2.5xULN. Outcomes were further categorized as: recovery with dose interruption or without dose interruption; adaptation, a subgroup of subjects who recovered to normalized (<ULN) ALT or baseline grade without dose interruption; no recovery, defined as no laboratory data documenting ALT return to ≤2.5xULN. For those subjects who recovered, duration of pazopanib treatment since recovery was calculated. Outcomes of re-challenge with pazopanib included positive re-challenge (ALT >3xULN recurred) or negative re-challenge (ALT >3xULN did not recur). Time to recurrence and factors that might predict recurrence, such as baseline characteristics, onset timing, and severity of the first events, were evaluated.

Patterns of liver injury were categorized based on the calculated R ratio into hepatocellular (R ≥5), cholestatic (R ≤2) or mixed (R >2 and <5) patterns, where the R ratio = (peak ALT in ULN)/(ALP in ULN from the same date). If ALP was missing for the peak ALTxULN, the highest ALTxULN with a non-missing ALP was used.

Multivariate analysis to identify potential predictive factors of ALT elevation

Nine baseline candidate factors including gender, age, race, ALT level, liver metastasis status, prior anticancer therapy, paracetamol use, tumor type, and performance status were identified and examined in stepwise logistic regression analysis to evaluate association with occurrence of ALT >3xULN, >5xULN, and >8xULN events, respectively. Odds ratios and 95% confidence intervals were presented for all terms remaining in the model.

Correlation of onset of ALT >3xULN and hypertension or use of paracetamol within the first 12 weeks was assessed using chi-squared tests. The association of clinical symptoms with ALT elevation was assessed by comparing the incidence of a group of selected AEs (including abdominal pain, abdominal pain upper, nausea, vomiting, decreased appetite/anorexia, jaundice, pyrexia, rash/pruritus) between Week 2-12 in patients with or without ALT >3xULN during this time frame.

Summary:

Demographics and Baseline Characteristics:

The median age for the three populations was similar (60, 54 and 55 years old for the RCC, STS and Ovarian populations, respectively); however, a greater proportion of subjects in the renal cell carcinoma (RCC) population were >60 year old (54%) compared with subjects in the soft tissue sarcoma (STS) and Ovarian populations (36% and 37%, respectively) (Table 2). A greater proportion of subjects (71%) in the RCC population were male compared with subjects in the STS population (44%). All subjects in the Ovarian population were female. The majority of subjects were white.

Table 2 Summary of Demographic Characteristics and Race (All Treated Population)

	RCC Population N=1149	STS Population N=382	Ovarian Population N=549	Total N=2080
Median age, years (range)	60 (18-88)	54 (18-83)	55 (22-80)	58 (18-88)
Age groups, n (%)				
< 50	172 (15)	142 (37)	165 (30)	479 (23)
50 - < 60	362 (32)	102 (27)	183 (33)	647 (31)
60 - < 70	377 (33)	92 (24)	154 (28)	623 (30)
≥ 70	238 (21)	46 (12)	47 (9)	331 (16)
Gender				
Female	338 (29)	214 (56)	549 (100)	1101 (53)
Male	811 (71)	168 (44)	0	979 (47)
Race[a], n	**1148**	**240**	**549**	**1937**
White, n (%)	846 (74)	169 (70)	367 (67)	1382 (71)
Asian, n (%)	281 (24)	57 (24)	179 (33)	517 (27)
African American/African Heritage, n (%)	15 (1)	4 (2)	2 (<1)	21 (1)
American Indian or Alaska Native, n (%)	3 (<1)	1 (<1)	1 (<1)	5 (<1)
Native Hawaiian or other Pacific Islander, n (%)	2 (<1)	0	0	2 (<1)
American Indian or Alaska Native & White, n (%)	1 (<1)	0	0	1 (<1)
Unknown, n (%)	0	9 (4)	0	9 (<1)

Data Source: Table 6.1100, Table 6.1300
Abbreviation: RCC = renal cell carcinoma; STS = soft tissue sarcoma
a. Race was not collected in STS Study VEG20002 (n=142)

The RCC and STS populations had higher incidences of baseline liver metastasis than the Ovarian population (Table 3). The RCC and STS populations also had higher incidences of baseline ALP > ULN than the Ovarian population, which may reflect higher tumor burden and/or bone metastasis in these populations. The Ovarian population had minimal radiologic disease at baseline because these studies were maintenance studies following chemotherapy.

Table 3 Summary of Baseline Disease Characteristics (All Treated Population)

	RCC Population N=1149	STS Population N=382	Ovarian Population N=549	Total N=2080
Baseline liver metastasis, n	**1132**	**368**	**85**	**1565**
Yes, n (%)	212 (18)	97 (25)	17 (3)	326 (16)
Baseline liver chemistry, n, n (%)	**1149**	**382**	**549**	**2080**
ALT ≤ ULN	1058 (92)	337 (88)	512 (93)	1907 (92)
ALT > ULN	87 (8)	45 (12)	35 (6)	167 (8)
Total bilirubin ≤ ULN	1099 (96)	368 (96)	538 (98)	2005 (96)
Total bilirubin > ULN	49 (4)	13 (3)	10 (2)	72 (3)
ALP ≤ ULN	912 (79)	264 (69)	506 (92)	1682 (81)
ALP > ULN	230 (20)	116 (30)	34 (6)	380 (18)
AST ≤ ULN	1084 (94)	342 (90)	519 (95)	1945 (94)
AST > ULN	63 (5)	40 (10)	28 (5)	131 (6)
Baseline performance status, n, n (%)	**1149**	**382**	**549**	**2080**
ECOG, n	**595**	**NA**	**549**	**1144**
0	297 (50)	NA	424 (77)	721 (63)
1	288 (48)	NA	123 (22)	411 (36)
2	10 (2)	NA	2 (<1)	12 (1)
KPS, n	**554**	**NA**	**NA**	**554**
100	199 (36)	NA	NA	199 (36)
90	212 (38)	NA	NA	212 (38)
80	100 (18)	NA	NA	100 (18)
≤ 70	37 (7)	NA	NA	37 (7)
Unknown	6 (1)	NA	NA	6 (1)
WHO, n	**NA**	**382**	**NA**	**382**
0	NA	188 (49)	NA	188 (49)
1	NA	193 (51)	NA	193 (51)
2	NA	1 (<1)	NA	1 (<1)

Data Source: Table 6.1400, Table 8.1100, Table 6.1200

Abbreviation: ALP = alkaline phosphatase; ALT= alanine aminotransferase; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance score; NA = not available; RCC = renal cell carcinoma; STS = soft tissue sarcoma; ULN = upper limit of normal; WHO = World Health Organization.

More subjects (34% and 33%) in the STS and Ovarian populations, respectively, had a maximum treatment duration of <12 weeks than in the RCC population (22%) (Table 4). Each tumor population had unique characteristics that were reflected in the early treatment discontinuation. For the STS population, the earlier discontinuation rate was primarily due to disease progression; for the Ovarian population, it was primarily due to Adverse Events (Data Source: GlaxoSmithKline Document Number RM2008/00278/00, GlaxoSmithKline Document Number 2010N109979_01, GSK Document Number 2013N158256_00, GlaxoSmithKline Document Number 2012N151679_00).

The majority (93%) of subjects did not use Paracetamol at the baseline assessment (Data Source: Table 6.1500).

Table 4 Pazopanib Exposure (All Treated Population)

	RCC Population N=1149	STS Population N=382	Ovarian Population N=549	Total N=2080
Maximum duration of pazopanib treatment, n (%)				
<3 weeks	50 (4)	21 (5)	61 (11)	132 (6)
3 - <6 weeks	65 (6)	48 (13)	47 (9)	160 (8)
6 - <9 weeks	76 (7)	35 (9)	42 (8)	153 (7)
9 - <12 weeks	52 (5)	25 (7)	29 (5)	106 (5)
12 - <24 weeks	205 (18)	104 (27)	58 (11)	367 (18)
24 - <48 weeks	270 (23)	98 (26)	108 (20)	476 (23)
≥ 48 weeks	431 (38)	51 (13)	204 (37)	686 (33)

Data Source: Table 8.1000
Abbreviation: RCC = renal cell carcinoma; STS = soft tissue sarcoma

Efficacy Results

No efficacy results were analyzed as a part of this meta-analysis.

Safety Results: Hepatobiliary Laboratory Abnormalities

Incidence and Severity of Hepatobiliary Laboratory Abnormalities

ALT >3xULN and AST >3xULN events occurred in 20% and 14% of subjects, respectively (Table 5). ALT elevation based on peak values of >3-5xULN, >5-8xULN, >8-20xULN and >20xULN occurred in 8%, 5%, 5%, and 1% of subjects, respectively. AST elevation based on peak values of AST >3-5xULN, >5-8xULN, >8-20xULN was 7%, 4%, 3% and 1%, respectively. The incidence of ALP elevation of ≥2xULN occurred in 21% of STS subjects, 13% of RCC subjects and 4% of Ovarian subjects, which is likely due to higher percentage of subjects in the RCC and STS populations with high tumor burden or bone metastasis.

Table 5 Hepatobiliary Laboratory Abnormalities Based on Peak Value (All Treated Population)

	RCC Population N=1149	STS Population N=382	Ovarian Population N=549	Total N=2080
Peak ALT>3xULN (excluding subjects with baseline elevations), n	**1137**	**375**	**533**	**2045**
Peak ALT >3xULN, n (%)	259 (23)	55 (15)	94 (18)	408 (20)
Peak ALT >3-5xULN, n (%)	100 (9)	26 (7)	40 (8)	166 (8)
Peak ALT >5-8xULN, n (%)	63 (6)	13 (3)	26 (5)	102 (5)
Peak ALT >8-20xULN, n (%)	76 (7)	11 (3)	24 (5)	111 (5)
Peak ALT >20xULN, n (%)	20 (2)	5 (1)	4 (<1)	29 (1)
Peak AST >3xULN (excluding subjects with baseline elevations), n	**1136**	**375**	**533**	**2044**
Peak AST >3xULN, n (%)	185 (16)	45 (12)	64 (12)	294 (14)
Peak AST >3-5xULN, n (%)	74 (7)	21 (6)	38 (7)	133 (7)
Peak AST >5-8xULN, n (%)	55 (5)	9 (2)	8 (2)	72 (4)
Peak AST >8-20xULN, n (%)	44 (4)	9 (2)	15 (3)	68 (3)
Peak AST >20xULN, n (%)	12 (1)	6 (2)	3 (<1)	21 (1)
Peak ALT or AST >3xULN, n	**1137**	**375**	**533**	**2045**
Peak ALT or AST >3-5xULN, n (%)	113 (10)	31 (8)	46 (9)	190 (9)
Peak ALT or AST >5-8xULN, n (%)	69 (6)	12 (3)	26 (5)	107 (5)
Peak ALT or AST >8-20xULN, n (%)	80 (7)	15 (4)	25 (5)	120 (6)
Peak ALT or AST >20xULN, n (%)	23 (2)	6 (2)	4 (<1)	33 (2)
Total Bilirubin ≥2xULN, n	**1126**	**375**	**533**	**2034**
Total Bilirubin ≥2xULN and Baseline Total Bilirubin ≤ULN/missing, n (%)	57 (5)	22 (6)	14 (3)	93 (5)
Total Bilirubin ≥2xULN and Baseline Total Bilirubin >ULN, n (%)	20 (2)	7 (2)	3 (<1)	30 (1)
ALP ≥2xULN and Baseline ALP, n	**1127**	**375**	**530**	**2032**
ALP ≥2xULN and Baseline ALP ≤ULN/missing, n (%)	62 (6)	11 (3)	14 (3)	87 (4)
ALP ≥2xULN and Baseline ALP >ULN, n (%)	75 (7)	68 (18)	6 (1)	149 (7)
Concurrent ALT >3xULN and Total Bilirubin ≥2xULN (Laboratory defined possible Hy's Law)[ab], n	**1137**	**375**	**533**	**2045**
Concurrent ALT >3xULN and Total Bilirubin ≥2xULN and Direct Bilirubin > 35%, n (%)	5 (<1)	1 (<1)	3 (<1)	9 (<1)
Concurrent ALT >3xULN and Total Bilirubin ≥2xULN and Direct Bilirubin ≤ 35%, n (%)	5 (<1)	2 (<1)	0	7 (<1)
Concurrent ALT >3xULN and Total Bilirubin ≥2xULN and Direct Bilirubin missing, n (%)	16 (1)	4 (1)	0	20 (<1)

Data Source: Table 8.1210, Table 8.1200

Abbreviation : ALP = alkaline phosphatase; ALT= alanine aminotransferase; AST = aspartate aminotransferase RCC = renal cell carcinoma; STS = soft tissue sarcoma; ULN = upper limit of normal

Note: The peak elevation for each subject is defined as the highest overall on-therapy lab parameter/ULN; n is the number of subjects with at least one post-baseline non-missing value for required lab parameters.

a. Bilirubin value can occur up to 28 days on or after ALT value.

b. One addition subject was identified from the Serious Adverse Events (SAE) narratives, resulting in a total of 37 possible Hy's laws events.

Clinical Adjudication of Cases Consistent with Hy's Law (concurrent ALT >3xULN and total bilirubin ≥2xULN)

Clinical adjudication determined that 9 subjects (9 of 2080 subjects or 0.4% of the integrated population) met Hy's law criteria for drug-induced liver injury (DILI). These cases were identified as follows.

Thirty-seven cases from the integrated population were initially identified as potential Hy's Law cases. Thirty-six (1.8%) subjects had concurrent ALT >3xULN and total bilirubin >=2xULN (laboratory findings consistent with Hy's Law, Table 5); one additional subject was identified from the SAE narratives, resulting in a total of 37 subjects. These 37 cases were clinically adjudicated based on available clinical, laboratory, and UGT1A1 genotyping data as described in Methodology.

Of the 37 subjects who had possible laboratory defined Hy's law criteria, 25 were assessed as either possibly (n=5), probably (n=18), or highly likely (n=2) having drug-induced liver injury (DILI) caused by pazopanib based on DILIN criteria. Nine of these 25 cases were assessed as meeting Hy's law criteria as noted above. [redacted] The liver chemistry abnormalities in the remaining 12 cases were assessed as unlikely related to pazopanib treatment.

A summary of adjudication is provided in Appendix Table 19 and Appendix Table 20. The 37 subjects who had possible laboratory defined Hy's law criteria are included in the case narratives.

Time to Onset of First ALT >3xULN Event

Median time to onset for all events was 42 days (5th, 95th percentile: 20, 182). Median time to onset of first ALT >3xULN event was shorter in the more severe (ALT>8-20xULN and ALT>20xULN) elevations (Table 6). Median time to onset for ALT >3-5xULN, >5-8xULN, >8-20xULN, and >20xULN group was 45 days (5th, 95th percentile: 20, 250), 40 days (5th, 95th percentile: 20, 179), 29 days (5th, 95th percentile: 20, 113), and 29 days (5th, 95th percentile: 15, 144), respectively.

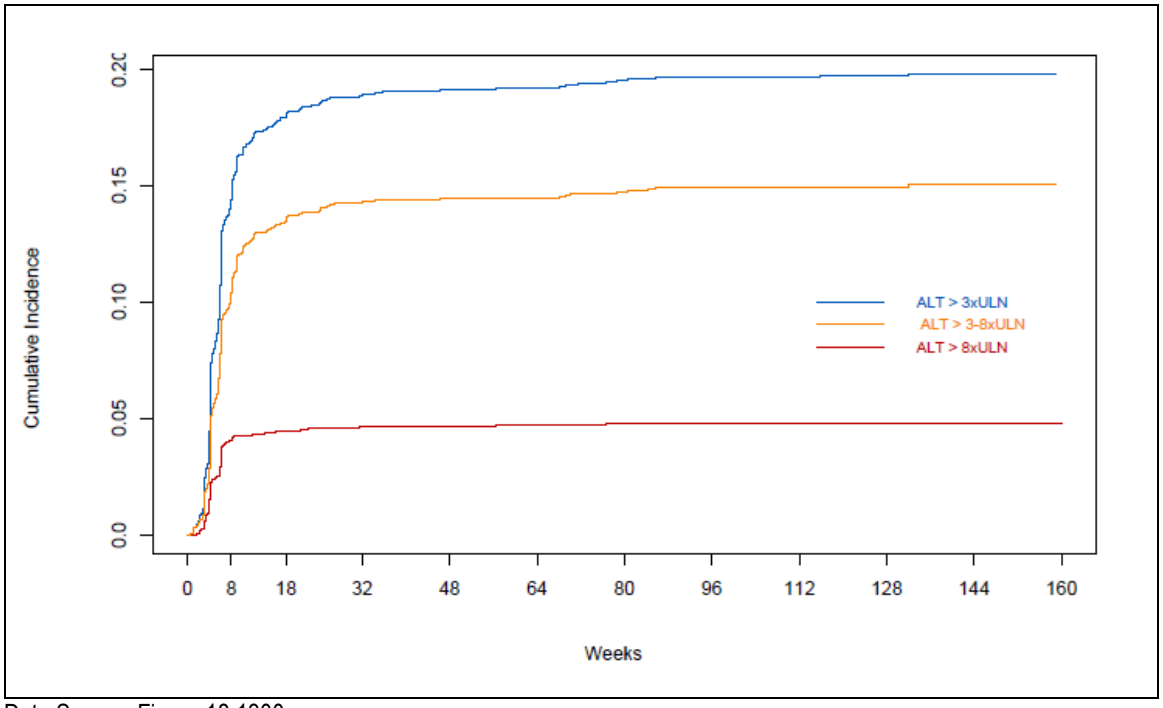
Most Subjects with an ALT >3xULN event had the event by end of 9 weeks (81%) or 18 weeks (92%) (Data Source: Table 8.3400). Figure 1 shows the cumulative incidence of ALT elevations over time. Figure 2 shows the incidence of ALT elevations at specific time points in studies grouped by the same liver chemistry test schedules.

Table 6 Time from First Dose of Pazopanib to Onset of First ALT Elevation >3xULN (All Treated Population)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN N=174	**Peak ALT >5-8XULN N=99**	**Peak ALT >8-20xULN N=107**	**Peak ALT >20xULN N=28**	**Total ALT >3xULN N=408**
Time to Onset, days					
Mean	83.9	58.3	49.9	42.8	65.9
SD	130.05	76.87	70.37	37.97	101.26
Median	44.5	40.0	29.0	29.0	42.0
5th percentile	20	20	20	15	20
95th percentile	250	179	113	144	182

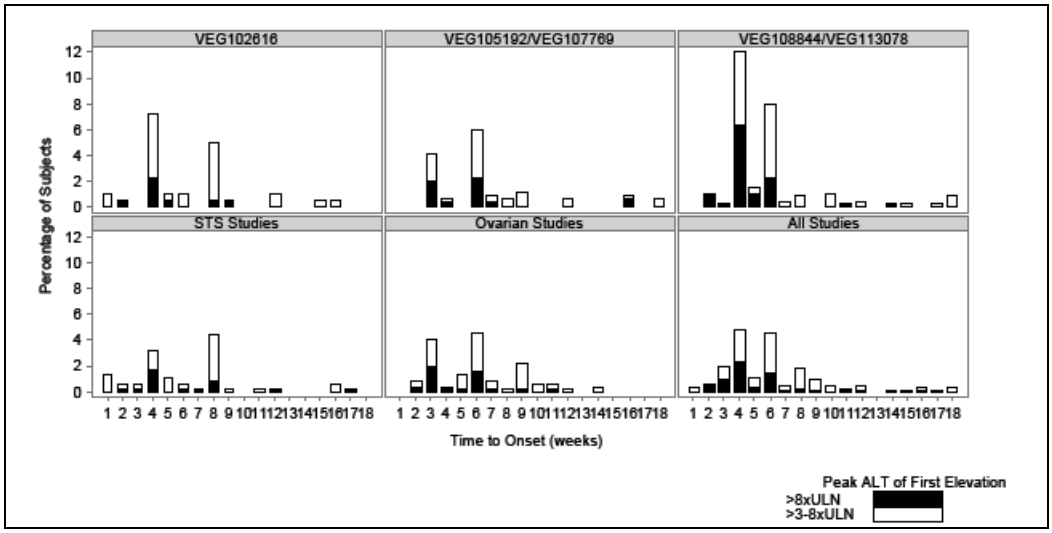
Data Source: Table 8.1900
Abbreviation: ALT= alanine aminotransferase; ULN = upper limit of normal; SD = Standard Deviation

Figure 1 Cumulative Incidence of On-therapy ALT>3xULN



Data Source: Figure 18.1300
Abbreviation: ALT= alanine aminotransferase; ULN = upper limit of normal
Note: There was no event onset beyond 160 weeks and therefore no curves were displayed beyond that for better visualization.

Figure 2 Time to Onset of the First ALT>3xULN by Liver Monitoring Schedule (All Treated Population)



Data Source: Figure 18.1000
Abbreviation: STS = soft tissue sarcoma; ULN = upper limit of normal; ALT= alanine aminotransferase

Note: Weekly incidence rates of ALT >3xULN events during the first 18 weeks are displayed as bar graphs for studies grouped with the same liver assessment schedules and separated by ALT >8xULN and ALT >3-8xULN events. For the first 18 weeks, protocol scheduled liver assessments were conducted on Week 1, 4, 8, 12 and 16 for the RCC VEG102616; Week 4, 8, 12 and 16 for the STS studies; Week 1, 3, 6, 9, 12, 15 and 18 for the RCC VEG105192/VEG107769 studies; Week 3, 6, 9, 12, 15 and 18 for the Ovarian studies; and Week 2, 4, 6, 10, 12, 16, 18 for the RCC VEG108844/VEG113078 studies. The denominator for the percentages was the total number of subjects with at least one post-baseline ALT assessment within each panel.

The incidence rate of ALT >3xULN at both Week 1 and Week 2 was <1% (Table 7). Most subjects had the same ALT elevation category at the onset of first ALT>3xULN event and at peak ALT elevation (Table 8). The majority (78%) of subjects had onset of ALT >3xULN event prior to the last dose of pazopanib treatment (Table 9). Twenty-two percent of subjects had onset of ALT >3xULN after the last dose of pazopanib, but the majority had the event onset within 14 days of the last dose of pazopanib.

Table 7 ALT Elevations >3xULN in Week 1 and 2 (All Treated Population)

	RCC Population N=1149	STS Population N=382	Total N=2080
Week 1 assessment, n	**1149**	**382**	**1531**
Number of subjects who had Week 1 assessment[a], n (%)	**595 (52)**	**383 (100)**	**977 (64)**
Number of ALT events in Week 1 (Day 1-10)	2 (<1)	5 (1)	7 (<1)
Week 2 assessment, n	**1149**	**NA**	**1149**
Number of subjects who had Week 2 assessment[b], n (%)	**526 (46)**	**NA**	**526 (46)**
Number of ALT events in Week 2 (Day 11-17)	5 (<1)	NA	5 (<1)

Data Source: Table 8.1600, Table 8.1700
Abbreviation: ALT= alanine aminotransferase; RCC = renal cell carcinoma; STS = soft tissue sarcoma; NA = not available
a. Ovarian assessments were not available for Week 1
b. Ovarian and STS assessments were not available for Week 2

Table 8 Shift Table of ALT Category at Onset and Peak for the First ALT Elevation >3xULN (All Treated Population)

		Peak ALT for First Elevation				
Onset ALT for First Elevation	**n**	**Peak ALT >3-5xULN**	**Peak ALT >5-8xULN**	**Peak ALT >8-20xULN**	**Peak ALT >20xULN**	**Total ALT >3xULN**
ALT >3-5xULN	219	174 (79)	23 (11)	21 (10)	1 (<1)	219 (100)
ALT >5-8xULN	91		76 (84)	13 (14)	2 (2)	91 (100)
ALT >8-20xULN	78			73 (94)	5 (6)	78 (100)
ALT >20xULN	20				20 (100)	20 (100)

Data Source: Table 8.2000
Abbreviation: ALT= alanine aminotransferase

Table 9 Time from the Last Dose of Pazopanib to Onset of the First ALT Elevation >3xULN (All Treated Population)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN N=174	Peak ALT >5-8XULN N=99	Peak ALT >8-20xULN N=107	Peak ALT >20xULN N=28	Total ALT >3xULN N=408
Time from onset, n (%)					
Still on drug at onset	145 (83)	82 (83)	73 (68)	19 (68)	319 (78)
1-3 days prior to onset	11 (6)	11 (11)	19 (18)	9 (32)	50 (12)
4-7 days prior to onset	6 (3)	3 (3)	5 (5)	0	14 (3)
8-14 days prior to onset	5 (3)	2 (2)	6 (6)	0	13 (3)
15-28 days prior to onset	6 (3)	1 (1)	4 (4)	0	11 (3)
>28 days prior to onset	1 (<1)	0	0	0	1 (<1)

Data Source: Table 8.2100
Abbreviation: ALT= alanine aminotransferase; ULN = upper limit of normal

Outcome/recovery of First ALT >3xULN Event

Most subjects (87%) with an ALT>3xULN event recovered to an ALT ≤2.5xULN (Table 10). Recovery rates based on peak ALT >3-5xULN, >5-8xULN, >8-20xULN, and >20xULN were 91%, 90%, 86%, and 54%, respectively. Seven additional subjects were identified as recovered from the SAE narratives (4 subjects in the peak ALT >8-20xULN group, and 3 subjects in the peak ALT >20xULN group), resulting in a total of 362 (89%) subjects who recovered (Table 10, Footnote b and c). Median time from onset to recovery was 30 days (5th, 95th percentile: 11, 155) and was longer in subjects who recovered without dose interruption.

One hundred eighty-four subjects recovered with dose interruption and 127 subjects recovered without dose interruption. Six additional subjects were identified as recovered with dose interruptions from laboratory data in the SAE narratives. Ninety-six subjects (24% of all recovered) demonstrated adaptation. More subjects with less severe ALT elevation (ALT>3-5xULN and >5-8xULN) recovered without dose interruption. All subjects in the ALT >20xULN group had dose interruption or discontinuation.

The median duration of pazopanib treatment was 195 days (5th, 95th percentile: 8, 867) for all recovered who continued treatment, and was 237 days in the peak ALT elevation >3-5xULN and >5-8xULN groups.

For the hepatic injury pattern of the first ALT elevation event, 60% of subjects had a pattern of hepotocellular injury (R>=5), 9% of subjects had a pattern of cholestatic injury (R<=2) and 30% of subjects had a mixed pattern of hepatocellular and cholestatic injury (R>2 to <5). As these R-values were solely calculated based on the liver chemistry laboratory values without clinical evaluation for other causes, not all of these cases are due to DILI. As these are subjects from an advanced cancer population, some subjects with baseline elevated ALP may be inappropriately categorized as having a mixed or cholestatic liver injury.

Table 10 Outcome and Pattern of First ALT >3ULN Event (All Treated Population)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN N=174	**Peak ALT >5-8xULN N=99**	**Peak ALT >8-20xULN N=107**	**Peak ALT >20xULN N=28**	**Total ALT >3xULN N=408**
Outcome of the first elevation event					
Recovered[a] (of total events in each category), n (%)	159 (91)	89 (90)	92[b] (86)	15[c] (54)	355 (87)
Recovered with dose interruption, n	64	50	61[b]	9[c]	184[c]
Recovered without dose interruption, n	84	31	12	0	127[c]
Adaptation[d], n	62	27	7	0	96
Onset after last dose of pazopanib, n	11	8	19	6	44
No recovery[e] (of total events in each category), n (%)	7 (4)	7 (7)	8 (7)	8 (29)	30 (7)
No follow-up[f] (of total events in each category), n (%)	8 (5)	3 (3)	7 (7)	5 (18)	23 (6)
Time from onset to recovery, days, n	**159**	**89**	**92**	**15**	**355**
Mean (SD)	49.9 (51.07)	53.6 (49.76)	38.6 (30.83)	32.1 (16.19)	47.1 (45.57)
Median (5th percentile, 95th percentile)	30.0 (7,168)	34.0 (8,169)	29.0 (14,113)	28.0 (19,85)	30.0 (8,155)
Time from onset to recovery with dose interruption, n	**64**	**50**	**61**	**9**	**184**
Mean (SD)	34.6 (38.40)	47.0 (52.97)	39.5 (32.57)	27.9 (9.01)	39.3 (40.51)
Median (5th percentile, 95th percentile)	22.0 (7,102)	29.0 (8,196)	30.0 (13,102)	22.0 (19,43)	29.0 (8,136)
Time from onset to recovery without dose interruption, n	**84**	**31**	**12**	**NA**	**127**
Mean (SD)	65.2 (56.72)	72.3 (43.58)	58.2 (33.22)	NA	66.3 (51.81)
Median (5th percentile, 95th percentile)	43.0 (9,181)	64.0 (22,169)	50.0 (14,155)	NA	45.0 (14,169)
Duration of pazopanib treatment after recovery, days					
Recovered with treatment continued, n	**134**	**71**	**57**	**7**	**269**
Median (5th percentile, 95th percentile)	236.5 (22,867)	237.0 (13,900)	110.0 (4,702)	22.0 (6,385)	195.0 (8,867)
Recovered with dose interruption, n	**52**	**43**	**45**	**7**	**147**
Median (5th percentile, 95th percentile)	261.5 (28,895)	198.0 (13,952)	89.0 (4,688)	22.0 (6,385)	186.0 (6,879)
Recovered without dose interruption, n	**82**	**28**	**12**	NA	**122**
Median (5th percentile, 95th percentile)	192.5 (21,836)	250.5 (60,790)	118.5 (14,924)	NA	218.5 (21,843)
Pattern of the first ALT elevation events[g], **n (%)**					
Hepatocellular (ratio >=5xULN)	71 (41)	68 (69)	83 (78)	24 (86)	246 (60)
Mixed (ratio >2-<5xULN)	77 (44)	25 (25)	19 (18)	3 (11)	124 (30)
Cholestasis (ratio <=2xULN)	26 (15)	6 (6)	5 (5)	1 (4)	38 (9)

Data Source: Table 8.2200, Table 8.2300, Table 8.2400, Table 8.3100
Abbreviation: ALT= alanine aminotransferase; ULN = upper limit of normal; SD = Standard Deviation; NA = not available

a. Recovery was defined as ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available. Recovery included re-challenge cases where dose was interrupted after an ALT>3xULN event, then ALT returned to 2.5xULN or below (only one test is required) before treatment restarted.

b. [redacted] Three of these additional subjects recovered with dose interruption, resulting in a total of 64 subjects with Peak ALT >8-20xULN who recovered with dose interruption. One subject had onset after last dose of pazopanib, resulting in a total of 20 subjects with Peak ALT >8-20xULN who had onset after last dose of pazopanib.

c. [redacted] All of these additional subjects recovered with dose interruption, resulting in a total of 12 subjects with Peak ALT >20xULN who recovered with dose interruption. Because of the additional subjects in the ALT>8-20ULN and ALT>20ULN categories, the totals in ALL ALT>3ULN increased to 362 subjects who recovered and 190 subjects who recovered with dose interruption.

d. Adaptation was defined as ALT > 3xULN followed by baseline grade or below (and must be <=2.5xULN) without any dose interruption between the ALT elevation and normalisation. Adaptation was a subgroup of recovered without dose interruption.

e. Not recovered was defined as at least one ALT result following the onset of the ALT elevation >3xULN but not meeting the definition for recovery.

f. No follow-up was defined as no ALT results available following the onset of the ALT elevation >3xULN.

g. The ratio was calculated as (ALT/ULN)/(ALP/ULN). Only the first ALT elevation >3xULN was included in this analysis.

Subjects with ALT elevation during the first 12 weeks had similar incidence of DILI-related symptoms as subjects without ALT elevation during the first 12 weeks, with the exception that decreased appetite/anorexia was slightly higher in those subjects with ALT elevation (Table 11). No relationship existed between magnitude of peak ALT for first elevation and incidence of DILI-related symptoms (Table 12).

Table 11 Selective AEs with Onset between Weeks 2 to 12 of Pazopanib Treatment in Subjects With Versus Without ALT >3xULN Within the First 12 weeks (All Treated Population)

	No ALT Elevation during Weeks 2 to 12 N=1728	ALT Elevation during Weeks 2 to 12 N=352
Abdominal pain	85 (5)	24 (7)
Abdominal pain upper	66 (4)	19 (5)
Decreased appetite/anorexia	185 (11)	55 (16)
Jaundice	3 (<1)	3 (<1)
Nausea	274 (16)	67 (19)
Pyrexia	34 (2)	13 (4)
Rash/pruritis	142 (8)	40 (11)
Vomiting	193 (11)	47 (13)

Data Source: Table 8.2900
Abbreviation: ALT= alanine aminotransferase

Table 12 Summary of Concurrent Selective AEs (All Treated Population)

	Peak ALT for First Elevation				
	Peak ALT >3-<=5xULN N=174	Peak ALT >5-<=8XULN N=99	Peak ALT >8-<=20xULN N=107	Peak ALT >20xULN N=28	Total ALT >3xULN N=408
Abdominal pain	7 (4)	5 (5)	5 (5)	1 (4)	18 (4)
Abdominal pain upper	11 (6)	2 (2)	1 (<1)	2 (7)	16 (4)
Decreased appetite/anorexia	18 (10)	9 (9)	12 (11)	4 (14)	43 (11)
Jaundice	1 (<1)	1 (1)	1 (<1)	0	3 (<1)
Nausea	25 (14)	15 (15)	11 (10)	4 (14)	55 (13)
Pyrexia	4 (2)	1 (1)	4 (4)	3 (11)	12 (3)
Rash/pruritis	11 (6)	8 (8)	9 (8)	1 (4)	29 (7)
Vomiting	20 (11)	10 (10)	8 (7)	4 (14)	42 (10)

Data Source: Table 8.3000
Abbreviation: ALT= alanine aminotransferase; ULN = upper limit of normal
Note: Concurrent was defined as an Adverse Event (AE) occurring from one week prior to the first ALT elevation > 3xULN until one week after recovery from that elevation. If a subject had more than one elevation > 3xULN then only the first elevation was used.

Adjudication of cases with no recovery

Of the 53 subjects with no recovery or no follow up (Table 10), 7 subjects had laboratory data in the SAE narratives that supported full recovery, resulting in a total of 46 subjects (11%) who did not demonstrate recovery from ALT elevation.

Nine of the 46 subjects died with markedly elevated ALT (peak ALT>20xULN, n=6; peak ALT>8-20xULN, n=3. [redacted] The causes of liver injury in these cases were assessed as unlikely associated with pazopanib treatment but were associated with multi-organ failures or ischemic liver injuries related to end-stage progression of cancer; therefore, the causes of death were unlikely associated with DILI due to pazopanib treatment.

Of the remaining 37 subjects, 17 had laboratory data indicating ALT trending down to Grade 2 and the remaining 20 had no follow-up data available (see Appendix Table 21 for a clinical summary of subjects identified as no recovery per lab data analysis). Nine subjects who died with elevated ALT are included in the case narratives.

Re-challenge

Most subjects (60%) who were re-challenged had a negative re-challenge (no recurrence of ALT >3xULN) (Table 13). Overall, 103 (25%) of the 408 subjects who initially developed ALT >3xULN were re-challenged with pazopanib following recovery. Twenty (19%) were re-challenged at the same dose as before ALT elevation and 83 (81%) were re-challenged at a reduced dose. Among those with recurrence of ALT elevation, the median time to recurrence of ALT elevation was 9 days (5th, 95th percentile: 5, 36) after recommencing pazopanib. Among the 39 subjects with recurrence of ALT elevation, 8 (21%) recurred with ALT >8-20xULN; none recurred with ALT >20xULN. Subjects with positive re-challenge had baseline characteristics similar to subjects with negative re-challenge; however, subjects with more severe first ALT level (ALT >8-20xULN) may have higher risk of positive re-challenge (Table 14).

Table 13 Summary of Re-Challenges for Subjects who Recovered from their First ALT Elevation >3xULN (All Treated Population)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN N=174	**Peak ALT >5-8XULN N=99**	**Peak ALT >8-20xULN N=107**	**Peak ALT >20xULN N=28**	**Total ALT >3xULN N=408**
Re-challenge[a], n	**33**	**28**	**36**	**6**	**103**
Dose reduction, n (%)	24 (73)	20 (71)	33 (92)	6 (100)	83 (81)
No dose reduction, n (%)	9 (27)	8 (29)	3 (8)	0	20 (19)
Post re-challenge[a], n	**33**	**28**	**36**	**6**	**103**
ALT > 3xULN not recurred, n (%)	23 (70)	19 (68)	16 (44)	4 (67)	62 (60)
ALT > 3xULN recurred, n (%)	10 (30)	9 (32)	18 (50)	2 (33)	39 (38)
No follow-up[b], n (%)	0	0	2 (6)	0	2 (2)
Post re-challenge ALT >3xULN recurred, n	**10**	**9**	**18**	**2**	**39**
ALT > 3-5xULN recurred, n (%)	8 (80)	5 (56)	4 (22)	0	17 (44)
ALT > 5-8xULN recurred, n (%)	2 (20)	2 (22)	10 (56)	0	14 (36)
ALT > 8-20xULN recurred, n (%)	0	2 (22)	4 (22)	2 (100)	8 (21)
ALT > 20xULN recurred, n (%)	0	0	0	0	0
Time to recurrence[c], days Number of subjects with ALT >3xULN recurred	**10**	**9**	**18**	**2**	**39**
Median	45.5	15.0	8.0	11.5	9.0
5th percentile	8	5	4	8	5
95th percentile	248	352	23	15	248

Data Source: Table 8.2500

Abbreviation: ALT= alanine aminotransferase; ULN = upper limit of normal

a. Re-challenge was defined as an ALT > 3xULN, which recovered to grade 1 or below following interruption and subsequently receiving study drug.

b. No follow-up is defined as no ALT results available following the onset of the ALT elevation > 3xULN.

c. Time from re-challenge to recurrence of ALT > 3xULN.

Table 14 Comparison of Baseline and First ALT Events Characteristics between Subjects with Positive or Negative Re-challenge (All Treated Population)

	No recurrent elevation N=64	Recurrent elevation N=39
Age, years	**64**	**39**
Mean (SD)	59.1 (10.85)	62.8 (9.42)
Median (Min-Max)	59.5 (37-82)	64.0 (36-82)
Sex, n (%)	**64**	**39**
Female	29 (45)	20 (51)
Male	35 (55)	19 (49)
Race, n (%)	**61**	**38**
Asian - central/south Asian heritage	0	1 (3)
Asian - east Asian heritage	15 (25)	6 (16)
Asian - Japanese heritage	3 (5)	3 (8)
Native Hawaiian or other Pacific Islander	1 (2)	0
White - Arabic/north African heritage	2 (3)	1 (3)
White - White/Caucasian/European heritage	40 (66)	27 (71)
Peak category of first ALT >3xULN event, n (%)	**64**	**39**
Alt >3-5xuln	23 (36)	10 (26)
Alt >5-8xuln	19 (30)	9 (23)
Alt >8-20xuln	18 (28)	18 (46)
Alt >20xuln	4 (6)	2 (5)
Time to onset of first ALT>3xULN event, days	**64**	**39**
Mean (SD)	55.5 (73.28)	48.3 (36.92)
Median (Min-Max)	42.0 (4-501)	43.0 (15-225)
Time to recovery of first ALT>3xULN event, days	**64**	**39**
Mean (SD)	23.3 (25.54)	30.1 (28.91)
Median (Min-Max)	19.5 (5-203)	22.0 (4-152)
Re-challenged with reduced dose, n (%)	**64**	**39**
Yes	47 (73)	34 (87)
No	15 (23)	5 (13)

Data Source: Table 8.2600, Table 8.3300
Abbreviation: ALT= alanine aminotransferase; ULN = upper limit of normal; SD = Standard Deviation

Multivariate Analysis to Identify Potential Predictive Factors of ALT Elevation

By logistic regression analysis, older age (≥60) was associated with a higher risk of developing ALT >3xULN, ALT >5xULN, and ALT >8xULN (Table 16). Subjects who were female gender, had a baseline ALT >ULN, no prior anticancer treatment (i.e. treatment-naïve), and better baseline performance status, were associated with a higher risk of developing ALT >3xULN. Table 15 displays a summary of ALT elevation incidence for baseline characteristics that were used as candidate variables using a logistic regression analysis.

Table 15 Summary of ALT Elevation Incidence by Logistic Regression Candidate Variables

	ALT Elevation >3xULN	ALT Elevation >5xULN	ALT Elevation >8xULN
Gender			
Male	197/ 979 (20)	111/ 979 (11)	68/ 979 (7)
Female	211/1101 (19)	123/1101 (11)	67/1101 (6)
Age Group			
< 60	180/1126 (16)	99/1126 (9)	58/1126 (5)
>= 60	228/ 954 (24)	135/ 954 (14)	77/ 954 (8)
Race Group			
White	295/1379 (21)	171/1379 (12)	101/1379 (7)
Asian	96/ 516 (19)	55/ 516 (11)	29/ 516 (6)
Other	4/ 43 (9)	2/ 43 (5)	2/ 43 (5)
Missing	13/ 142 (9)	6/ 142 (4)	3/ 142 (2)
Baseline ALT			
<=ULN	360/1907 (19)	207/1907 (11)	120/1907 (6)
>ULN	47/ 167 (28)	26/ 167 (16)	14/ 167 (8)
Missing	1/ 6 (17)	1/ 6 (17)	1/ 6 (17)
Baseline Liver Metastases			
Yes	14/ 91 (15)	6/ 91 (7)	2/ 91 (2)
No	394/1989 (20)	228/1989 (11)	133/1989 (7)
Prior Anti-Cancer Therapy			
Yes	177/1161 (15)	100/1161 (9)	53/1161 (5)
No	231/ 919 (25)	134/ 919 (15)	82/ 919 (9)
Baseline Paracetamol Use			
Yes	22/ 144 (15)	11/ 144 (8)	8/ 144 (6)
No	386/1936 (20)	223/1936 (12)	127/1936 (7)
Indication			
RCC	259/1149 (23)	153/1149 (13)	92/1149 (8)
STS	55/ 382 (14)	27/ 382 (7)	16/ 382 (4)
Ovarian	94/ 549 (17)	54/ 549 (10)	27/ 549 (5)
Baseline Performance Status			
WHO 0 or ECOG 0 or KPS 100-90	290/1320 (22)	164/1320 (12)	94/1320 (7)
WHO 1-2 or ECOG 1-2 or KPS < 90	117/ 754 (16)	69/ 754 (9)	40/ 754 (5)
Unknown	1/ 6 (17)	1/ 6 (17)	1/ 6 (17)

Data Source: Table 8.3200

Abbreviation: ALT= alanine aminotransferase; ULN = upper limit of normal; RCC = renal cell carcinoma; STS = soft tissue sarcoma; ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization.

Table 16 Logistic Regression Analysis of Variables Associated with ALT Elevations (All Treated Population)

Covariate	Odds Ratio	95% CI	p-value
First ALT>3xULN			
Sex: Female vs. Male	1.3	(1.01, 1.67)	.0456
Age group: < 60 vs. >= 60	0.61	(0.49, 0.77)	<.001
Baseline ALT: <= ULN vs. > ULN	0.53	(0.36, 0.77)	<.001
Prior anti-cancer therapy: No vs. Yes	1.88	(1.45, 2.43)	<.001
Baseline performance status: WHO 0 or ECOG 0 or KPS 100-90 vs. WHO 1-2 or ECOG 1-2 or KPS < 90	1.56	(1.22, 2.00)	<.001
First ALT>5xULN			
Age group: < 60 vs. >= 60	0.61	(0.45, 0.84)	.0024
Baseline ALT: <= ULN vs. > ULN	0.6	(0.36, 0.99)	.0476
Prior anti-cancer therapy: No vs. Yes	1.45	(1.06, 1.98)	.0188
First ALT>8xULN			
Age group: < 60 vs. >= 60	0.56	(0.37, 0.85)	.0072

Data Source: Table 8.1300, Table 8.1400, Table 8.1500
Abbreviation: ALT= alanine aminotransferase; CI = confidence interval; ULN = upper limit of normal; ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization; KPS = Karnofsky performance score.

Assessment of Correlation with ALT Elevation

Analysis of paracetamol use and onset of ALT elevation resulted in a weak negative correlation (Pearson chi-square P = 0.030, phi coefficient -0.048), i.e. paracetamol use was associated with a lower incidence of ALT elevation (Table 17). Correlation of ALT elevation and occurrence of hypertension within the first 12 weeks resulted in no correlation demonstrated (Table 18).

Table 17 Summary of Correlation between the first ALT Elevation >3xULN and Hypertension during the first 12 weeks of the Study (All Treated Population)

	No Hypertension N=1195	Hypertension N=885
No ALT elevation	964 (81)	708 (80)
ALT elevation	231 (19)	177 (20)
Pearson Chi-Square p-value		0.704
Phi Coefficient		0.008

Data Source: Table 8.2700
Abbreviation: ALT= alanine aminotransferase

Table 18 Summary of Correlation between the first ALT Elevation >3xULN and Paracetamol Use during the first 12 weeks of the Study (All Treated Population)

	No Paracetamol Use N=1522	Paracetamol Use N=885
No ALT elevation	1206 (79)	466 (84)
ALT elevation	316 (21)	92 (16)
Pearson Chi-Square p-value		0.030
Phi Coefficient		-0.048

Data Source: Table 8.2800
Abbreviation: ALT= alanine aminotransferase

Conclusions:

- Data from this meta-analysis support the current guidelines on regular liver chemistry tests after initiation of pazopanib, especially during the first 9 or 10 weeks, and demonstrate the safety of re-challenge.
- By multivariate analysis, subjects who were older age (≥60) had a higher risk of developing ALT >3xULN, ALT >5xULN and ALT >8xULN.
- There was no correlation between hypertension and ALT elevation.
- The majority of ALT elevations in pazopanib-treated subjects were isolated asymptomatic elevations that resolved over time. Dose modifications were used successfully in some subjects by investigators in the management of liver chemistry abnormalities.
- The majority of liver chemistry abnormalities were reversible.
- The severity of ALT elevation did not appear to affect the time to recovery; however, interruption of therapy did accelerate recovery time and is recommended in more severe cases (ALT >8xULN). This supports the guideline that dose interruption is required if ALT exceeds 8xULN.
- The majority of subjects who were re-challenged did not have recurrence of ALT elevation, underlining the apparent adaptation to therapy with time. Those subjects who had a repeat elevation after re-challenge recovered after discontinuing pazopanib. No incidences of ALT >20xULN or cases of liver failure after re-challenge support the safety of this approach.
- Most subjects who met criteria for adaptation were able to continue pazopanib with or without dose modifications to manage the ALT elevation.
- No liver failure was identified by expert clinical review as causally related to pazopanib treatment.

Effective Date: 30-JUL-2014

1. POST-TEXT TABLES AND FIGURES

Appendix Table 19 Summary of Possible Laboratory Defined Hy's Law Subjects: Listing of Initial and Final Adjudications for 37 Subjects Meeting Hy's Law Liver Enzymes Laboratory Criteria

STUDY ID	SUBJID	Tumor Type	UGT1A1*6	UGT1A1*28	UGT1A1 predicted function	[redacted] initial DILI assessment	Final DILI assessment with concensus of [redacted] and [redacted] (19Dec13)	[redacted] initial Hy's law assessment	Final Hy's law assessment with concensus of [redacted] and [redacted] (19Dec13)
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.									

Appendix Table 20 Summary of Final Adjudications on DILI assessment and Hy's law

DILIN assessment category[a]	Number of Subjects	Hy's Law
highly likely (>= 75% possibility)	2	0
probably (> 50-75% possibility)	18	8
possibly (>25-50% possibility)	5	1
unlikely (<=25% possibility)	12	0
TOTAL numbers of Subjects	**37**	**9**

Data Source: Table 28.1300

a. Potential association with pazopanib-induced liver injury based on the causality criteria by DILI Network. (Fontana et al. Hepatology 52:730-742, 2010)

Appendix Table 21 SUMMARY LISTING OF STATUS FOR 53 SUBJECTS WITH ALT>3XULN WHO HAVE NO FOLLOW-UP OR NOT RECOVERED

STUDY ID	SUBJ ID	LIVER SAE	Peak ALT Category	First Peak ALT value (xULN)	Recovered Status per manual review	Comments
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.						

This section contained patient narratives which are textual descriptions of medical history, treatment and outcome for individual patients who experienced a clinically important adverse event including serious adverse events during the trial. They have been excluded to protect patient privacy. This data may be made available subject to an approved research proposal and a determination of the ability to provide information from the specific narratives whilst protecting the patient's privacy. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 6.1000
Summary of Study Populations

	RCC (N=1149)	Sarcoma (N=382)	Ovarian (N=549)	Total (N=2080)
All Treated Population	1149 (100%)	382 (100%)	549 (100%)	2080 (100%)

Note: Subjects are included in the All Treated population if they have been randomized and taken at least one dose of study medication.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR

Population: All Subjects Treated by Pazopanib

Table 6.1100
Summary of Demographic Characteristics

	RCC (N=1149)	Sarcoma (N=382)	Ovarian (N=549)	Total (N=2080)
Age (yrs)				
n	1149	382	549	2080
Mean	60.2	52.3	55.2	57.4
SD	10.61	15.24	10.52	12.02
Median	60.0	54.0	55.0	58.0
Min.	18	18	22	18
Max.	88	83	80	88
Age Groups (yrs)				
n	1149	382	549	2080
< 50	172 (15%)	142 (37%)	165 (30%)	479 (23%)
50 - < 60	362 (32%)	102 (27%)	183 (33%)	647 (31%)
60 - < 70	377 (33%)	92 (24%)	154 (28%)	623 (30%)
>= 70	238 (21%)	46 (12%)	47 (9%)	331 (16%)
Sex				
n	1149	382	549	2080
Female	338 (29%)	214 (56%)	549 (100%)	1101 (53%)
Male	811 (71%)	168 (44%)	0	979 (47%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 6.1200
Summary of Performance Status at Baseline

	RCC (N=1149)	STS (N=382)	Ovarian (N=549)	Total (N=2080)
ECOG				
n	595		549	1144
0	297 (50%)		424 (77%)	721 (63%)
1	288 (48%)		123 (22%)	411 (36%)
2	10 (2%)		2 (<1%)	12 (1%)
KPS				
n	554			554
100	199 (36%)			199 (36%)
90	212 (38%)			212 (38%)
80	100 (18%)			100 (18%)
<= 70	37 (7%)			37 (7%)
Unknown	6 (1%)			6 (1%)
WHO				
n		382		382
0		188 (49%)		188 (49%)
1		193 (51%)		193 (51%)
2		1 (<1%)		1 (<1%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR

Population: All Subjects Treated by Pazopanib

Table 6.1300
Summary of Race and Racial Combination Details

	RCC (N=1149)		Sarcoma (N=382)		Ovarian (N=549)		Total (N=2080)	
n	1148		240		549		1937	
African American/African Heritage	15	(1%)	4	(2%)	2	(<1%)	21	(1%)
American Indian or Alaska Native	3	(<1%)	1	(<1%)	1	(<1%)	5	(<1%)
Asian	281	(24%)	57	(24%)	179	(33%)	517	(27%)
Central/South Asian Heritage	20	(2%)	0		1	(<1%)	21	(1%)
Japanese/East Asian Heritage/ South East Asian Heritage	260	(23%)	57	(24%)	178	(32%)	495	(26%)
Mixed Asian Heritage	1	(<1%)	0		0		1	(<1%)
Native Hawaiian or other Pacific Islander	2	(<1%)	0		0		2	(<1%)
White	846	(74%)	169	(70%)	367	(67%)	1382	(71%)
American Indian or Alaska Native & White	1	(<1%)	0		0		1	(<1%)
Unknown	0		9	(4%)	0		9	(<1%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 6.1400
Summary of Disease Burden at Baseline

	RCC (N=1149)	STS (N=382)	Ovarian (N=549)	Total (N=2080)
Number of Metastatic Sites				
n	1149	382	549	2080
1	298 (26%)	108 (28%)	0	406 (20%)
2	376 (33%)	143 (37%)	0	519 (25%)
>=3	468 (41%)	131 (34%)	0	599 (29%)
Unknown	7 (<1%)	0	0	7 (<1%)
NA	0	0	549 (100%)	549 (26%)
Location of Disease at Baseline				
n	1132	368	65	1565
Abdomen/Abdominal Wall	110 (10%)	0	5 (<1%)	115 (6%)
Abdominal Cavity	0	64 (17%)	0	64 (3%)
Adrenal Gland	115 (10%)	0	1 (<1%)	116 (6%)
Adrenals	42 (4%)	0	0	42 (2%)
Ascites	4 (<1%)	11 (3%)	11 (2%)	26 (1%)
Bone	263 (23%)	51 (13%)	0	314 (15%)
Bowel	1 (<1%)	0	0	1 (<1%)
Breast	4 (<1%)	0	0	4 (<1%)
Bronchus	2 (<1%)	0	0	2 (<1%)
Cartilage	1 (<1%)	0	0	1 (<1%)
Cervix	1 (<1%)	0	0	1 (<1%)
Chest Wall	53 (5%)	0	2 (<1%)	55 (3%)
Cns	2 (<1%)	0	0	2 (<1%)
Colon	10 (<1%)	0	1 (<1%)	11 (<1%)
Diaphragm	4 (<1%)	0	2 (<1%)	6 (<1%)
Duodenum	1 (<1%)	0	0	1 (<1%)
Esophagus/Oesophagus	3 (<1%)	0	0	3 (<1%)
Gastric	3 (<1%)	0	0	3 (<1%)
Gastroesophageal Junction	1 (<1%)	0	0	1 (<1%)
Head And Neck	7 (<1%)	2 (<1%)	0	9 (<1%)
Heart	4 (<1%)	0	0	4 (<1%)
Kidney	295 (26%)	0	1 (<1%)	296 (14%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 6.1400
Summary of Disease Burden at Baseline

	RCC (N=1149)	STS (N=382)	Ovarian (N=549)	Total (N=2080)
Liver	212 (18%)	97 (25%)	17 (3%)	326 (16%)
Lower Extremity	0	13 (3%)	0	13 (<1%)
Lung	866 (75%)	276 (72%)	10 (2%)	1152 (55%)
Lymph Node	0	66 (17%)	0	66 (3%)
Lymph Nodes	521 (45%)	0	12 (2%)	533 (26%)
Mediastinum	26 (2%)	0	1 (<1%)	27 (1%)
Muscles	11 (<1%)	0	0	11 (<1%)
Other	177 (15%)	0	11 (2%)	188 (9%)
Other Site	0	102 (27%)	0	102 (5%)
Other Soft Tissue	0	53 (14%)	0	53 (3%)
Ovary	5 (<1%)	0	1 (<1%)	6 (<1%)
Pancreas	64 (6%)	0	1 (<1%)	65 (3%)
Pelvic	2 (<1%)	0	0	2 (<1%)
Pericardial Effusion	3 (<1%)	0	0	3 (<1%)
Pericardium	2 (<1%)	0	0	2 (<1%)
Peritoneum/Omentum	44 (4%)	0	15 (3%)	59 (3%)
Pleura	79 (7%)	0	3 (<1%)	82 (4%)
Pleural Effusion	15 (1%)	29 (8%)	6 (1%)	50 (2%)
Primary Tumor	0	46 (12%)	0	46 (2%)
Rectum	3 (<1%)	0	0	3 (<1%)
Retro-Intra Abdominal	0	13 (3%)	0	13 (<1%)
Retroperitoneum	14 (1%)	0	2 (<1%)	16 (<1%)
Skeletal	7 (<1%)	0	0	7 (<1%)
Skin	6 (<1%)	14 (4%)	0	20 (<1%)
Small Intestine	5 (<1%)	0	1 (<1%)	6 (<1%)
Spinal Cord	5 (<1%)	0	0	5 (<1%)
Spleen	20 (2%)	0	3 (<1%)	23 (1%)
Stomach	1 (<1%)	0	0	1 (<1%)
Subcutaneous Tissue	1 (<1%)	0	0	1 (<1%)
Thoracic	0	8 (2%)	0	8 (<1%)
Thyroid	6 (<1%)	0	0	6 (<1%)
Trachea	6 (<1%)	0	0	6 (<1%)
Trunk	0	4 (1%)	0	4 (<1%)

[redacted]

Population: All Subjects Treated by Pazopanib

Table 6.1400
Summary of Disease Burden at Baseline

	RCC (N=1149)	STS (N=382)	Ovarian (N=549)	Total (N=2080)
Upper Extremity	0	2 (<1%)	0	2 (<1%)
Vessels	3 (<1%)	0	0	3 (<1%)
Visceral Gastro Intestinal	0	4 (1%)	0	4 (<1%)
Visceral Gynecological	0	4 (1%)	0	4 (<1%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 6.1500
Summary of Paracetamol Use

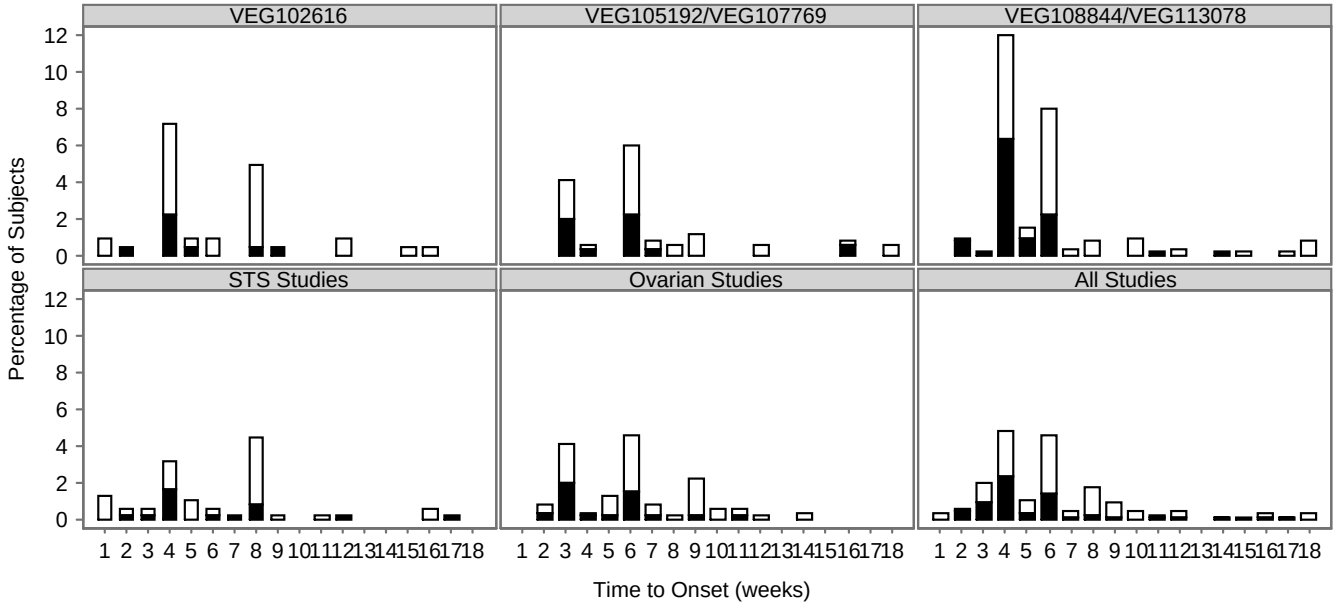
	RCC (N=1149)	Sarcoma (N=382)	Ovarian (N=549)	Total (N=2080)
Paracetamol Use at Baseline				
n	1149	382	549	2080
Yes	86 (7%)	36 (9%)	22 (4%)	144 (7%)
No	1063 (93%)	346 (91%)	527 (96%)	1936 (93%)
Paracetamol Use at the Time of the first ALT Elevation > 3xULN [1]				
n with ALT elevation > 3xULN	260	57	95	412
Yes	33 (13%)	12 (21%)	12 (13%)	57 (14%)
No	227 (87%)	45 (79%)	83 (87%)	355 (86%)

[1] at the time of the first ALT elevation is defined as at least one dose of paracetamol on the day of the ALT elevation or in the two weeks prior.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Figure 18.1000
Stacked Bar Chart of Time to Onset of the First ALT Elevation >3xULN by Liver Monitoring Schedule

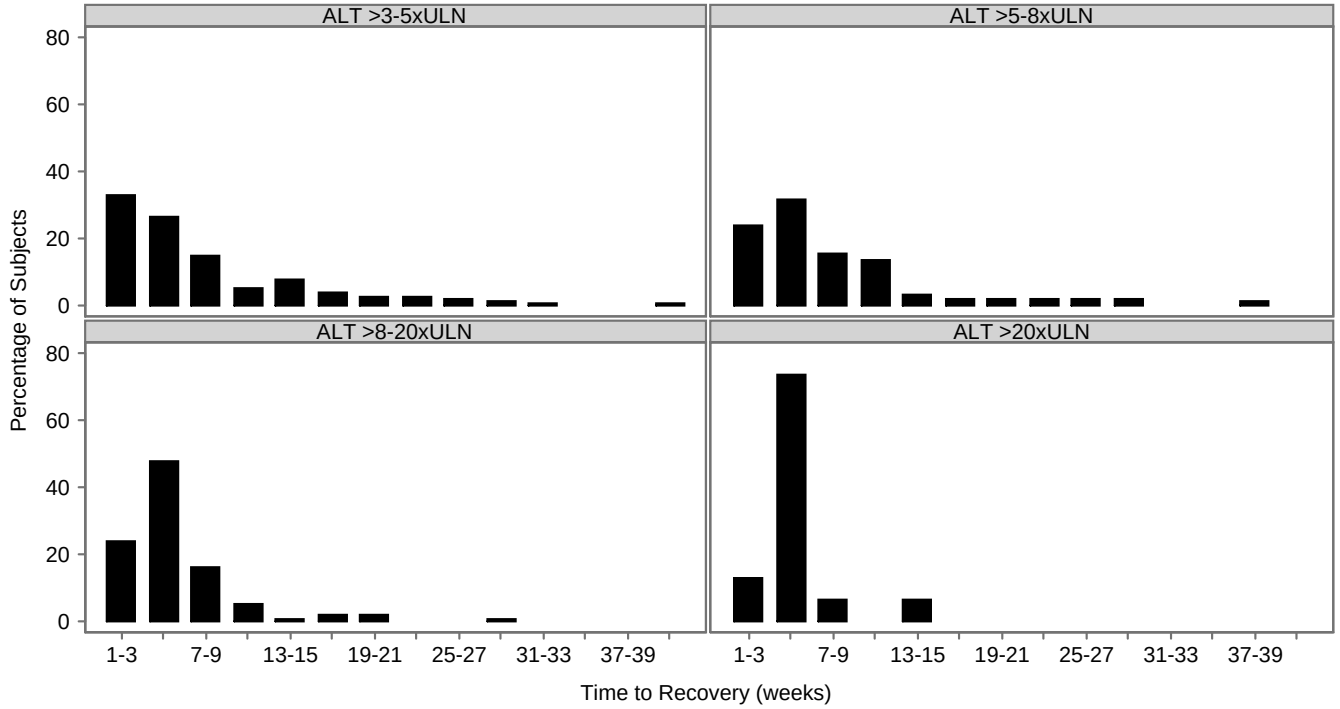


Note: x axis is truncated at 18 weeks. There are 49 ALT elevations beyond this point ranging from 20 weeks to 132 weeks.
Note: The denominator for the percentages is the total number of subjects with at least one post-baseline ALT assessment within each panel.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Figure 18.1100
Bar Chart of Time to Recovery from the First ALT Elevation >3xULN by First Elevation Series

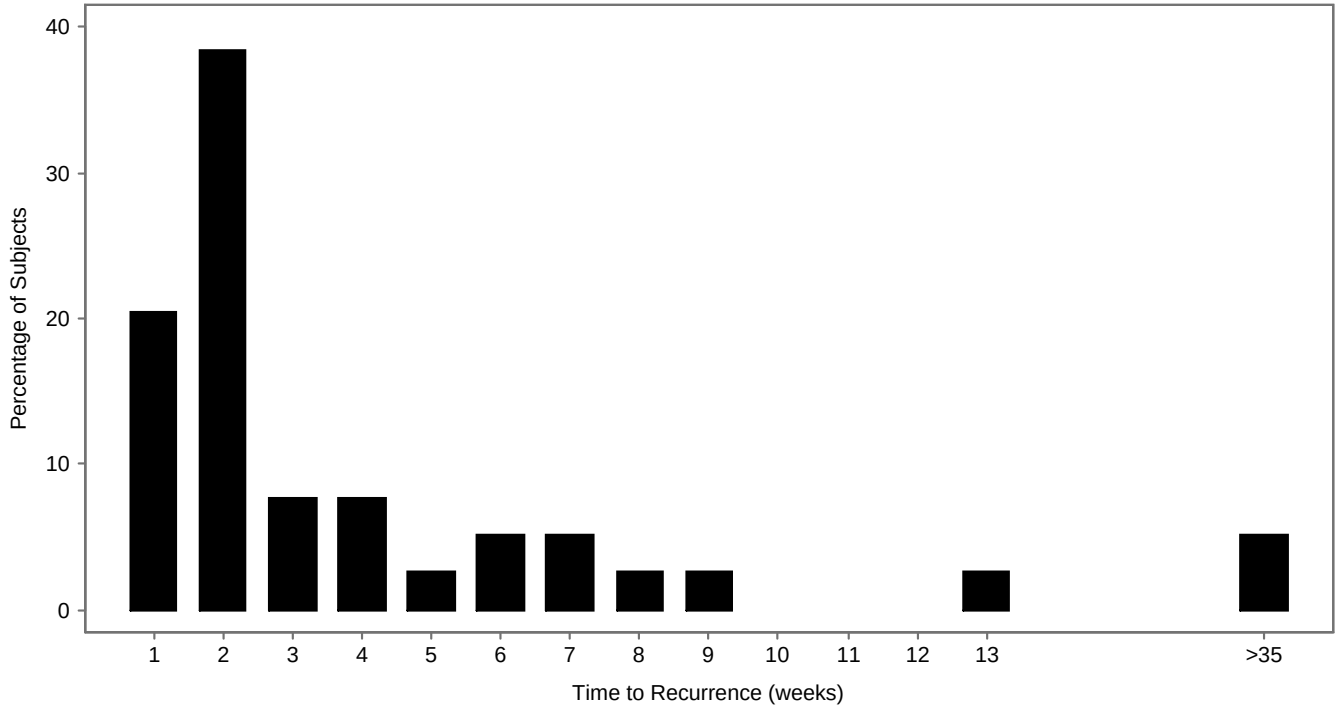


Note: The denominator for the percentages is the total number of subjects who recovered within each panel.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

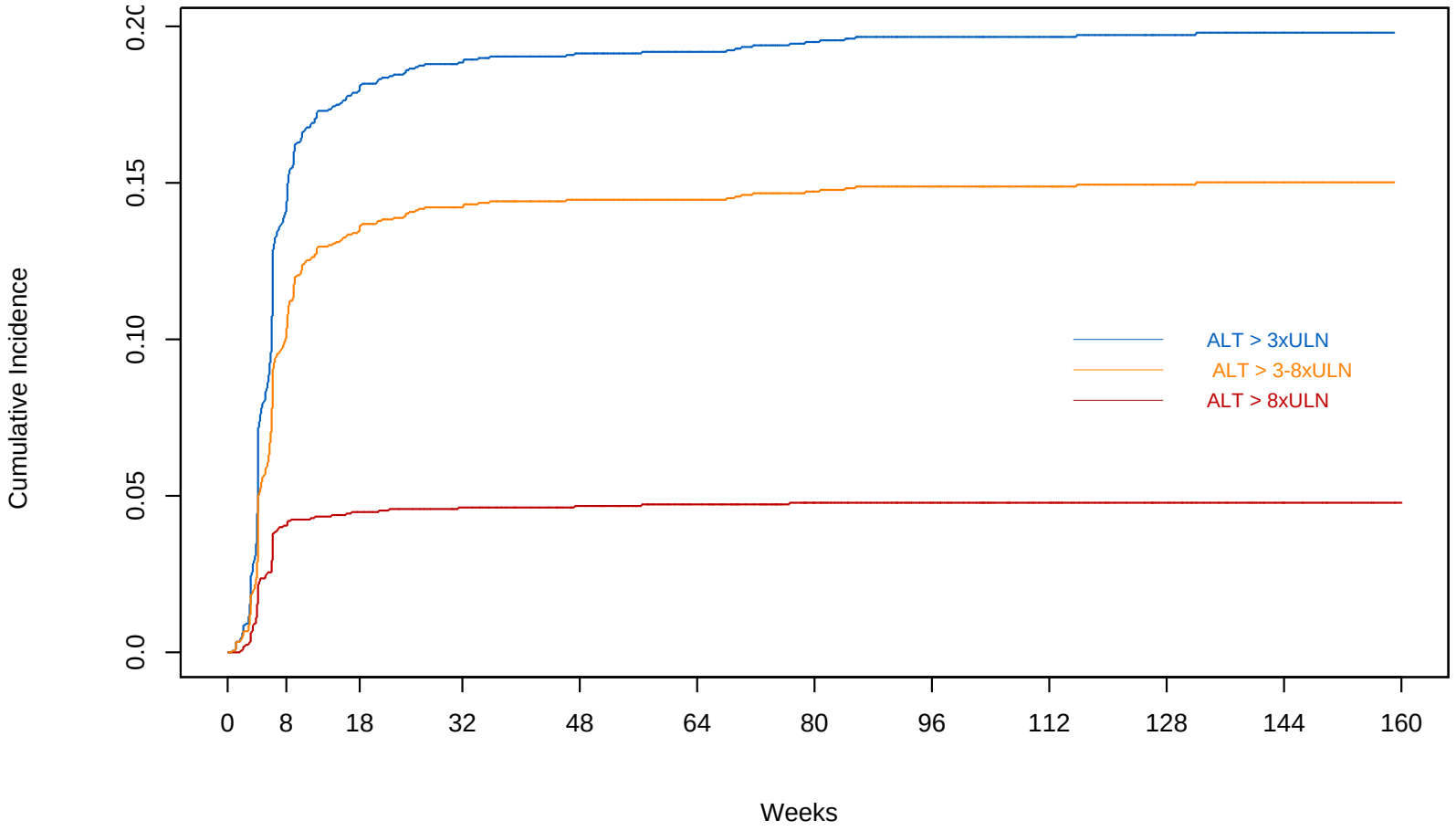
Figure 18.1200
Bar Chart of Time to Recurrence



Note: The denominator for the percentages is the total number of subjects who recovered within each panel.

[redacted]

Figure 18.1300
Cumulative Incidence of On-therapy ALT>3xULN



Note: There is no event onset beyond 160 weeks and therefore no curves are displayed beyond that for better visulization.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR

Population: All Subjects Treated by Pazopanib

Table 8.1000
Duration of Exposure to Pazopanib

	RCC (N=1149)	Sarcoma (N=382)	Ovarian (N=549)	Total (N=2080)
<3 weeks	50 (4%)	21 (5%)	61 (11%)	132 (6%)
3 - <6 weeks	65 (6%)	48 (13%)	47 (9%)	160 (8%)
6 - <9 weeks	76 (7%)	35 (9%)	42 (8%)	153 (7%)
9 - <12 weeks	52 (5%)	25 (7%)	29 (5%)	106 (5%)
12 - <24 weeks	205 (18%)	104 (27%)	58 (11%)	367 (18%)
24 - <48 weeks	270 (23%)	98 (26%)	108 (20%)	476 (23%)
>=48 weeks	431 (38%)	51 (13%)	204 (37%)	686 (33%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1100
Summary of Liver Function Tests at Baseline

	RCC (N=1149)	Sarcoma (N=382)	Ovarian (N=549)	Total (N=2080)
Baseline ALT				
n	1149	382	549	2080
<= ULN	1058 (92%)	337 (88%)	512 (93%)	1907 (92%)
> ULN	87 (8%)	45 (12%)	35 (6%)	167 (8%)
Missing	4 (<1%)	0	2 (<1%)	6 (<1%)
Baseline AST				
n	1149	382	549	2080
<= ULN	1084 (94%)	342 (90%)	519 (95%)	1945 (94%)
> ULN	63 (5%)	40 (10%)	28 (5%)	131 (6%)
Missing	2 (<1%)	0	2 (<1%)	4 (<1%)
Baseline ALP				
n	1149	382	549	2080
<= ULN	912 (79%)	264 (69%)	506 (92%)	1682 (81%)
> ULN	230 (20%)	116 (30%)	34 (6%)	380 (18%)
Missing	7 (<1%)	2 (<1%)	9 (2%)	18 (<1%)
Baseline Total Bilirubin				
n	1149	382	549	2080
<= ULN	1099 (96%)	368 (96%)	538 (98%)	2005 (96%)
> ULN	49 (4%)	13 (3%)	10 (2%)	72 (3%)
Missing	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1200
Summary of Hepatobiliary Laboratory Abnormalities Based on Peak Value

Laboratory Criteria [1]	RCC (N=1149)		Sarcoma (N=382)		Ovarian (N=549)		Total (N=2080)	
n	1137		375		533		2045	
Peak ALT >3xULN	260	(23%)	55	(15%)	95	(18%)	410	(20%)
Peak ALT >3-5xULN	101	(9%)	26	(7%)	40	(8%)	167	(8%)
Peak ALT >5-8xULN	63	(6%)	13	(3%)	26	(5%)	102	(5%)
Peak ALT >8-20xULN	76	(7%)	11	(3%)	25	(5%)	112	(5%)
Peak ALT >20xULN	20	(2%)	5	(1%)	4	(<1%)	29	(1%)
Peak ALT >3xULN and baseline ALT <=2.5xULN/missing	259	(23%)	55	(15%)	94	(18%)	408	(20%)
n	1136		375		533		2044	
Peak AST >3xULN	186	(16%)	45	(12%)	65	(12%)	296	(14%)
Peak AST >3-5xULN	74	(7%)	21	(6%)	38	(7%)	133	(7%)
Peak AST >5-8xULN	56	(5%)	9	(2%)	8	(2%)	73	(4%)
Peak AST >8-20xULN	44	(4%)	9	(2%)	16	(3%)	69	(3%)
Peak AST >20xULN	12	(1%)	6	(2%)	3	(<1%)	21	(1%)
Peak AST >3xULN and baseline AST <=2.5xULN/missing	185	(16%)	45	(12%)	64	(12%)	294	(14%)
n	1137		375		533		2045	
Peak ALT or AST >3-5xULN	113	(10%)	31	(8%)	46	(9%)	190	(9%)
Peak ALT or AST >5-8xULN	69	(6%)	12	(3%)	26	(5%)	107	(5%)
Peak ALT or AST >8-20xULN	80	(7%)	15	(4%)	25	(5%)	120	(6%)
Peak ALT or AST >20xULN	23	(2%)	6	(2%)	4	(<1%)	33	(2%)

[1] Subjects may be counted in more than one category of 'Laboratory Criteria'.
[2] Bilirubin value can occur up to 28 days on or after ALT value.
Note: The peak elevation for each subject is defined as the highest overall on-therapy lab parameter/ULN.
Note: n is the number of subjects with at least one post-baseline non-missing value for required lab parameters.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1200
Summary of Hepatobiliary Laboratory Abnormalities Based on Peak Value

Laboratory Criteria [1]	RCC (N=1149)		Sarcoma (N=382)		Ovarian (N=549)		Total (N=2080)	
n	1126		375		533		2034	
Total Bili >=2xULN and Baseline Total Bili <=ULN/missing	57	(5%)	22	(6%)	14	(3%)	93	(5%)
Total Bili >=2xULN and Baseline Total Bili >ULN	20	(2%)	7	(2%)	3	(<1%)	30	(1%)
n	1127		375		530		2032	
ALP >=2xULN and Baseline ALP <=ULN/missing	62	(6%)	11	(3%)	14	(3%)	87	(4%)
ALP >=2xULN and Baseline ALP >ULN	75	(7%)	68	(18%)	6	(1%)	149	(7%)
n [2]	1137		375		533		2045	
Concurrent ALT >3xULN and Total Bili >=2xULN and Direct Bili > 35%	5	(<1%)	1	(<1%)	3	(<1%)	9	(<1%)
Concurrent ALT >3xULN and Total Bili >=2xULN and Direct Bili <= 35%	5	(<1%)	2	(<1%)	0		7	(<1%)
Concurrent ALT >3xULN and Total Bili >=2xULN and Direct Bili missing	16	(1%)	4	(1%)	0		20	(<1%)

[1] Subjects may be counted in more than one category of 'Laboratory Criteria'.
[2] Bilirubin value can occur up to 28 days on or after ALT value.
Note: The peak elevation for each subject is defined as the highest overall on-therapy lab parameter/ULN.
Note: n is the number of subjects with at least one post-baseline non-missing value for required lab parameters.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1210
Summary of Hepatobiliary Laboratory Abnormalities Based on Peak Value
Excluding Subjects with Baseline Elevations

Laboratory Criteria [1]	RCC (N=1149)		Sarcoma (N=382)		Ovarian (N=549)		Total (N=2080)	
n	1137		375		533		2045	
Peak ALT >3xULN	259	(23%)	55	(15%)	94	(18%)	408	(20%)
Peak ALT >3-5xULN	100	(9%)	26	(7%)	40	(8%)	166	(8%)
Peak ALT >5-8xULN	63	(6%)	13	(3%)	26	(5%)	102	(5%)
Peak ALT >8-20xULN	76	(7%)	11	(3%)	24	(5%)	111	(5%)
Peak ALT >20xULN	20	(2%)	5	(1%)	4	(<1%)	29	(1%)
n	1136		375		533		2044	
Peak AST >3xULN	185	(16%)	45	(12%)	64	(12%)	294	(14%)
Peak AST >3-5xULN	74	(7%)	21	(6%)	38	(7%)	133	(7%)
Peak AST >5-8xULN	55	(5%)	9	(2%)	8	(2%)	72	(4%)
Peak AST >8-20xULN	44	(4%)	9	(2%)	15	(3%)	68	(3%)
Peak AST >20xULN	12	(1%)	6	(2%)	3	(<1%)	21	(1%)

[1] Subjects may be counted in more than one category of 'Laboratory Criteria'.
Note: The peak elevation for each subject is defined as the highest overall on-therapy lab parameter/ULN.
Note: n is the number of subjects with at least one post-baseline non-missing value for required lab parameters.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1300
Summary of Logistic Regression Analysis of Variables Associated with Subjects whose first ALT Elevation is >3xULN

N/n [1]	Covariate	Odds Ratio	95% CI	p-value
2080/1926	Sex: Female vs. Male	1.3	(1.01, 1.67)	.0456
	Age group: < 60 vs. >= 60	0.61	(0.49, 0.77)	<.001
	Baseline ALT: <= ULN vs. > ULN	0.53	(0.36, 0.77)	<.001
	Prior anti-cancer therapy: No vs. Yes	1.88	(1.45, 2.43)	<.001
	Basline performance status: WHO 0 or ECOG 0 or KPS 100-90 vs. WHO 1-2 or ECOG 1-2 or KPS < 90	1.56	(1.22, 2.00)	<.001

[1] N/n: Population/Subjects with data available for all covariates.
Note: Candidate variables were gender, age, race, baseline ALT, baseline liver metastases, prior anti-cancer therapy, baseline paracetamol use, baseline performance status and tumour type.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1400
Summary of Logistic Regression Analysis of Variables Associated with Subjects whose first ALT Elevation is >5xULN

N/n [1]	Covariate	Odds Ratio	95% CI	p-value
2080/1926	Age group: < 60 vs. >= 60	0.61	(0.45, 0.84)	.0024
	Baseline ALT: <= ULN vs. > ULN	0.6	(0.36, 0.99)	.0476
	Prior anti-cancer therapy: No vs. Yes	1.45	(1.06, 1.98)	.0188

[1] N/n: Population/Subjects with data available for all covariates.
Note: Candidate variables were gender, age, race, baseline ALT, baseline liver metastases, prior anti-cancer therapy, baseline paracetamol use, baseline performance status and tumour type.

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1500
Summary of Logistic Regression Analysis of Variables Associated with Subjects whose first ALT Elevation is >8xULN

N/n [1]	Covariate	Odds Ratio	95% CI	p-value
2080/1926	Age group: < 60 vs. >= 60	0.56	(0.37, 0.85)	.0072

[1] N/n: Population/Subjects with data available for all covariates.
Note: Candidate variables were gender, age, race, baseline ALT, baseline liver metastases, prior anti-cancer therapy, baseline paracetamol use, baseline performance status and tumour type.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1600
Incidence of ALT Elevations >3xULN in Week 1 for Subjects in Studies with Week 1 Lab Assessments
(VEG102616, VEG105192, VEG107769, VEG20002 and VEG110727)

	RCC (N=1149)	Sarcoma (N=382)	Total (N=1531)
n [1]	595 (52%)	382 (100%)	977 (64%)
Number of events in week 1 (days 1-10)	2 (<1%)	5 (1%)	7 (<1%)

[1] Number of subjects who had a week 1 assessment.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1700
Incidence of ALT Elevations >3xULN in Week 2 for Subjects in Studies with Week 2 Lab Assessments
(VEG108844 and VEG113078)

	RCC (N=1149)
n [1]	526 (46%)
Number of events occurred in week 2 (days 11-17)	5 (<1%)

[1] Number of subjects who had a week 2 assessment.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR

Population: All Subjects Treated by Pazopanib

Table 8.1800
Summary of the First ALT Elevation > 3xULN

Laboratory Criteria [1]	All Subjects (N=2080)
n	2045
Peak ALT >3xULN	408 (20%)
Peak ALT >3-5xULN	174 (9%)
Peak ALT >5-8xULN	99 (5%)
Peak ALT >8-20xULN	107 (5%)
Peak ALT >20xULN	28 (1%)
Peak ALT >3xULN and baseline ALT <=2.5xULN/missing	408 (20%)
n [2]	2045
Concurrent ALT>3xULN and Total Bili >=2xULN and Direct Bili <= 35%	7 (<1%)
Concurrent ALT>3xULN and Total Bili >=2xULN and Direct Bili > 35%	9 (<1%)
Concurrent ALT>3xULN and Total Bili >=2xULN and Direct Bili missing	20 (<1%)

[1] Subjects may be counted in more than one category of 'Laboratory Criteria'.
[2] Bilirubin value can occur up to 28 days on or after ALT value.
Note: The peak elevation for each subject is defined as the highest lab parameter/ULN within the first elevation i.e. the highest ALT/ULN between the date of elevation and the date of recovery.
Note: n is the number of subjects with at least one post baseline non-missing ALT value.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.1900
Time from First Dose of Pazopanib to Onset of First ALT Elevation >3xULN (Days)

	First Elevation Series				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
n	174	99	107	28	408
Mean	83.9	58.3	49.9	42.8	65.9
SD	130.05	76.87	70.37	37.97	101.26
Median	44.5	40.0	29.0	29.0	42.0
Min.	4	7	12	15	4
Max.	924	501	536	170	924
Q1	32	29	28	24	29
Q3	69	50	43	43	57
IQR	37	21	15	19	28
5th Percentile	20	20	20	15	20
10th Percentile	26	22	22	17	22
90th Percentile	128	124	74	118	114
95th Percentile	250	179	113	144	182

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2000
Shift Table of ALT Category at Onset and Peak for the First ALT Elevation >3xULN

		First Elevation Series				
Onset ALT for First Elevation	n	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
ALT >3-5xULN	219	174 (79%)	23 (11%)	21 (10%)	1 (<1%)	219 (100%)
ALT >5-8xULN	91		76 (84%)	13 (14%)	2 (2%)	91 (100%)
ALT >8-20xULN	78			73 (94%)	5 (6%)	78 (100%)
ALT >20xULN	20				20 (100%)	20 (100%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2100
Time from the Last Dose of Pazopanib to Onset of the First ALT Elevation >3xULN (days)

	First Elevation Series				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
n	174	99	107	28	408
Still on drug at onset	145 (83%)	82 (83%)	73 (68%)	19 (68%)	319 (78%)
1-3 days prior to onset	11 (6%)	11 (11%)	19 (18%)	9 (32%)	50 (12%)
4-7 days prior to onset	6 (3%)	3 (3%)	5 (5%)	0	14 (3%)
8-14 days prior to onset	5 (3%)	2 (2%)	6 (6%)	0	13 (3%)
15-28 days prior to onset	6 (3%)	1 (1%)	4 (4%)	0	11 (3%)
>28 days prior to onset	1 (<1%)	0	0	0	1 (<1%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2200
Summary of Outcome of the First ALT Elevation >3xULN

	First Elevation Series				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
n	174	99	107	28	408
Recovered [1][2]	159 (91%)	89 (90%)	92 (86%)	15 (54%)	355 (87%)
Adaptation[3]	62 (36%)	27 (27%)	7 (7%)	0	96 (24%)
Recovered without Dose Interruption and not meeting definition of adaptation	22 (13%)	4 (4%)	5 (5%)	0	31 (8%)
Rechallenge	33 (19%)	28 (28%)	36 (34%)	6 (21%)	103 (25%)
Recovered with Dose Interruption and not meeting definition of rechallenge	31 (18%)	22 (22%)	25 (23%)	3 (11%)	81 (20%)
Elevation after treatment discontinuation	11 (6%)	8 (8%)	19 (18%)	6 (21%)	44 (11%)
Not recovered[4]	7 (4%)	7 (7%)	8 (7%)	8 (29%)	30 (7%)
No Follow-up[5]	8 (5%)	3 (3%)	7 (7%)	5 (18%)	23 (6%)

[1]Denom. for pct. is the number of subj. with an ALT elev. >3xULN within the peak ALT cat. [2] Recovery definition: ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study trt disc. with no further data available. Recovery includes rechallenge cases where dose was interrupted after an ALT>3xULN event, then ALT returned to 2.5xULN or below (only one test is required) before treatment restarted. [3] Adaptation definition: ALT > 3xULN followed by baseline grade or below (and must be <=2.5xULN) without any dose interruption between the ALT elevation and normalisation.
[4] Not recovered definition: at least one ALT result following the onset of the ALT elevation >3xULN but not meeting the definition for recovery.
[5] No follow-up is defined as no ALT results available following the onset of the ALT elevation >3xULN.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2200
Summary of Outcome of the First ALT Elevation >3xULN

	First Elevation Series				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
Time from Dose Interruption to Recovery for rechallenge subjects (days)					
n	33	28	36	6	103
Mean	11.4	18.9	23.5	27.3	18.6
SD	7.40	9.43	8.84	8.04	10.02
Median	10.0	16.5	22.0	24.5	18.0
Min.	2	5	7	20	2
Max.	35	49	45	38	49
Q1	6	14	17	21	12
Q3	15	24	29	36	26
IQR	9	10	13	15	14
5th Percentile	3	6	12	20	5
10th Percentile	3	7	13	20	6
90th Percentile	19	29	36	38	34
95th Percentile	28	34	42	38	36

[1]Denom. for pct. is the number of subj. with an ALT elev. >3xULN within the peak ALT cat. [2] Recovery definition: ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study trt disc. with no further data available. Recovery includes rechallenge cases where dose was interrupted after an ALT>3xULN event, then ALT returned to 2.5xULN or below (only one test is required) before treatment restarted. [3] Adaptation definition: ALT > 3xULN followed by baseline grade or below (and must be <=2.5xULN) without any dose interruption between the ALT elevation and normalisation.
[4] Not recovered definition: at least one ALT result following the onset of the ALT elevation >3xULN but not meeting the definition for recovery.
[5] No follow-up is defined as no ALT results available following the onset of the ALT elevation >3xULN.

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2300
Summary of Time from Onset of the First ALT Elevation >3xULN to Recovery or Adaptation (days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
n with ALT >3xULN	159	89	92	15	355
All Recovered					
n	159	89	92	15	355
Mean	49.9	53.6	38.6	32.1	47.1
SD	51.07	49.76	30.83	16.19	45.57
Median	30.0	34.0	29.0	28.0	30.0
Min.	4	5	8	19	4
Max.	288	263	201	85	288
Q1	15	22	22	22	21
Q3	64	69	43	36	57
IQR	49	47	21	14	36
5th Percentile	7	8	14	19	8
10th Percentile	8	15	15	21	11
90th Percentile	116	131	64	43	112
95th Percentile	168	169	113	85	155

Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2300
Summary of Time from Onset of the First ALT Elevation >3xULN to Recovery or Adaptation (days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
Recovered with Dose Interruption					
n	64	50	61	9	184
Mean	34.6	47.0	39.5	27.9	39.3
SD	38.40	52.97	32.57	9.01	40.51
Median	22.0	29.0	30.0	22.0	29.0
Min.	4	5	8	19	4
Max.	191	263	201	43	263
Q1	10	18	22	22	18
Q3	43	53	43	36	43
IQR	34	35	21	14	26
5th Percentile	7	8	13	19	8
10th Percentile	7	14	15	19	9
90th Percentile	77	103	58	43	72
95th Percentile	102	196	102	43	136

Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2300
Summary of Time from Onset of the First ALT Elevation >3xULN to Recovery or Adaptation (days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
Recovered without Dose Interruption					
n	84	31	12		127
Mean	65.2	72.3	58.2		66.3
SD	56.72	43.58	33.22		51.81
Median	43.0	64.0	50.0		45.0
Min.	8	19	14		8
Max.	288	187	115		288
Q1	29	43	36		29
Q3	86	85	80		85
IQR	57	42	44		56
5th Percentile	9	22	14		14
10th Percentile	15	28	20		19
90th Percentile	155	134	113		141
95th Percentile	181	169	115		169

Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2300
Summary of Time from Onset of the First ALT Elevation >3xULN to Recovery or Adaptation (days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
Adaptation					
n	62	27	7		96
Mean	77.3	75.1	70.1		76.1
SD	60.31	45.75	36.89		54.75
Median	55.5	64.0	75.0		57.0
Min.	8	19	20		8
Max.	288	187	115		288
Q1	29	43	41		32
Q3	113	85	113		113
IQR	84	42	72		81
5th Percentile	21	22	20		20
10th Percentile	23	22	20		22
90th Percentile	168	156	115		156
95th Percentile	188	169	115		187

Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2300
Summary of Time from Onset of the First ALT Elevation >3xULN to Recovery or Adaptation (days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
Elevation after treatment discontinuation					
n	11	8	19	6	44
Mean	21.7	22.5	23.2	38.3	24.8
SD	29.69	19.63	9.27	22.92	19.87
Median	10.0	18.0	22.0	29.0	21.5
Min.	5	8	14	27	5
Max.	106	69	47	85	106
Q1	6	12	15	28	15
Q3	22	22	27	32	28
IQR	16	11	12	4	13
5th Percentile	5	8	14	27	6
10th Percentile	5	8	14	27	8
90th Percentile	39	69	43	85	43
95th Percentile	106	69	47	85	69

Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2400
Duration of Treatment after Recovery for Subjects who Recover from their First ALT Elevation >3xULN
(days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
n with ALT >3xULN	134	71	57	7	269
All Recovered					
n	134	71	57	7	269
Mean	305.8	309.5	217.1	121.3	283.2
SD	260.68	282.69	259.52	159.38	267.00
Median	236.5	237.0	110.0	22.0	195.0
Min.	1	8	2	6	1
Max.	1019	1067	924	385	1067
Q1	98	69	14	15	63
Q3	465	403	338	312	420
IQR	367	334	324	297	357
5th Percentile	22	13	4	6	8
10th Percentile	39	25	6	6	15
90th Percentile	727	781	673	385	702
95th Percentile	867	900	702	385	867

Note: This is the duration of treatment from the time of recovery.
Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2400
Duration of Treatment after Recovery for Subjects who Recover from their First ALT Elevation >3xULN
(days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
Recovered with Dose Interruption					
n	52	43	45	7	147
Mean	327.2	296.4	196.1	121.3	268.3
SD	270.84	310.37	237.10	159.38	274.65
Median	261.5	198.0	89.0	22.0	186.0
Min.	4	8	2	6	2
Max.	1019	1067	702	385	1067
Q1	98	39	10	15	38
Q3	501	403	254	312	420
IQR	403	364	244	297	382
5th Percentile	28	13	4	6	6
10th Percentile	37	15	6	6	9
90th Percentile	705	820	661	385	688
95th Percentile	895	952	688	385	879

Note: This is the duration of treatment from the time of recovery.
Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2400
Duration of Treatment after Recovery for Subjects who Recover from their First ALT Elevation >3xULN
(days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
Recovered without Dose Interruption					
n	82	28	12		122
Mean	292.2	329.8	295.9		301.2
SD	254.78	238.01	330.79		257.46
Median	192.5	250.5	118.5		218.5
Min.	1	13	14		1
Max.	943	900	924		943
Q1	98	183	63		103
Q3	433	425	490		459
IQR	335	242	427		356
5th Percentile	21	60	14		21
10th Percentile	43	69	30		45
90th Percentile	727	781	900		760
95th Percentile	836	790	924		843

Note: This is the duration of treatment from the time of recovery.
Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2400
Duration of Treatment after Recovery for Subjects who Recover from their First ALT Elevation >3xULN
(days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
Adaptation					
n	61	24	7		92
Mean	298.8	334.3	397.6		315.6
SD	262.05	226.91	386.44		262.56
Median	192.0	260.0	259.0		240.5
Min.	1	60	14		1
Max.	943	900	924		943
Q1	110	186	57		122
Q3	433	425	900		463
IQR	323	239	843		342
5th Percentile	21	69	14		21
10th Percentile	45	91	14		57
90th Percentile	812	690	924		812
95th Percentile	843	781	924		900

Note: This is the duration of treatment from the time of recovery.
Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2400
Duration of Treatment after Recovery for Subjects who Recover from their First ALT Elevation >3xULN
(days)

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT >20xULN	Total ALT >3xULN
Elevation after treatment discontinuation					
n	0	0	0	0	0
Mean					
SD					
Median					
Min.					
Max.					
Q1					
Q3					
IQR					
5th Percentile					
10th Percentile					
90th Percentile					
95th Percentile					

Note: This is the duration of treatment from the time of recovery.
Note: Recovery is defined as an ALT staying at 2.5xULN or below for two consecutive visits or dropping to 2.5xULN or below once after study treatment discontinuation with no further data available.
Note: Adaptation 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. Adaptation is a subgroup of recovered without dose interruption.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2500
Summary of Re-Challenges for Subjects who Recovered from their First ALT Elevation >3xULN

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT 20xULN	Total ALT >3xULN
Re-Challenge [1]					
n	33	28	36	6	103
Dose reduction	24 (73%)	20 (71%)	33 (92%)	6 (100%)	83 (81%)
No dose reduction	9 (27%)	8 (29%)	3 (8%)	0	20 (19%)
Post Re-Challenge [1]					
n	33	28	36	6	103
ALT > 3xULN Not Recurred	23 (70%)	19 (68%)	16 (44%)	4 (67%)	62 (60%)
ALT > 3xULN Recurred	10 (30%)	9 (32%)	18 (50%)	2 (33%)	39 (38%)
No Follow-up [2]	0	0	2 (6%)	0	2 (2%)
Post Re-Challenge ALT >3xULN Recurred					
n	10	9	18	2	39
ALT > 3-5xULN Recurred	8 (80%)	5 (56%)	4 (22%)	0	17 (44%)
ALT > 5-8xULN Recurred	2 (20%)	2 (22%)	10 (56%)	0	14 (36%)
ALT > 8-20xULN Recurred	0	2 (22%)	4 (22%)	2 (100%)	8 (21%)
ALT > 20xULN Recurred	0	0	0	0	0

[1] Re-challenge is defined as an ALT > 3xULN, which recovered to grade 1 or below following interruption and subsequently receiving study drug.
[2] No follow-up is defined as no ALT results available following the onset of the ALT elevation > 3xULN.
[3] Time from re-challenge to recurrence of ALT > 3xULN.

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2500
Summary of Re-Challenges for Subjects who Recovered from their First ALT Elevation >3xULN

	Peak ALT for First Elevation				
	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT 20xULN	Total ALT >3xULN
Time to Recurrence [3]					
n with ALT >3xULN Recurred	10	9	18	2	39
Mean	61.6	55.3	9.3	11.5	33.4
SD	69.75	111.84	4.79	4.95	66.49
Median	45.5	15.0	8.0	11.5	9.0
Min.	8	5	4	8	4
Max.	248	352	23	15	352
Q1	25	8	7	8	8
Q3	63	33	9	15	33
IQR	38	25	2	7	25
5th Percentile	8	5	4	8	5
10th Percentile	8	5	6	8	6
90th Percentile	168	352	20	15	63
95th Percentile	248	352	23	15	248

[1] Re-challenge is defined as an ALT > 3xULN, which recovered to grade 1 or below following interruption and subsequently receiving study drug.
[2] No follow-up is defined as no ALT results available following the onset of the ALT elevation > 3xULN.
[3] Time from re-challenge to recurrence of ALT > 3xULN.

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2600
Summary of Baseline Characteristics and Characteristics of the first ALT Elevation >3xULN for Subjects who are Re-challenged

		No Recurrent Elevation (N=64)	Recurrent Elevation (N=39)
Age (yrs)	n	64	39
	Mean	59.1	62.8
	SD	10.85	9.42
	Median	59.5	64.0
	Min.	37	36
	Max.	82	82
Sex	n	64	39
	Female	29 (45%)	20 (51%)
	Male	35 (55%)	19 (49%)
Race	n	61	38
	Asian - Central/South Asian Heritage	0	1 (3%)
	Asian - East Asian Heritage	15 (25%)	6 (16%)
	Asian - Japanese Heritage	3 (5%)	3 (8%)
	Native Hawaiian or Other Pacific Islander	1 (2%)	0
	White - Arabic/North African Heritage	2 (3%)	1 (3%)
	White - White/Caucasian/European Heritage	40 (66%)	27 (71%)
Peak category of first ALT elevation	n	64	39
	ALT >3-5xULN	23 (36%)	10 (26%)
	ALT >5-8xULN	19 (30%)	9 (23%)
	ALT >8-20xULN	18 (28%)	18 (46%)
	ALT >20xULN	4 (6%)	2 (5%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2600
Summary of Baseline Characteristics and Characteristics of the first ALT Elevation >3xULN for Subjects who are Re-challenged

		No Recurrent Elevation (N=64)	Recurrent Elevation (N=39)
Time to first elevation (days)	n	64	39
	Mean	55.5	48.3
	SD	73.28	36.92
	Median	42.0	43.0
	Min.	4	15
	Max.	501	225
Time to recovery from the first elevation (days)	n	64	39
	Mean	23.3	30.1
	SD	25.54	28.91
	Median	19.5	22.0
	Min.	5	4
	Max.	203	152

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2700
Summary of Correlation between the first ALT Elevation >3xULN and Hypertension during the first 12 weeks of the Study

	No Hypertension	Hypertension
n	1195	885
No ALT elevation	964 (81%)	708 (80%)
ALT elevation	231 (19%)	177 (20%)
Pearson Chi-Square p-value		0.704
Phi Coefficient		0.008

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.2800
Summary of Correlation between the first ALT Elevation >3xULN and Paracetamol Use during the first 12 weeks of the Study

	No Paracetamol Use	Paracetamol Use
n	1522	558
No ALT elevation	1206 (79%)	466 (84%)
ALT elevation	316 (21%)	92 (16%)
Pearson Chi-Square p-value		0.030
Phi Coefficient		-0.048

[redacted]

Protocol: VEG_INT_RCCSTSOVAR

Population: All Subjects Treated by Pazopanib

Table 8.2900
Summary of Adverse Events during weeks 2 to 12 of the Study

	No ALT Elevation during weeks 2 to 12 (N=1728)		ALT Elevation during weeks 2 to 12 (N=352)	
n	1728		352	
Abdominal pain	85	(5%)	24	(7%)
Abdominal pain upper	66	(4%)	19	(5%)
Decreased appetite/Anorexia	185	(11%)	55	(16%)
Jaundice	3	(<1%)	3	(<1%)
Nausea	274	(16%)	67	(19%)
Pyrexia	34	(2%)	13	(4%)
Rash/Pruritis	142	(8%)	40	(11%)
Vomiting	193	(11%)	47	(13%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR

Population: All Subjects Treated by Pazopanib

Table 8.3000
Summary of Concurrent Adverse Events

	Peak ALT for First Elevation								Total ALT	
	Peak ALT >3-<=5xULN		Peak ALT >5-<=8xULN		Peak ALT >8-<=20xULN		Peak ALT >20xULN		>3xULN	
n with ALT >3xULN	174		99		107		28		408	
Abdominal pain	7	(4%)	5	(5%)	5	(5%)	1	(4%)	18	(4%)
Abdominal pain upper	11	(6%)	2	(2%)	1	(<1%)	2	(7%)	16	(4%)
Decreased appetite/Anorexia	18	(10%)	9	(9%)	12	(11%)	4	(14%)	43	(11%)
Jaundice	1	(<1%)	1	(1%)	1	(<1%)	0		3	(<1%)
Nausea	25	(14%)	15	(15%)	11	(10%)	4	(14%)	55	(13%)
Pyrexia	4	(2%)	1	(1%)	4	(4%)	3	(11%)	12	(3%)
Rash/Pruritis	11	(6%)	8	(8%)	9	(8%)	1	(4%)	29	(7%)
Vomiting	20	(11%)	10	(10%)	8	(7%)	4	(14%)	42	(10%)

Note: Concurrent is defined as an AE occurring from one week prior to 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.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.3100
Characterisation of the Pattern of Liver Laboratory Abnormalities

	Peak ALT for First Elevation				
	Peak ALT >3-<=5xULN	Peak ALT >5-<=8xULN	Peak ALT >8-<=20xULN	Peak ALT >20xULN	Total ALT >3xULN
n with peak ALT >3xULN	174	99	107	28	408
Cholestasis (Ratio <=2xULN)	26 (15%)	6 (6%)	5 (5%)	1 (4%)	38 (9%)
Mixed (Ratio >2-<5xULN)	77 (44%)	25 (25%)	19 (18%)	3 (11%)	124 (30%)
Hepatocellular (Ratio >=5xULN)	71 (41%)	68 (69%)	83 (78%)	24 (86%)	246 (60%)

Note: The ratio is calculated as (ALT/ULN)/(ALP/ULN).
Note: Only the first ALT elevation >3xULN included in this analysis.

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.3200
Summary of Logistic Regression Candidate Variables

		ALT Elevation >3xULN	ALT Elevation >5xULN	ALT Elevation >8xULN
Gender	Male	197/ 979 (20%)	111/ 979 (11%)	68/ 979 (7%)
	Female	211/1101 (19%)	123/1101 (11%)	67/1101 (6%)
Age Group	< 60	180/1126 (16%)	99/1126 (9%)	58/1126 (5%)
	>= 60	228/ 954 (24%)	135/ 954 (14%)	77/ 954 (8%)
Race Group	White	295/1379 (21%)	171/1379 (12%)	101/1379 (7%)
	Asian	96/ 516 (19%)	55/ 516 (11%)	29/ 516 (6%)
	Other	4/ 43 (9%)	2/ 43 (5%)	2/ 43 (5%)
	Missing	13/ 142 (9%)	6/ 142 (4%)	3/ 142 (2%)
Baseline ALT	<=ULN	360/1907 (19%)	207/1907 (11%)	120/1907 (6%)
	>ULN	47/ 167 (28%)	26/ 167 (16%)	14/ 167 (8%)
	Missing	1/ 6 (17%)	1/ 6 (17%)	1/ 6 (17%)
Baseline Liver Metastases	Yes	14/ 91 (15%)	6/ 91 (7%)	2/ 91 (2%)
	No	394/1989 (20%)	228/1989 (11%)	133/1989 (7%)
Prior Anti-Cancer Therapy	Yes	177/1161 (15%)	100/1161 (9%)	53/1161 (5%)
	No	231/ 919 (25%)	134/ 919 (15%)	82/ 919 (9%)
Baseline Paracetamol Use	Yes	22/ 144 (15%)	11/ 144 (8%)	8/ 144 (6%)
	No	386/1936 (20%)	223/1936 (12%)	127/1936 (7%)
Indication	RCC	259/1149 (23%)	153/1149 (13%)	92/1149 (8%)
	STS	55/ 382 (14%)	27/ 382 (7%)	16/ 382 (4%)
	Ovarian	94/ 549 (17%)	54/ 549 (10%)	27/ 549 (5%)
Baseline Performance Status	WHO 0 or ECOG 0 or KPS 100-90	290/1320 (22%)	164/1320 (12%)	94/1320 (7%)
	WHO 1-2 or ECOG 1-2 or KPS < 90	117/ 754 (16%)	69/ 754 (9%)	40/ 754 (5%)
	Unknown	1/ 6 (17%)	1/ 6 (17%)	1/ 6 (17%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 8.3300
Summary of Re-Challenges for Subjects Who Recovered from their First Elevation >3xULN

	Peak ALT >3-5xULN	Peak ALT >5-8xULN	Peak ALT >8-20xULN	Peak ALT 20xULN	Total ALT >3xULN
Post Re-Challenge for Subjects with Dose Reductions [1]					
n	24	20	33	6	83
ALT > 3xULN Not Recurred	16 (48%)	12 (43%)	15 (42%)	4 (67%)	47 (46%)
ALT > 3xULN Recurred	8 (24%)	8 (29%)	16 (44%)	2 (33%)	34 (33%)
No Follow-up [2]	0	0	2 (6%)	0	2 (2%)
Post Re-Challenge for Subjects without Dose Reductions [1]					
n	9	8	3		20
ALT > 3xULN Not Recurred	7 (21%)	7 (25%)	1 (3%)		15 (15%)
ALT > 3xULN Recurred	2 (6%)	1 (4%)	2 (6%)		5 (5%)
Dose at Re-challenge for Subjects with Recurrence					
n	10	9	18	2	39
800mg	1 (3%)	0	1 (3%)	0	2 (2%)
600mg	2 (6%)	3 (11%)	12 (33%)	0	17 (17%)
400mg	5 (15%)	6 (21%)	5 (14%)	2 (33%)	18 (17%)
200mg	2 (6%)	0	0	0	2 (2%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR

Population: All Subjects Treated by Pazopanib

Table 8.3400
Summary of Cumulative Incidence of First ALT Elevation >3xULN

Event	All Subjects (N=2080)
ALT > 3xULN	
n	408
Number of Events Occurred up to 1 week	2 (<1%)
Number of Events Occurred up to 2 weeks	13 (3.2%)
Number of Events Occurred up to 3 weeks	32 (7.8%)
Number of Events Occurred up to 4 weeks	91 (22.3%)
Number of Events Occurred up to 5 weeks	166 (40.7%)
Number of Events Occurred up to 6 weeks	222 (54.4%)
Number of Events Occurred up to 7 weeks	280 (68.6%)
Number of Events Occurred up to 8 weeks	297 (72.8%)
Number of Events Occurred up to 9 weeks	330 (80.9%)
Number of Events Occurred up to 10 weeks	339 (83.1%)
Number of Events Occurred up to 11 weeks	346 (84.8%)
Number of Events Occurred up to 12 weeks	352 (86.3%)
Number of Events Occurred up to 13 weeks	357 (87.5%)
Number of Events Occurred up to 14 weeks	358 (87.7%)
Number of Events Occurred up to 15 weeks	361 (88.5%)
Number of Events Occurred up to 16 weeks	364 (89.2%)
Number of Events Occurred up to 17 weeks	370 (90.7%)
Number of Events Occurred up to 18 weeks	375 (91.9%)
Number of Events Occurred up to 19 weeks	376 (92.2%)
Number of Events Occurred up to 20 weeks	376 (92.2%)
Number of Events Occurred up to 21 weeks	380 (93.1%)
Number of Events Occurred up to 22 weeks	381 (93.4%)
Number of Events Occurred up to 23 weeks	382 (93.6%)
Number of Events Occurred up to 24 weeks	383 (93.9%)
Number of Events Occurred up to 25 weeks	386 (94.6%)
Number of Events Occurred up to 50 weeks	396 (97.1%)
Number of Events Occurred up to 100 weeks	406 (99.5%)

[redacted]

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 28.1300
Listing of Subjects with Concurrent ALT and BILI Elevations

Study Subj.

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Note: BILI elevation can be up to 28 days after the ALT elevation.

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 28.1400
Listing of Exposure for Subjects with ALT>3xULN

Unique subject ID	Start date of dose	End date of dose	Study day of start of dose	Study day of end of dose	Dose
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.					

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 28.1500
Listing of Adverse Events for Subjects with ALT>3xULN

Unique subject ID	MedDRA preferred term dictionary text	Outcome of event	Start date/ End date	Start day/ End day	Maximum grade/ Serious	Action taken/ Relationship to investigation product

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 28.1600
Listing of Liver Function Tests for Subjects with ALT>3xULN

Unique subject ID	Test	SI numeric result in std units	Normal range upper limit	Actual date of collection	Actual study day of collection	/ULN

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Protocol: VEG_INT_RCCSTSOVAR
Population: All Subjects Treated by Pazopanib

Table 28.1700
Listing of Study Treatment Discontinuation for Subjects with ALT>3xULN

Unique subject ID	Date of last dose	Reason IP ended

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Division: Worldwide Development
Retention Category: GRS019
Information Type: Meta-Analysis Plan

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

Compound Number: GW786034

Effective Date: 02-OCT-2013

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

Author:

[redacted]
Principal Statistician — **Date**

Email Approved by: 02-OCT-2013

[redacted]
Director of Statistics and Programming — **Date**

02-OCT-2103

[redacted]
Director of Clinical Development — **Date**

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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, 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 ≥ 5
- Mixed pattern of DILI if R > 2 and < 5
- Cholestatic pattern of DILI if R ≤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. [redacted] and an external medical oncologist Dr. [redacted] 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. [redacted] and [redacted]) 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

Other Data Listings

Page

Listing 28.1000 Listing of the Time of Last Dose of Pazopanib Prior to the onset of the First ALT Elevation >3xULN (All Subjects Treated by Pazopanib Population) 2
Listing 28.1100 Listing of the Characterisation of the Pattern of Liver Laboratory Abnormalities (All Subjects Treated by Pazopanib Population) 5
Listing 28.1200 Listing of Outcome of ALT Elevations (All Subjects Treated by Pazopanib Population) 18
Listing 28.1210 Listing of Outcome of ALT Elevations including Peak ALT within First Elevation (All Subjects Treated by Pazopanib Population) 31

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the ***GSK Clincal Study Register****.*

INVESTIGATOR SIGNATURE PAGE

STUDY TITLE: Meta-Analysis of Liver Chemistry Abnormalities with GW786034 (Pazopanib) Treatment in Advanced/Metastatic Renal Cell Carcinoma, Soft Tissue Sarcoma and Ovarian Cancer

I have read this report and confirm that to the best of my knowledge Study 200276 was carried out as described in this GlaxoSmithKline Report

Name of Investigator: Thomas Powles, MD

Affiliation: Barts Cancer Institute, Queen Mary University of London

London EC1A 7BE, UK [redacted]

Signature of Investigator: _____

Date: 30-7-2014

SPONSOR SIGNATORY SIGNATURE PAGE

STUDY TITLE: Meta-Analysis for Liver Analyses with GW786034 (Pazopanib) Treatment in Advanced/Metastatic Renal Cell Carcinoma, Soft Tissue Sarcoma and Ovarian Cancer

Study: 200276

Development Phase: [II, III,]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted] MD PhD

Title of Sponsor Signatory: Director, Clinical Development

MDC Oncology

Signature: [redacted]

Date: 30 July, 2014