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

Compound Number: GW786034

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Description: This analysis plan describes the integrated safety summaries to support a regulatory post marketing requirement for GW786034 (pazopanib) to examine the safety of dose modification of pazopanib and patient rechallenge with pazopanib following hepatoxicity in subjects with advanced/metastatic renal cell carcinoma and soft tissue sarcoma

Subject: GW786034, Pazopanib, safety, liver dysfunction

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ABBREVIATIONS

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
PMR	Post marketing requirement
RCC	Renal cell carcinoma
STS	Soft tissue sarcoma
SDAP	Summary document analysis plan
ULN	Upper limit of normal

Trademark Information

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1. INTRODUCTION

This analysis plan describes the integrated summaries of safety data to support a regulatory post marketing requirement:

Clinical PMR 1549-1: Examine the safety of dose modification of pazopanib and patient rechallenge with pazopanib following hepatoxicity. This examination should include at least 1500 treated patients and may be derived from ongoing or completed trials, including VEG108844, VEG110727, and VEG110655.

Data from the following studies will be included in this integrated summary:

- VEG102616 (a phase II study in subjects with locally-recurrent or metastatic clear-cell renal cell carcinoma)

- VEG105192 (a randomised, double-blind, placebo-controlled, multi-centre phase III study comparing pazopanib and placebo in patients with locally recurrent or metastatic renal cell carcinoma)

- VEG107769 (an open-label extension study in subjects previously enrolled on protocol VEG105192)

- VEG108844 and VEG113078 (the randomised, open-label, multi-centre phase III studies comparing pazopanib and sunitinib in patients with locally advanced and/or metastatic renal cell carcinoma)

- VEG20002 (a phase II study in subjects with relapsed or refractory soft tissue sarcoma)

- VEG110727 (a randomised, double-blinded, placebo-controlled, multi-centre phase III study comparing pazopanib and placebo in patients with soft tissue sarcoma whose disease has progressed during or following prior therapy)

The existing integrated renal cell carcinoma (RCC) and soft tissue sarcoma (STS) datasets will be used; no new integration will be performed. The analyses will be performed on the integrated RCC and STS data separately and the RCC and STS data will not be integrated together. The following documents describe the existing integrated data:

- SDAP for RCC, GlaxoSmithKline document number 2012N154430_00

- SDAP for STS, GlaxoSmithKline studies VEG20002 and VEG110727

The ‘seven studies’ will refer to VEG102616, VEG105192, VEG107769, VEG108844, VEG113078, VEG20002 and VEG110727 in this analysis plan from this point forward.

2. OBJECTIVE(S) AND ENDPOINT(S)

The primary objective of these analyses described in this document will be to characterise the liver safety profile of pazopanib in subjects with locally recurrent and/or metastatic renal cell carcinoma or advanced or recurrent soft tissue sarcoma.

3. DATA SOURCES/STUDIES INCLUDED

The following phase II and III protocols provide 1500 pazopanib treated subjects and will serve as the basis of the submission:

- VEG102616, a multi-centre phase II study to evaluate safety and efficacy of pazopanib 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 in subjects with locally recurrent or metastatic renal cell carcinoma; double blinded; randomised; pazopanib (800 mg once daily) 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 to assess the safety and efficacy of pazopanib in subjects with advanced RCC who have previously been enrolled in study VEG105192 and have documented disease progression after receiving placebo treatment (N=80). A data cut off of 15th March 2010 will be used for purposes of these analyses.
- VEG108844 in subjects with locally recurrent or metastatic renal cell carcinoma; open-label; randomised; pazopanib (800 mg once daily) 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 to evaluate safety and efficacy of pazopanib 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 in subjects with soft tissue sarcoma whose disease has progressed during or following prior therapy; double blinded; randomized; Pazopanib (800 mg once daily) versus placebo (N=369, pazopanib treated n = 240). A data cut off of 22nd November 2010 will be used for purposes of these analyses.

4. PLANNED ANALYSES

The remainder of this analysis plan will detail analyses of integrated liver safety summaries for the seven 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 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 the seven studies, subjects were treated until disease progression. Subjects may have also withdrawn from study treatment for other reasons prior to disease progression such as unacceptable toxicity. 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.

Liver adaptation and rechallenge datasets will be created for the integrated RCC studies, but the existing sarcoma ones will be used.

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. SAFETY ANALYSES

The all treated population will be used for the analysis of safety data.

9.1. Analyses of Liver Function Tests

Liver toxicity is one of the key aspects of the safety profile for pazopanib. Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided.

Possible Hy's law cases are defined as any elevated ALT>3×ULN, total bilirubin≥2×ULN and ALP<3×ULN/missing. Total bilirubin≥2×ULN can be within 28 days following the ALT elevation. ALP<3xULN/missing means it is satisfied unless all ALPs within the 28-day window are >=3xULN at the time of bilirubin elevation.

A summary of liver re-challenges, adaptations and recovery will be provided. The re-challenge is defined as an ALT elevation, followed by treatment interruption and subsequently an ALT value of Grade 1 or below on or prior to re-starting study treatment, where the ALT elevation means ALT>3xULN during on-therapy window and ≤ 3xULN at baseline. The adaptation is defined as an ALT elevation followed by an ALT assessment returning to baseline grade or below without any dose interruption between the ALT elevation and normalisation. Recovery is defined as ALT Grade 1 or below for 2 consecutive visits or Grade 1 or below for one visit if subject discontinued and no subsequent ALT data are available. Records outside on-therapy window will be included to evaluate recovery.

10. REFERENCES

GlaxoSmithKline Document Number 2012N154430_00 Summary Document Analysis Plan for GW786034 and Renal Cell Carcinoma

GlaxoSmithKline studies VEG20002 and VEG110727, Summary Document Analysis Plan for GW786034 and Soft Tissue Sarcoma

GlaxoSmithKline Document Number UM2005/00099/00 Study ID VEG102616. Reporting and Analysis Plan for VEG102616 - A Phase II Study of Pazopanib Using a Randomised Discontinuation Design in Subjects with Locally Recurrent or Metastatic Clear-Cell Renal Cell Carcinoma.

GlaxoSmithKline Document Number UM2005/00245/00 Study ID VEG105192. Reporting and Analysis Plan for VEG105192 -- A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Pazopanib (GW786034) Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma.

GlaxoSmithKline Document Number UM2008/00178/00 Study ID VEG107769. Reporting and Analysis Plan for Protocol VEG107769 - An open-label extension study to assess the safety and efficacy of pazopanib in subjects with renal cell carcinoma previously enrolled on protocol VEG105192.

GlaxoSmithKline Document Number UM2008/00127/00 Study ID VEG10108844. Reporting and Analysis Plan for VEG108844 and VEG113078 – Randomized, Open-Label Studies to Evaluate the Efficacy and Safety of Pazopanib Compared to Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma

GlaxoSmithKline Document Number YM2009/00009/00 Study ID VEG20002. Reporting and Analysis Plan for VEG20002 - A phase II study of GW786034 in patients with relapsed or refractory soft tissue sarcoma.

GlaxoSmithKline Document Number YM2009/00008/00 Study ID VEG110727. Reporting and Analysis Plan for VEG110727 - A randomized double-blind phase III trial of Pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or following prior therapy.

11. ATTACHMENTS

11.1. List of Trials

VEG102616

VEG105192

VEG107769

VEG108844

VEG113078

VEG20002

VEG110727

11.2. Table of contents for Data Display Specifications

11.2.1. Renal Cell Carcinoma

Number	Title	Population
8.4000	Summary of Hepatobiliary Laboratory Abnormalities	All Treated
8.4100	Summary of Liver Re-Challenges, Adaptations and Recovery	All Treated
28.1000	Listing of Potential Hy's Law Cases	All Treated
28.1100	Listing of Subjects with Re-Challenges	All Treated
28.1200	Listing of Subjects with Adaptation	All Treated

11.2.2. Soft Tissue Sarcoma

Number	Title	Population
8.4000	Summary of Hepatobiliary Laboratory Abnormalities	All Treated
8.4100	Summary of Liver Re-Challenges, Adaptations and Recovery	All Treated
28.1000	Listing of Potential Hy's Law Cases	All Treated
28.1100	Listing of Subjects with Re-Challenges	All Treated
28.1200	Listing of Subjects with Adaptation	All Treated

Note that only one set of shells is presented below, but these will be produced for both the RCC and STS data separately.

11.3. Data Display Specifications

Protocol: VEGRCCSUB/VEGSTSSUB
Population: All RCC/STS Subjects Treated by Pazopanib

Table 8.4000
Summary of Hepatobiliary Laboratory Abnormalities

Laboratory Criteria [1]	All Subjects (N=xxxx)
n	xxx
ALT>3xULN and Total Bili>=2xULN [2]	xx (xx%)
ALT>3xULN, Total Bili>=2xULN and ALP<3xULN/Missing [2]	xx (xx%)
n	xxx
ALT >3xULN and INR >1.5 [4]	xx (xx%)
n	xxx
ALT(/ULN) / ALP (ULN) >= 5 and ALT > 3xULN	xx (xx%)
n	xxx
ALT or AST >3xULN	xx (xx%)
ALT or AST >5xULN	xx (xx%)
ALT or AST >8xULN	xx (xx%)
ALT or AST >20xULN	xx (xx%)
n	xxx
ALT >3xULN	xx (xx%)
ALT >5xULN	xx (xx%)
ALT >8xULN	xx (xx%)
ALT >20xULN	xx (xx%)
ALT >3xULN and ≤3xULN/Missing at Baseline	xx (xx%)

Continued....

[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: n is the number of subjects with at least one post baseline non-missing value for required parameters of the criteria.

Table 8.4000 *(Continued....)*
Summary of Hepatobiliary Laboratory Abnormalities

Laboratory Criteria [1][2]	All Subjects (N=xxxx)
n	xxx
AST >3xULN	xx (xx%)
AST >5xULN	xx (xx%)
AST >8xULN	xx (xx%)
AST >20xULN	xx (xx%)
AST >3xULN and ≤3xULN/Missing at Baseline	xx (xx%)
n	xxx
Total Bili ≥2xULN	xx (xx%)
Total Bili ≥2xULN and <2xULN/Missing at Baseline	xx (xx%)
n	xxx
ALP ≥3xULN	xx (xx%)
ALP ≥3xULN and <3xULN/Missing at Baseline	xx (xx%)

Programming notes

- For [2], identify any ALT>3xULN with ATTYPECD=50 and no drug interruption first, then for each ALT elevation, get all total bilirubin values within 28 days of ALT elevation (from the ALT elevation date to ALT elevation date +28, and it can be outside of the on-therapy window or DIFLG='Y') to see whether there is a total bili.>=2xULN. For ALT(/ULN) / ALP(/ULN) ≥ 5, it is the number of subjects with non-missing ALT and ALP on the same day post baseline. There is no time window for this combination, i.e., they need to meet the criteria on the same day.
- The little 'n' for the first segment should be the number of subjects with non-missing ALT (ATTYPECD=50 and no drug interruption) and non-missing total bili within 28 days of an ALT. It is the number of subjects with non-missing ALT and ALP on the same day with ATTYPECD=50 and no drug interruption for the 2nd segment the 3rd segment.
- Only include baseline records and the records with ATTYPECD=50 and no drug interruption. For the first segment, bilirubin does not have to be on-therapy to meet the criteria as specified in bullet 1.

Protocol: VEGRCCSUB/VEGSTSSUB
Population: All RCC/STS Subjects Treated by Pazopanib

Table 8.4100
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=xxxx)
Re-Challenge [1]	
n	xx
Without Dose Reduction	x (xx%)
With Reduced Dose	x (xx%)
Peak ALT before Re-Challenge [1]	
n	xx
ALT >3xULN and ALT <=5xULN	x (xx%)
ALT >5xULN and ALT <=8xULN	x (xx%)
ALT >8xULN	x (xx%)
Post Re-Challenge [1]	
n	xx
Recurrent Elevation of ALT	x (xx%)
No Recurrent Elevation of ALT	x (xx%)
No Follow-up	x (xx%)

Continued....

Note: ALT elevation is defined as ALT > 3x Upper Limit of Normal (ULN) post baseline, who have ALT<= 3x ULN at baseline.
[1] Re-challenge is defined as an ALT > 3xULN, which recovered to grade 1 or below following interruption and subsequently receiving study drug.
[2] Adaptation is defined as an ALT > 3xULN followed by baseline grade or below without any dose interruption between the ALT elevation and normalisation.
[3] Recovery is defined as an ALT staying at grade 1 or below for two consecutive visits or dropping to grade 1 or below once after study treatment discontinuation with no further data available.

Table 8.4100 (*Continued....)*
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=xxxx)
More Severe Elevation Following Re-Challenge[1]	
n	xx
Yes	x (xx%)
No	x (xx%)
No Follow-up	x (xx%)
Time to Dose Interruption/delay (days)	
n	xx
Mean	xx.x
SD	xx.xx
Median	xx.x
Min.	xx
Max.	xx
Duration of Interruption/delay (days)	
n	xx
Mean	xx.x
SD	xx.xx
Median	xx.x
Min.	xx
Max.	xx
Duration of Re-Treatment (days)	
n	xx
Mean	xx.x
SD	xx.xx
Median	xx.x
Min.	xx
Max.	xx

Continued.....

Table 8.4100 *(Continued....)*
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=xxxx)
Time to Recurrent ALT Elevation Post Re-Challenge (days)[1]	
n	xx
Mean	xx.x
SD	xx.xx
Median	xx.x
Min.	xx
Max.	xx
Adaptation [2]	
n	xx
Without Dose Reduction	x (xx%)
With Dose Reduction	x (xx%)
Time to Adaptation (days) [2]	
n	xx
Mean	xx.x
SD	xx.xx
Median	xx.x
Min.	xx
Max.	xx

Continued....

Table 8.4100 *(Continued....)*
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=xxxx)
Peak ALT before Adaptation [2]	
n	xx
ALT >3xULN and ALT <=5xULN	x (xx%)
ALT >5xULN and ALT <=8xULN	x (xx%)
ALT >8xULN	x (xx%)
Time to First ALT Elevation(days)	
n	xx
Mean	xx.x
SD	xx.xx
median	xx.x
Min.	xx
Max.	xx
Outcome of ALT Elevations	
n	xx
Recovered [3]	x (xx%)
Not Recovered	x (xx%)
No Follow-up	x (xx%)
Outcome following ALT Elevations within 7 Days On or Prior to Study Treatment Discontinuation	
n	xx
Recovered [3]	x (xx%)
Not Recovered	x (xx%)
No Follow-up	x (xx%)

Continued...

Table 8.4100 *(Continued....)*
Summary of Liver Re-Challenges, Adaptations and Recovery

	All Subjects (N=xxxx)
Peak ALT for Subjects with ALT Elevations within 7 Days on or Prior to Study Treatment Discontinuation	
n	xx
ALT >3xULN and ALT <=5xULN	x (xx%)
ALT >5xULN and ALT <=8xULN	x (xx%)
ALT >8xULN	x (xx%)
Time to Recovery [3] Post Dose Interruption prior to Re-Challenge or Discontinuation with ALT Elevations within 7 Days on or Prior to Study Treatment Discontinuation (days)	
n	xx
Mean	xx.x
SD	xx.xx
median	xx.x
Min.	xx
Max.	xx

Programming Notes:

- There are two reference datasets for this table, one is rechallenges and the other one is adaptation.
- For Peak ALT before Re-challenge, use maxmult in the dataset rechallenges.
- For peak ALT before adaptation, get the maximum ALT between atdt and atdt0 first based on the dataset adaptation (atdt=<lbdt<atdt0).
- For time to first ALT elevation: use time from the first dose date to the first date with ALT>3xULN.
- For outcome of ALT elevations: For each ALT elevation, find the first recovery date with ALT at grade 1 or below and to see whether the following ALT is either grade 1 or below or no more ALT tests available for the subject. As long as there is one such ALT elevation that meets the criteria, then the subject should be counted as ‘recovered’. If there is not ALT tests available at all following any of the ALT elevation, then the subject should be counted as ‘No follow-up’, otherwise, the subject will be counted as ‘not recovered’.
- For outcome following ALT elevations within 7 days on or prior to treatment discontinuation: Find the subjects with an ALT>3xULN within 7 days prior to the last dose date (make sure the subject is in the

IPDISC dataset). For the outcome of these subjects, follow the same logic specified in the previous bullet.

- For time to recovery post study treatment interruption prior to re-challenge or discontinuation due to ALT elevations: include re-challenges subjects and subjects who had ALT elevation within 7 days on or prior to treatment discontinuation and recovered. For re-challenge subjects, use t2recov directly. For subjects who had ALT elevation within 7 days on or prior to treatment discontinuation, the time need to be calculated in the display code, which is the time from the day after the last dose date to the first time the subject's ALT is grade 1 or below (only for subjects who are counted in the 'recovered' category.

Protocol: VEGRCCSUB/VEGSTSSUB
Population: All RCC/STS Subjects Treated by Pazopanib

Listing 28.1000
Listing of Potential Hy's Law Cases

Study ID	Centre ID/ Subj.	Age(y)/ Sex/ Race	Planned Relative Time	Date/ Study Day	Lab Test (unit)	--Converted Data-- Value	ULN	Value/ ULN) (xULN	Tox Grade
VEG105192	10001/ 26356	63/ Male/ White	Week 5	08JAN2002/ 35	ALT AST Total Bili Direct Bili ALKP				
			…						
VEG105192	10001/ 36172	50/ Male/ White	Week 3	08JAN2002/ 21	ALT AST Total Bili Direct Bili ALKP				

Note: Potential Hy's law cases are defined as ALT>3xULN, Total Bilirubin>=2xULN and Alkaline Phosphatase<3xULN/missing.

Protocol: VEGRCCSUB/VEGSTSSUB
Population: All RCC/STS Subjects Treated by Pazopanib

Listing 28.1100
Listing of Subjects with Re-Challenges [1]

Study ID	Centre ID / Subj.	Age(y)/ Sex	Elevation onset date/ Study Day	Date of interruption/ Re-treatment onset date	Dose at Elevation/ Dose at re-challenge	Peak ALT before re-treatment	Recurrent post re-challenge/ Duration of re-treatment (day)
VEG105192	10001/ 26356	63/ Male	08JAN2002				
VEG105192	10001/ 36172	50/ Male	08JAN2002				

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

Protocol: VEGRCCSUB/VEGSTSSUB
Population: All RCC/STS Subjects Treated by Pazopanib

Listing 28.1200
Listing of Subjects with Adaptation [1]

Study ID	Centre ID/ Subj.	Age(y)/ Sex	Elevation onset date/ Study day	Adaptation onset date/ Study day	Dose at Elevation	Dose at Adaptation	Peak ALT before Adaptation (/ULN)
VEG105192	10001/ 26356	63/ Male	08JAN2002/ 35	20JAN2002/ 47	800	600	4.5
VEG105192	10001/ 36172	50/ Male	08JAN2002/ 21	18JAN2002/ 31	800	600	3.2

[1] Adaptation is defined as an ALT > 3xULN followed by baseline grade or below without any dose interruption between the ALT elevation and normalisation.