Section A: Clarification on effectiveness data

A1. **Priority request:** With regard to the ongoing head-to-head study of pazopanib versus sunitinib (COMPARZ and sub study VEG113078), please provide an explanation and/or justification on clinical or other grounds the value of the non-inferiority margin (1.22) in treatment effect between pazopanib and sunitinib that would mean that a difference greater than this would be clinically important.	Choosing a margin for the evaluation of treatment s for diseases causing irreversible morbidity can be very difficult to justify, but finding margins to allow the performance of non-inferiority trials is in the public interest. Non-inferiority trials can provide a controlled setting which can yield valuable insights into the relative differences of two agents which have been independently shown to be safe and efficacious. The goal of the VEG10844 study is to provide evidence in support of the use of pazopanib in this renal cell cancer population, given that sunitinib is already an approved option in current use. The choice between pazopanib and sunitinib will be made by physicians on the basis of their comparative safety and efficacy profiles. In this setting GSK has chosen to conduct a trial comparing pazopanib to sunitinib to support pazopanib as an additional TKI for renal cell cancer that may have greater efficacy and/or a different or better toxicity profile for some subjects. The original margin of 1.25 in Study VEG108844 was primarily chosen to demonstrate that the efficacy (as measured by PFS) of pazopanib is not substantially inferior to sunitinib in such a way that would rule out the value of pazopanib as an alternate therapy choice in this setting. This margin was chosen in consultation with external experts in the field of RCC. These experts indicated a willingness to accept an approximate 2-month decrement in the median PFS when evaluating treatments with different toxicity profiles, given the reference point of sunitinib median PFS of ~11 months. The margin of 1.25 meets this criterion with a possible loss of efficacy of 2.2 months as compared to the estimated median PFS of 11 months for sunitinib, when assuming proportional hazards. Also, if in fact the true median PFS for pazopanib is 2 months less than sunitinib for the same population (assuming sunitinib PFS of ~11 months and proportional hazards), there is a very low probability of this study demonstrating a result of non-inferiority.

	Statistically, a good non-inferiority study has the following properties: • There is a low probability of finding a statistical result of non-inferiority if the hazard ratio between the two agents is undesirable. • There is a high probability of finding non-inferiority if the test agent has even a small advantage over the comparator agent. Another measure often used to determine margins of non-inferiority studies is percentage of effect retention. With the margin of 1.25 this study is designed to retain well over 50% of the sunitinib effect relative to interferon-alpha with high confidence when using the conservative "two-sided 95% confidence interval method." Note this effect retention is retention of the effect relative to an active comparator and thus, this is a conservative estimate of the percentage of the total sunitinib effect preserved relative to placebo. With this margin, the study was designed to enrol 876 subjects and to consider at least 631 events, making it one of the largest studies ever conducted in advanced renal cell carcinoma. A study of this size should provide sufficient precision around a comparison between pazopanib and sunitinib to facilitate an evaluation of the relative risk benefit profiles. Overall, the margin of 1.25 appears to be clinically reasonable and one that would allow the study to be a size that can be reasonably conducted. Whether this margin is justified by the difference in safety profiles of pazopanib and sunitinib can only be determined by results of the study. Following the CHMP meeting on January 19th, 2010, GSK was informed of a positive trend vote in favour of conditional approval of the pazopanib MAA for "Advanced Renal Cell Carcinoma". It was also communicated that the post-marketing requirement would consist of an ongoing study comparing pazopanib to sunitinib, the COMPARZ trial, (Study VEG108844) with potentially minor modifications to its non-inferiority margin which at that stage was set at 1.25. On January 24th, 2010, GSK submitted a document outlining the statistical assumptions of the trial, including the non-inferiority margin and the power of the study to exclude clinically important differences in specific safety parameters. GSK justified that, as designed, (80% power to demonstrate non-inferiority in PFS based on a margin of 1.25), VEG108844 should serve to fulfil the specific obligation for conditional approval. The

	margin of 1.25 was chosen in consultation with lead experts in renal cell carcinoma (RCC), and had been agreed by the trial investigators and ethics committees (see appendix A for letter from Professor Motzer). In addition, GSK argued that a change in the upper bound of the non-inferiority confidence interval of 0.03 (from 1.25 to 1.22 as suggested by SAG-O) would result in a substantially larger study and significantly delayed timelines for reporting the final results to physicians, patients, and to the CHMP, while providing a clinically irrelevant gain in information (difference of only 6 days). On January 26, a teleconference was held with the Rapporteurs to discuss the study statistical assumptions. While the Rapporteur agreed with the chosen margin of 1.25, the Co-Rapporteur requested a new margin of 1.22. GSK argued that, for a difference of less than 11 days, such an increase in sample size was unnecessary to characterise the comparable efficacy and safety of pazopanib versus sunitinib, and that the increase in sample size and delay in reporting would be problematic to investigators and ethics committees. The CHMP guidance "Guideline on Choice of the Non-Inferiority Margin" states the following regarding indications where there is more than one treatment available, as is the case of advanced RCC where sunitinib and bevacizumab/interferon are both available: *"If there are already many treatments being used interchangeably for the disease under consideration a possible approach might be to consider the information available from all of them. From this a delta may be constructed which summarises the information known about the relative efficacy of these products, and the new trial can be designed to provide a similar level of knowledge of the relative efficacy of the new product."* This portion of the guidance suggests that one should consider the current information regarding the relative efficacy of sunitinib and bevacizumab/interferon when selecting the margin. There are two published indirect comparisons between these agents for which indirect hazard ratios and confidence intervals have been computed. Mills *et al* [1]estimate the indirect hazard ratio between sunitinib and bevacizumab/interferon as

[1] Mills EJ, Rachlis B, O'Regan C, Thabane L, Perri D: Metastatic renal cell cancer treatments: an indirect meta-analysis. *BMC Cancer* 9, 34-42 (2009)

	0.75 (0.60, 0.93) while Thompson Coon *et al*[2], estimate the hazard ratio between sunitinib and bevacizumab/interferon as 0.796 (0.63, 1.0). If these ratios are inverted to estimate the ratio of bevacizumab/interferon to sunitinib the results are 1.33 (1.08, 1.67) and 1.26 (1.0, 1.59) respectively. These values suggest that ruling out a hazard ratio greater than 1.25 would be sufficient to ensure a similar level of knowledge of the relative efficacy of pazopanib to sunitinib as already exists with sunitinib relative to bevacizumab/interferon. As stated, GSK believes that Study VEG108844, as designed with a non-inferiority margin of 1.25, fulfils the proposed requirement for conditional approval as outlined in the CHMP guidance. VEG108844 is one of the largest studies ever conducted in advanced RCC (N = 876). The choice of the margin employed in this trial was done in consultation with the principal investigator, Dr Robert Motzer. Dr. Motzer is an internationally recognised authority in the field of RCC, and was instrumental in the development of currently licensed targeted therapies for this disease, including sunitinib. GSK felt that a margin of 1.25 would meet the requirements specified in the CHMP guidance document "Guideline on the Choice of the Non-inferiority Margin," and acknowledged the desire of the Co-Rapporteur to provide more precision on the estimate of the efficacy comparison of pazopanib and sunitinib. To address the Co-Rapporteur's concern, GSK proposed a plan to analyse combined data from two ongoing studies of identical design i.e. the studies have the same inclusion/exclusion criteria, disease and safety assessment criteria and schedules. The analysis of the combined data (i.e. integrated data from Study VEG108844 and VEG113078) will provide 80% power based on a margin of 1.22 (i.e. the upper limit of the CI for the PFS HR between pazopanib and sunitinib must be at or below 1.22 to declare non-inferiority). A margin of 1.22 aligns

[2] Thompson Coon JS, Liu Z, Hoyle M, Rogers G, Green C, Moxham T, Welch K, Stein K. Sunitinib and bevacizumab for first-line treatment of metastatic renal cell carcinoma: a systematic review and indirect comparison of clinical effectiveness. *Br J Cancer.* 2009;101:238–243

	with the guidance received from SAG-O, who suggested that such a comparative trial should rule out a difference of 2 months at the median points on the curve. In order to maintain 80% power, with the new margin of 1.22, an additional 163 PFS events for a total of 794 events, and an additional 200 subjects for a total of 1076 subjects are now required. Using the sample size and the margin, it is possible to back-calculate that the required point estimate of the HR for PFS will need to be approximately 1.06 or less in order to declare non-inferiority[3]. This strict non-inferiority margin seeks to ensure that should pazopanib be found to be non-inferior to sunitinib, clinicians and their patients can be confident that the two drugs have very similar efficacy.
A2. **Priority request:** Please provide the median (and interquartile range) follow-up time for treatment-naïve patients randomised to (a) the pazopanib and(b) placebo arms of VEG1015192 for the new clinical cut off date of 15 March 2010.	**Summary of Duration of Follow-Up (Treatment Naive)** Duration of Follow-up (days) n: Placebo (N=78) 78; Pazopanib (N=155) 155 Min.: 27; 21 1st Quartile: 153.0; 259.0 Median: 661.0; 607.0 3rd Quartile: 1120.0; 1088.0 Max.: 1327; 1317

[3] Note these calculations are based on an unadjusted HR, even though the final analysis will be stratified because this is a best estimate given it is not possible to entirely predict how the stratification will impact the results.

A3. **Priority request:** Please provide the interquartile range for the median time to crossover for placebo patients, as this is not available in Table 1.5 of section 1.3.1 (page 10 of the addendum submission).	**Summary of Time to Crossover (Treatment Naive)** Placebo (N=78) Survival (months) n 40 Min. 2 1st Quartile 4.6 Median 8.1 3rd Quartile 13.8 Max. 25
A4. **Priority request:** From Table 1.1 on page 8 of the addendum submission, the section on "Primary reason for early termination from study" which was included in Table 5.10 of the original submission (page 67) is missing. Please confirm that	**Table. Primary reason for early termination from study (up to March 15, 2010)** Placebo (N=78) / Pazopanib (N=155) / Total (N=233) Primary reason for withdrawal Lost to follow-up: 3 (4%) / 8 (5%) / 11 (5%) Protocol Violation: 0 / 0 / 0 Subject decided to withdraw from study: 2 (3%) / 11 (7%) / 13 (6%) Sponsor terminated study: 0 / 0 / 0 Other: 0 / 0 / 0

since the interim analysis there has been no change in the data that would be provided for this section.

A5. **Priority request:** Please provide an explanation for the apparent anomaly between Table 1.2, on page 8 of the addendum, where the mean daily dose of pazopanib is 800mg/day when dose interruptions are included and Table 5.52, on page 118 in the original submission, where the mean daily dose of <800mg/day.

This was a mistake. Median instead of Mean values were provided in Table 1.2 (addendum) and Table 5.52 (original submission). Mean values are provided below:

		Placebo	**Pazopanib**
Daily Dose (mg) - dose interruptions Excluded	Mean	784.3	704.2
	SD	76.07	182.03
Daily Dose (mg) - dose interruptions Included	Mean	778.0	680.6
	SD	102.95	219.22

A6. **Priority request:** With regard to the baseline factors adjusted for in the analysis and listed in the second last paragraph of section 1.4 (iv) on page 15 of the addendum, please provide the following::

a) the interquartile range for the median time since diagnosis for

i) treatment naïve pazopanib patients in VEG105192
ii) treatment naïve placebo patients in VEG105192

	Placebo (N=78)	Pazopanib (N=155)	Total (N=233)
Time Since Diagnosis (months)			
n	71	143	214

a) the interquartile range for the median time since diagnosis for
i) treatment naïve pazopanib patients in VEG105192
ii) treatment naïve placebo patients in VEG105192
iii) patients in VEG107769

b) the proportion of patients with a time since diagnosis of <1 year/≥1 year for
i) treatment naïve pazopanib patients in VEG105192
ii) treatment naïve placebo patients in VEG105192
iii) patients in VEG107769

c) the number of metastatic sites for
i) treatment naïve pazopanib patients in VEG105192
ii) treatment naïve placebo patients in VEG105192
iii) patients in

Min.	1	0	0
1st Quartile	2.7	3.0	3.0
Median	8.5	7.9	7.9
3rd Quartile	27.3	29.2	27.3
Max.	152	176	176

iii) patients in VEG107769

	Placebo (N=40)	Pazopanib (N=1)	Total (N=41)
Time Since Diagnosis (months)			
n	36	1	37
Min.	1	5	1
1st Quartile	4.2	4.6	4.2
Median	13.5	4.6	13.4
3rd Quartile	45.7	4.6	44.9
Max.	152	5	152

b) the proportion of patients with a time since diagnosis of <1 year/≥1 year for

i) treatment naïve pazopanib patients in VEG105192
ii) treatment naïve placebo patients in VEG105192

Time Since Diagnosis	Placebo (N=78)	Pazopanib (N=155)	Total (N=233)
< 1 Year	38 (49%)	81 (52%)	119 (51%)
>= 1 Year	33 (42%)	62 (40%)	95 (41%)

VEG107769

d) the proportion of patients with liver metastases/without liver metastases for
i) treatment naïve pazopanib patients in VEG105192
ii) treatment naïve placebo patients in VEG105192
iii) patients in VEG107769

Missing	7 (9%)	12 (8%)	19 (8%)

iii) patients in VEG107769

Time Since Diagnosis	Placebo (N=40)	Pazopanib (N=1)	Total (N=41)
< 1 Year	16 (40%)	1 (100%)	17 (41%)
>= 1 Year	20 (50%)	0	20 (49%)
Missing	4 (10%)	0	4 (10%)

c) the number of metastatic sites for

i) treatment naïve pazopanib patients in VEG105192
ii) treatment naïve placebo patients in VEG105192

Number of Sites of Disease [1]	Placebo (N=78)	Pazopanib (N=155)	Total (N=233)
0	1 (1%)	0	1 (<1%)
1	13 (17%)	34 (22%)	47 (20%)
2	28 (36%)	42 (27%)	70 (30%)
3-4	31 (40%)	60 (39%)	91 (39%)
>4	5 (6%)	19 (12%)	24 (10%)

iii) patients in VEG107769

Number of Sites of Disease [1]	(N=40)	(N=1)	(N=41)
1	8 (20%)	0	8 (20%)
2	20 (50%)	1 (100%)	21 (51%)
3-4	11 (28%)	0	11 (27%)
>4	1 (3%)	0	1 (2%)

d) the proportion of patients with liver metastases/without liver metastases for

i) treatment naïve pazopanib patients in VEG105192
ii) treatment naïve placebo patients in VEG105192

	Placebo	Pazopanib
Liver	17 (22%)	41 26%)

iii) patients in VEG107769

[1]	Placebo (N=40)	Pazopanib (N=1)	Total (N=41)
Liver	4 (10%)	0	4 (10%)

A7. **Priority request:** Baseline data has not been reported for patients in VEG107769 who were treatment naïve at entry to the parent VEG105192 study, although median overall survival is reported for this group in Table 1.8 (page 17 of the addendum). Please provide baseline data for this group of 41 patients, particularly for

Baseline data for patients in VEG107769 who were treatment naïve at entry (N=41) according to:

a) age (mean, SD and median, IQR and range)

Age (yrs)	
n	41
mean	61.1
SD	11.75
median	64.0
Q1	52.0

the following relevant baseline factors:

a) age (mean, SD and median, IQR and range)
b) gender (number/% male, number/% female)
c) MSKCC risk score (intermediate-poor/favourable)
d) time since diagnosis (median, IQR and range/proportion with time since diagnosis of <1 year/≥1 year)
e) stage of disease at initial diagnosis (stage I or II/stage III or IV)
f) number of metastatic sites
g) presence of liver metastatses (yes/no)
h) ECOG status (0, 1, 2, unknown)

Q3	70.0
Min	25
Max.	80

b) gender (number/% male, number/% female)

Gender	
N	41
Female	8 (20%)
Male	33 (80%)

c) MSKCC risk score (intermediate-poor/favourable)

Motzer Risk Category	
Favourable Risk	17 (41%)
Intermediate risk	20 (49%)
Poor risk	1 (2%)
Unknown	3 (7%)

d) time since diagnosis (median, IQR and range/proportion with time since diagnosis of <1 year/≥1 year)

Time since diagnosis

(days)	
n	37
Min	144
Q1	434.0
Median	777.0
Q3	1675.0
Max.	5362

Time since diagnosis (category)	
< 1yeaar	7 (17%)
>= 1 year	30 (73%)
Missing	4 (10%)

e) stage of disease at initial diagnosis (stage I or II/stage III or IV)

Stage	
I	6 (15%)
II	9 (22%)

III	11 (27%)
IV	15 (37%)

f) number of metastatic sites

Number of metastatic sites category	
0	1 (2%)
1	4 (10%)
2	15 (37%)
3-4	19 (46%)
>4	2 (5%)

g) presence of liver metastases (yes/no)

Liver metastases	
yes	5 (12%)

h) ECOG status (0, 1, 2, unknown)

ECOG Performance Status	
0	14 (34%)

1	22 (54%)
2	5 (12%)

A8. **Priority request:** With regard to Table 1.8 on page 17 of the addendum, please provide interquartile ranges for both median overall survival results in this table.

Summary of Kaplan-Meier Estimates of Overall Survival (First-line Stratum)

	Placebo (N=78)	**Pazopanib** (N=155)
Number of Subjects		
Died (event)	49 (63%)	99 (64%)
Censored, follow-up ended	29 (37%)	56 (36%)
Adjusted Hazard Ratio [1]		
Estimate	1.01	
95% CI	(0.72,1.42)	
Stratified Log-rank P-value [1]	0.525	
Estimate of overall survival (months) [2]		
1st Quartile	6.1	10.8
95% CI	(3.8,9.9)	(7.7,13.3)
Median	23.5	22.9
95% CI	(12.0,34.3)	(17.6,25.4)
3rd Quartile	--	41.0
95% CI	(35.0,--)	(35.9,--)

A9. **Priority request:** Please provide updated versions of Tables 5.17 and 5.19 from the original submission

Table 5.17: OS in VEG105192 – Subjects censored at cross-over (Treatment-naive population, 15 March cut-off)

	Overall study population	**Treatment-naive population**

(pages 73 and 74).

	Pazopanib N=290	Placebo N=145	Pazopanib N=155	Placebo N=78
Subjects died, n (%)	189 (65)	50 (34)	98 (63)	26 (33)
Subjects censored, cross-over to pazopanib	1 (<1)	79 (54)	1 (1)	40 (51)
Kaplan-Meier estimates for OS, median (months)	22.9	20.1	22.9	NC
95% CI	19.9-25.4	15.6-NC	17.6-25.4	9.8-NC
Hazard ratio* (95% CI)	0.89 (0.65-1.23)		1.01 (0.65,1.55)	
Stratified log-rank p-value	p=0.232		p=0.514	

Table 5.19: OS in VEG105192 – Including time-dependent cross-over status as covariate

Variable	Treatment naive population (N= 233)			
	May 23, 2008 Data		March 15, 2010 Data	
	HR (95% CI)	p-value†	HR (95% CI)	p-value†
Univariate analysis				
Pazopanib	0.684 (0.428-1.095)	0.1137	1.075 (0.696-1.661)	0.7446
Time-dependent crossover (Yes / No)	0.698 (0.302-1.613)	0.4008	1.107 (0.623-1.968)	0.7297
Multivariate analysis				
Pazopanib	0.517 (0.319-0.837)	0.0073	0.941 (0.607-1.459)	0.7865

Age (Continuous variable)	0.992 (0.972-1.013)	0.4529	0.991 (0.975-1.008)	0.2909
Gender (Female / Male)	1.607 (1.016-2.542)	0.0428	1.204 (0.832-1.742)	0.326
MSKCC risk score (Intermediate-poor / Favourable)	1.714 (1.041-2.823)	0.0343	1.736 (1.194-2.525)	0.0039
Years since diagnosis (<1 year / ≥1 year)	2.523 (1.471-4.325)	0.0008	1.695 (1.150-2.497)	0.0076
Stage of disease at diagnosis (Stage III or IV / Stage I or II)	1.366 (0.736-2.533)	0.3228	1.210 (0.781-1.873)	0.3931
Presence of liver metastases (Yes / No)	1.195 (0.706-2.023)	0.5080	1.243 (0.817-1.891)	0.3088
No. of metastatic sites (Continuous)	1.443 (1.200-1.735)	0.0001	1.323 (1.154-1.516)	<.0001
Time-dependent crossover (Yes / No)	0.940 (0.396-2.235)	0.889	1.255 (0.703-2.241)	0.442

Please find below a revised Table 17 (original Table 17 was part of the appendix 1 document) that incorporates the estimates from table 5.19 above. It also includes results for the 2010 OS data with censoring on XO only. It should be note that that previous results in table 17 that were labeled "Cox regression with censoring at cross-over" for the March 15, 2010 data were actually the results for censoring on cross-over or receipt of other anti-cancer therapy.

Table 17. Alternative estimates of HR for OS for pazopanib vs. placebo in treatment-naïve patients in VEG105192 based on May 23, 2008 data cut-off and March 15, 2010 data cut-off (Pazopanib: N=155; Placebo: N=78)

Population/Method of estimation	May 23, 2008 Data			March 15, 2010 Data		
	HR	95% CI	P	HR	95% CI	P
Cox regression ITT population						

Unadjusted	0.752	0.491	1.153	0.1909	1.027	0.728	1.447	0.881
Adjusted	0.524	0.336	0.817	0.0043	0.859	0.602	1.223	0.399
Cox regression with censoring at cross-over								
Unadjusted	0.683	0.426	1.093	0.1123	1.051	0.680	1.627	0.8219
Adjusted	0.508	0.312	0.825	0.0062	0.917	0.588	1.428	0.7005
Cox regression with censoring at cross-over or receipt of other anti-cancer therapy								
Unadjusted	--	--	--	--	0.797	0.493	1.289	0.355
Adjusted	--	--	--	--	0.640	0.390	1.049	0.077
Cox regression with cross-over as time-dependent covariate								
Unadjusted	0.684	0.428	1.095	0.1137	1.075	0.696	1.661	0.7446
Adjusted	0.517	0.319	0.837	0.0073	0.941	0.607	1.459	0.7865
IPCW, informative censoring defined as								
Cross-over to pazopanib (placebo patients only)	0.450	0.280	0.721	0.001	0.781	0.407	1.392	0.370
Cross-over to pazopanib or receipt of other anti-cancer therapy (placebo and pazopanib patients)	--	--	--	--	0.642	0.266	1.248	0.160
RPSFT								

	Un-weighted								
	Unadjusted	0.345	0.086	1.276	na	na	na	na	na
	Adjusted	0.206	0.054	0.593	na	0.310	0.073	1.715	0.194
	Weighted	--	--	--	--	0.501	0.136	2.348	0.548

Note: Confidence intervals and p-values for IPCW and RPSFT analyses for March 2010 data are based on bootstrapping

A10. **Priority request:** Please confirm that the updated Table 1.10 in the addendum (page 18) accounted for receipt of other cancer therapy whereas Table 5.18 in the original submission (page 74) did not. There appears to be a discrepancy in the titles of these tables.	Please note that titles for Tables 1.10 (addendum - page 18) and Table 5.18 (original submission – page 74) are correct.
A11. **Priority request:** Please provide 'numbers at risk' tables be provided for Figures 1.3 B and C (page 23 of addendum), as shown for Figure 5.5 in the interim analysis from the original submission (page 76).	Product limit estimates for the RPSFT analyses of OS are attached. Relevant tables with the numbers at risk at each failure/censor time are included in appendix B

A12. **Priority request:** Please provide baseline data for patients with no post-study therapy as discussed in section (iv) of 1.5.2 (page 24 of addendum), for those factors mentioned, i.e.: a. ECOG PS b. number of metastatic sites c. MSKCC risk scores	**Group 1 – Subjects with no post-study therapy regardless (Treatment-naive population, 15 March 2010 cut-off)** Baseline data according to **a. ECOG PS** .

	Placebo (N=29)	Pazopanib (N=117)	Total (N=146)
ECOG Performance Status			
0	7 (24%)	46 (39%)	53 (36%)
1	22 (76%)	71 (61%)	93 (64%)

b. number of metastatic sites

Number of Sites of Disease [1]	Placebo (N=29)	Pazopanib (N=117)	Total (N=146)
0	1 (3%)	0	1 (<1%)
1	3 (10%)	29 (25%)	32 (22%)
2	6 (21%)	30 (26%)	36 (25%)
3-4	15 (52%)	46 (39%)	61 (42%)
>4	4 (14%)	12 (10%)	16 (11%)

c. MSKCC risk scores

MSKCC Risk Category [1]	Placebo (N=29)	Pazopanib (N=117)	Total (N=146)
Favourable Risk	5 (17%)	41 (35%)	46 (32%)
Intermediate Risk	19 (66%)	70 (60%)	89 (61%)
Poor Risk	5 (17%)	2 (2%)	7 (5%)
Unknown	0	4 (3%)	4 (3%)

Group 2 – Subjects with no post-study therapy, excluding subjects still on study therapy (Treatment-naive population, 15 March 2010 cut-off)

Baseline data according to

a. ECOG PS

	Placebo (N=29)	Pazopanib (N=103)	Total (N=132)
ECOG Performance Status			
0	7 (24%)	37 (36%)	44 (33%)
1	22 (76%)	66 (64%)	88 (67%)

b. number of metastatic sites

Number of Sites of Disease	Placebo (N=29)	Pazopanib (N=103)	Total (N=132)
0	1 (3%)	0	1 (<1%)
1	3 (10%)	24 (23%)	27 (20%)
2	6 (21%)	24 (23%)	30 (23%)
3-4	15 (52%)	44 (43%)	59 (45%)
>4	4 (14%)	11 (11%)	15 (11%)

c. MSKCC risk scores

MSKCC Risk Category	Placebo (N=29)	Pazopanib (N=103)	Total (N=132)
Favourable Risk	5 (17%)	34 (33%)	39 (30%)
Intermediate Risk	19 (66%)	64 (62%)	83 (63%)

Poor Risk	5 (17%)	2 (2%)	7 (5%)
Unknown	0	3 (3%)	3 (2%)

Group 3 – Subjects eligible for post-study therapy but chose not to receive (excluding subjects still on pazopanib, died on study medication or withdrew from study (Treatment-naive population, 15 March 2010 cut-off)

Baseline data according to

a. ECOG PS

	Placebo (N=19)	Pazopanib (N=78)	Total (N=97)
ECOG Performance Status			
0	4 (21%)	29 (37%)	33 (34%)
1	15 (79%)	49 (63%)	64 (66%)

b. number of metastatic sites

Number of Sites of Disease	Placebo (N=19)	Pazopanib (N=78)	Total (N=97)
0	1 (5%)	0	1 (1%)
1	2 (11%)	20 (26%)	22 (23%)
2	5 (26%)	19 (24%)	24 (25%)
3-4	9 (47%)	32 (41%)	41 (42%)
>4	2 (11%)	7 (9%)	9 (9%)

c. MSKCC risk scores

MSKCC Risk Category	Placebo	Pazopanib	Total

	(N=19) (N=78) (N=97) --- Favourable Risk 3 (16%) 28 (36%) 31 (32%) Intermediate Risk 14 (74%) 47 (60%) 61 (63%) Poor Risk 2 (11%) 1 (1%) 3 (3%) Unknown 0 2 (3%) 2 (2%)
A13. **Priority request:** Please confirm that the hazard ratios for Pazopanib vs placebo/BSC in Tables 1.19, 1.20, 1.21, 1.22 and 1.23 in the addendum (pages 18 and 19) are also based on scan dates as reported in corresponding Tables 5.37, 5.38, 5.39a, 5.39b and 5.39c of the interim analysis provided in the original manufacturer's submission (pages 101-102).	These are tables showing data for overall survival. Scan dates only come into play with the Progression Free Survival analysis. On this respect, please note that data on PFS was not updated which means that it should be assumed that data around PFS is the same as the data submitted in April 2010.
A14. **Priority request:** With regard to page 8 of the Appendix 1 document provided alongside the addendum – In the IPCW baseline	"Study week" and "study week squared" were calculated for all patients and intervals. "Study week" was defined as the number of weeks elapsed since randomization at the end of each patient-interval. "Study week squared" was calculated as the square of study week. The means and standard deviations (SDs) for "Study week" and "study week squared" for the pazopanib and placebo groups are reported in the table

model, study week is reported as an additional term as being the number of weeks from randomisation. Please provide the following:

a) the endpoint for this measure (and whether this was included for all patients)
b) the means and standard deviations for the pazopanib and placebo groups.

below:

Table. Descriptive statistics on study week and study week squared covariates used in logistic regression predicting informative censoring for OS in VEG105192 trial

	Pazopanib			Placebo		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
At the beginning of cross-over eligibility period						
Study week	113	43.5	37.3	70	29.3	28.5
Study week squared	113	3269	5574	70	1659	2903
At the end of study (i.e., death or censoring)						
Study week	113	74.8	51.3	70	41.9	37.4
Study week squared	113	8203	9761	70	3129	5790
Overall						
Study week	3245	58.2	45.6	882	35.8	34.3
Study week squared	3245	5466	7175	882	2455	4576

It should be noted that the terms “study week” and “study week squared” were included as covariates in the logistic models that were used to calculate the numerator and denominator of the stabilized weights but *<u>were not</u>* included as covariates in the IPCW Cox proportional hazards model that was used to estimate the HR for OS for pazopanib vs. placebo.

A15. **Priority request:** With regard to page 9 of the Appendix 1 document provided alongside the addendum – when the hazard ratio and confidence interval were calculated for the IPCW analysis, please explain why the preferred method of calculating a p-value (described in footnote 1) was not used.	There are a variety of methods to obtain p-values based on the bootstrap. The method that we employed yields p-values that are consistent with the 95% confidence intervals based on the percentiles of the bootstrap distribution. The alternative described in the footnote is "preferred" in the sense that it is derived by re-sampling under the null hypothesis that there are no differences between the groups. Although in practice the two approaches generally yield similar results, the p-values generated under the latter approach may not be consistent with the confidence intervals derived based on the bootstrap percentiles. We used the former because of its consistency with the confidence intervals, and because the latter approach, applied in the context of the IPCW and RPSFT analyses, was practically infeasible given time constraints. Future analyses will examine the robustness of the findings to alternative approaches to bootstrap estimation.
A16. **Priority request:** With regard to pages 26, 29 and 34 of the Appendix 1 document provided alongside the addendum - In the IPCW analysis, time since progression was used as an interaction term with disease progression. Please clarify whether time since progression was also included as a term on its own in the time-	Prior to November 12, 2008, placebo patients were eligible to cross-over to pazopanib only after disease progression. After this date, placebo patients were allowed to cross-over to pazopanib regardless of progression status. It was therefore necessary to include in the logistic model predicting informative censoring for placebo patients all pre-progression patient intervals after November 12, 2008 (along with the post-progression patient intervals (regardless of date). Because the risk of informative censoring might differ pre- and post-progression, it was necessary to include in the logistic model predicting informative censoring for placebo patients a variable to distinguish between these time periods. Also, for those who progressed, risk of informative censoring might vary by time since progression. We therefore included in the logistic model predicting informative censoring for placebo patients a covariate that was set to zero for all pre-progression intervals and equal to one for all post-progression intervals (i.e., "Progression"). We also included in the model a covariate that was equal to zero for all patient-intervals before progression and equal to time since progression for intervals after progression ("Progressed x time since progression"). For

dependent covariate model. If so, what are the descriptive statistics for this variable (equivalent to those shown for other covariates in Tables 3, 6 and 11)?	placebo patients who did not progress prior to death or censoring (informative or otherwise), this latter variable was equal to zero for all intervals. We did not include in the model a variable for "time since progression", as it would not add any information (because time since progression is not meaningful for patients without progression). Because pazopanib patients were not eligible for cross-over, and were eligible to receive other anti-cancer therapy only after progression (even after November 12, 2008), only those patient intervals after progression were included in the logistic model to predict informative censoring for pazopanib patients. A variable for progression status was therefore not required (as it would be equal to one for all patient intervals). For pazopanib patients, the variable labelled "Progressed x time since progression" is equivalent to "time since progression (because the variable "Progressed" is equal to one for all intervals).
Section B: Clarification on cost effectiveness data	
B1. **Priority request:** In Table 2.3 "Summary of economic model base case for sunitinib" the values for PFS and PPS are 11.0 and 15.4 where as the corresponding values in Table 6.28 of the original submission (page 192) were 11.4 and 15.0. Please indicate which of these	It was a mistake. Correct values are: 11.0 and 15.4

values are used in the cost-effective analysis.	
[redacted]	[redacted]
Section C: Textual clarifications and additional points	
C1. In the PAS submission template document on pages 18 and 19 the heading and results on table 4.4 and 4.5 are exactly the same. Cost	It was a mistake (wrong table 4.4 was inserted). Please find correct table below:

effectiveness results without the 12.5% discount are not reported. Please provide these results.

Table 4.4. Incremental base case results

Technology (and comparators)	Total Cost	Total QALY	Incremental cost	Incremental QALY	ICERs vs. baseline	Incremental analysis
BSC (baseline)	4,085	0.987				
IFN	8,379	1.249	4,294	0.262	16,395	16,396
Sunitinib	36,179	1.898	27,799	0.649	35,231	42,832
Pazopanib	40,441	1.966	4,263	0.068	37,126	62,414

QALY, quality adjusted life year; ICERs, incremental cost-effectiveness ratios

NB: An updated report on the crossover analyses undertaken as part of this submission is included as appendix D. Please note that the following changes have been implemented:

1. Version change to 1.2
2. Date changed to August 17, 2010
3. Page numbers added
4. Footnote on page 8 modified.
5. Study week and study week squared added to Table 3
6. “Progressed x time since progression” changed to “Time since progression” in Table 3. Footnote added describing calculation of “Time since progression” and use of this variable in logistic model.
7. Footnote added to Tables 6 and 11 describing calculation of Time Since Progression and use in logistic model

8. Table 17 modified to include results for Cox model with cross-over as time-dependent covariate using 2010 data, and to include separate rows for results with Cox regression with censoring at cross-over, and Cox regression with censoring at cross-over or receipt of other anti-cancer therapy
9. Figure 5 modified to include numbers at risk and confidence bands.
10. Miscellaneous minor editorial and typographical changes and corrections.