pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pazopanib hydrochloride (Votrient) Resubmission for Metastatic Renal Cell Carcinoma

October 23, 2013

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of the review was to evaluate the efficacy and safety of pazopanib on patient outcomes compared to sunitinib in the treatment of patients with advanced or metastatic RCC who have received no prior systemic therapies or who have received prior treatment with cytokines. The scope of the pCODR review included patients with advanced RCC to account for the potential clinical use of pazopanib in this population.

Pazopanib has a Health Canada indication for the treatment of patients with metastatic (clear cell) renal cell carcinoma (RCC) who have received no prior systemic therapies or who have received prior treatment with cytokines for metastatic disease.

Pazopanib is a multi-target tyrosine kinase inhibitor and its targets include VEGF receptor, PDGF receptor, and c-KIT receptor. The recommended dose of pazopanib is 800 mg administered orally once daily.

The present review is a re-submission based on the availability of comparative efficacy data with sunitinib, which was not available at the time of the original review.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The efficacy and safety of pazopanib (800 mg) po daily taken continuously was compared with sunitinib (50 mg) po daily taken cyclically (one cycle = 4 weeks on, 2 weeks off) in two multinational, manufacturer-sponsored randomized controlled trials known as COMPARZ[1] and PISCES.[2]

COMPARZ (n=1110) was an open-label, active-controlled, parallel-group, Phase III randomized trial conducted in 210 centres in 14 countries (including Canada). COMPARZ was designed to test the non-inferiority (NI) of pazopanib compared with sunitinib on progression-free survival (PFS). The upper-bound of the 95% confidence interval (CI) for the between-treatment hazard ratio (HR) was compared against a pre-specified NI margin of 1.25.

Baseline characteristics were well balanced between groups. Patients in COMPARZ had a mean age of 61 years, were mostly male (73.2%), almost 2/3 Caucasian (63.7%) and 1/3 Asian (34.4%). Almost all patients (98.2%) had renal cell carcinoma with either clear cell (92.9%) or predominantly clear cell histology (5.3%). Memorial–Sloan Kettering Cancer Center (MSKCC) risk was 'favorable' or 'intermediate' in about 86% of patients and 80% by Heng risk scoring. About 3/4 of patients had a Karnofsky Performance Scale score of 90 or 100. Most patients (83.2%) had undergone a prior nephrectomy.

PISCES[2] (n=168) was a 22-week double-blind, cross-over trial conducted in 40 centres in 5 European countries. The study randomized the order of treatment administration according to two periods – SP (sunitinib first then pazopanib) or PS (pazopanib first then sunitinib); a two-week wash-out separated the finish of the first treatment from the start of the next treatment. The primary efficacy outcome of PISCES was to determine which drug was preferred by patients through a questionnaire.

Similar to COMPARZ, PISCES patients had a mean age of about 62 years and were mostly male (67.3%). The majority (93.5%) of patients were Caucasian and about 90% had renal

cell carcinoma with clear cell histology; 72.0% of patients had an ECOG score of 0. Like COMPARZ, most patients (88.7%) had previously undergone a nephrectomy.

Efficacy

The primary endpoint was progression free survival. In the ITT analysis, comprised of all randomised subjects,[3] the median PFS in pazopanib and sunitinib treated patients were 8.4 vs. 9.5 months, respectively. This translated into a non-statistically significant hazard ratio (HR) of 1.05 (95% CI, 0.90 to 1.22). In the PP analysis, comprised of all randomised subjects who received at least one dose of study treatment and who comply closely with the study protocol,[3] the median PFS in pazopanib and sunitinib treated patients was 8.4 vs. 10.2 months, respectively. This corresponds to a HR of 1.07 (95% CI, 0.91 to 1.26). Since the upper-bound of the 95% CI in the ITT analysis did not exceed the pre-specified NI margin of 1.25, the non-inferiority hypothesis was confirmed. Non-inferiority was not assessed in the PP analysis, and could not be confirmed, the upper-bound of the 95% confidence interval exceeded 1.25 which was set for the ITT analysis. Ten and eleven percent of patients were excluded from the PP analysis in the pazopanib and sunitinib group, respectively. The majority of patients were excluded from the PP analysis for reasons of the baseline scan being performed outside the 4 week window prior to treatment start and due to the lack of measurable disease.

Health-related quality of life (HRQoL) was a secondary endpoint and assessed through a series of self-reported questionnaires both the COMPARZ study and the PISCES study. The primary endpoint in PISCES was patient preference and was evaluated through the use of a questionnaire.[2] Numerically, the data showed that patients preferred pazopanib over sunitinib treatment in both period 1 and period 2 of treatment. In general, while some of these results favoured pazopanib, and none statistically favoured sunitinib, data were difficult to interpret for a number of reasons, lack of published information on minimal clinically important differences in the setting of RCC, timing of assessments. Also, in the COMPARZ study, the timing of assessments corresponded to the time at which peak treatment-related toxicity may be most likely to occur in sunitinib-treated patients making pazopanib treatment appear more favourable. In the PISCES study, treatment interruptions were not permitted, which does not reflect use of either TKI in clinical practice, where adverse events are often managed through treatment interruptions.

Harms

The most frequent adverse events related to either pazopanib or sunitinib treatments were diarrhoea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes. The adverse event rates for pazopanib, in particular for important side effects such as dyspepsia, mucositis/stomatitis, fatigue, hand-foot syndrome, myelosuppression and altered taste were lower than for sunitinib while pazopanib treated patients experienced significantly more hepatotoxicity.

1.2.2 Additional Evidence

pCODR received input on the pazopanib resubmission for mRCC from one patient advocacy group, Kidney Cancer Canada. Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

No supplemental issues were identified during the development of the review.

1.2.3 Interpretation and Guidance

Need and Burden of Illness

Kidney cancer accounts for approximately 3% of malignant diseases in Canada with approximately 90-95% being renal cell carcinomas (RCC). An estimated 5600 new cases (all stages) will be diagnosed in 2012 with approximately 1700 deaths reported highlighting the unfavourable prognosis of this disease and the need for effective therapy.[4] The estimated 5 year survival across all stages is 67% but the prognosis for patients with metastatic disease remains dismal and only very few survive longer than five years. Surgery remains the only curative treatment option and metastatic patients are generally considered incurable.

Targeted agents such as the small molecule tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib), the mTOR inhibitors (everolimus and temsirolimus) and the monoclonal antibody bevacizumab have evolved as the new standard therapies for the treatment of metastatic kidney cancer.[5-12] Although sunitinib is considered standard first-line therapy in Canada, none of the currently available systemic treatment options for metastatic disease however (including targeted therapy, immunotherapy (cytokines) or conventional chemotherapy) is considered curative and all of these therapies are associated with various degrees of side effects. Thus, there remains a need for novel therapies in the treatment of metastatic RCC, which have increased efficacy or have an improved toxicity profile.

Effectiveness

The study achieved non-inferiority in the primary endpoint PFS based on the ITT analysis. When results from both the ITT and PP analyses are not consistent, one cannot conclude non-inferiority with certainty. As non-inferiority in the PP analysis could not be concluded, this lack of demonstrated concordance between the results of the ITT and PP analyses casts some uncertainty around the non-inferiority of pazopanib to sunitinib. Upon review of feedback provided by the manufacturer, it is acknowledged that a body of evidence supports the use of the ITT population in non-inferiority trials. However, a body of literature supports that the PP analysis is the more conservative analysis set, with confirmatory results in the ITT analysis.[13-15] Ideally both ITT and PP should be considered and be positive for greatest certainty. The requirement for demonstrating non-inferiority for both ITT and PP, does not necessarily guarantee the validity of a non-inferiority conclusion and it is important to assess the reasons for the exclusion of patients.[16] The majority of patients were excluded from the PP analysis for reasons of the baseline scan being performed outside the 4 week window prior to treatment start and due to the lack of measurable disease and were equally distributed between the 2 treatment groups. Thus, it is unlikely that these exclusions would have biased the trial towards noninferiority. The decrease in power for PP due to withdrawals (10% and 11% in pazopanib and sunitinib, respectively) may have impacted results and power may not have been sufficient to prove noninferiority in the PP analysis.

Quality of life analysis also favoured pazopanib and showed advantages for pazopanib, which appear clinically relevant. It is important to note that the quality of life questionnaires used in COMPARZ were not available to assess their validity at the time of this review and hence have to be interpreted with caution. This is also corroborated by the PISCES study, which was a randomized patient preference study. Despite a number of methodological issues such as the lack of published information on minimal clinically important differences in the setting of RCC, the study also suggested a patient preference for pazopanib.

Safety

Pazopanib was well tolerated with an overall low incidence of grade 3 and 4 toxicity. The most frequent adverse events related to pazopanib treatment were diarrhea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes and these were manageable in the majority of patients. COMPARZ demonstrated a lower incidence of certain toxicities, such as hand-foot syndrome, with pazopanib as compared to sunitinib.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to pazopanib in the treatment of advanced and metastatic RCC based on the previous pCODR assessment of the randomized controlled trial, Study VEG105192,[17] and based on the two studies included in the systematic review, COMPARZ and PISCES. VEG105192 demonstrated a clinically and statistically significant benefit in progression-free survival for pazopanib compared with placebo, while COMPARZ and PISCES demonstrated noninferiority of pazopanib to sunitinib based on ITT analysis as well as important differences in clinically meaningful side effects.

In making this conclusion, the Clinical Guidance Panel also considered that:

- The original pCODR review of pazopanib,[17] based on Study VEG105192 found that there was a clinically and statistically significant benefit in progression-free survival for pazopanib compared with placebo.
- COMPARZ supports the use of pazopanib in patients with clear cell histology or clear cell component and good performance status (ECOG 0 and 1).
- While significant advances have been achieved in recent years in the treatment of metastatic kidney cancer, it remains an incurable disease. Approximately one quarter of patients with RCC present with metastases at diagnosis and at least one half of all patients will eventually develop advanced disease.
- Limited treatment options exist for patients with metastatic RCC. Sunitinib has been the only drug approved and funded in most provinces for patients with good performance status and/or good or intermediate risk disease. While sunitinib, the current standard first-line option in Canada for the vast majority of patients, is an effective therapy, it is also associated with a number of substantial side effects, including hypertension, fatigue, diarrhoea and hand-foot syndrome, all of which can greatly impact a patient's quality of life, optimal administration of therapy and subsequent outcomes.
- Pazopanib was well tolerated with an overall low incidence of grade 3 and 4 toxicity. The most frequent adverse events related to pazopanib treatment were diarrhea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes and these were manageable in the majority of patients. COMPARZ demonstrated a lower incidence of certain toxicities, such as hand-foot syndrome, with pazopanib as compared to sunitinib.
- Pazopanib is a clinically useful treatment option for patients with advanced or metastatic disease because it has a more favourable toxicity profile in certain clinically meaningful side effects compared with other tyrosine kinase inhibitors such as sunitinib or sorafenib and, demonstrates noninferior efficacy by ITT analysis.
- Oncologists should have the option to choose between pazopanib and sunitinib in order to allow optimal treatment of patients with a maximum treatment effect. Toxicity interfering with delivery of either drug should not be considered failure to VEGF TKI and an opportunity to switch to the other drug should be allowed as long as there is no tumor progression. Ideally

patients deserve an optimised exposure to a VEGF TKI such as sunitinib or pazopanib before being deemed resistant. This data and toxicity profile allows two appropriate drugs to achieve this clinical benefit

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding pazopanib (Votrient) for metastatic renal cell carcinoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding pazopanib (Votrient) conducted by the Genitourinary Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on pazopanib (Votrient) and a summary of submitted Provincial Advisory Group Input on pazopanib (Votrient) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Pazopanib has a Health Canada indication for the treatment of patients with metastatic (clear cell) renal cell carcinoma (RCC) who have received no prior systemic therapies or who have received prior treatment with cytokines for metastatic disease. The recommended dose is 800 mg administered orally once daily. Pazopanib is a multi-target tyrosine kinase inhibitor; its targets include VEGF receptor, PDGF receptor, and c-KIT receptor. The action of pazopanib at these receptors reduces the proliferation of cancer cells through inhibition of angiogenesis pathways. Other multi-target tyrosine kinase inhibitors available in Canada for the treatment of advanced RCC includes sunitinib and sorafenib. As first-line treatment for advanced RCC, sunitinib is considered the most relevant comparator to pazopanib, as identified by both PAG and the pCODR Clinical Guidance Panel.[17]

The present review is a re-submission based on the availability of comparative efficacy data with sunitinib, which was not available at the time of the original review.

2.1.2 Objectives and Scope of pCODR Review

The objective of the review was to evaluate the effect of pazopanib on patient outcomes compared to standard therapies in the treatment of patients with advanced or metastatic RCC who have received no prior systemic therapies or who have received prior treatment with cytokines. The scope of the pCODR review included patients with advanced RCC to account for the potential clinical use of pazopanib in this population.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

The efficacy and safety of pazopanib 800 mg po daily taken continuously was compared with sunitinib 50 mg po daily taken cyclically (one cycle = 4 weeks on, 2 weeks off) in two multinational, manufacturer-sponsored randomized controlled trials known as COMPARZ[1] and PISCES.[2]

COMPARZ

COMPARZ[1] (n=1110) was an open-label, active-controlled, parallel-group, Phase III randomized trial conducted in 210 centres in 14 countries (including Canada). COMPARZ was designed to test the non-inferiority (NI) of pazopanib compared with sunitinib on progression-free survival (PFS) based on independent review committee assessment. The upper-bound of the 95% confidence interval (CI) for the between-treatment hazard ratio (HR) was compared against a pre-specified NI margin of 1.25. This NI margin was based on sunitinib trial data showing a median PFS of 11 months in sunitinib-treated patients and expert opinion that accepted a decrement in median PFS of approximately 2 months.[1] Following higher than anticipated rates of drop-out and discordance between the independent review committee and investigators in adjudicating outcomes, COMPARZ amended its protocol to include all 183 patients randomized to a concurrently running Asian trial (VEG113078) of similar design in order to increase its sample size.[1]

Baseline characteristics were well balanced between groups. COMPARZ patients had a mean age of 61 years, were mostly male (73.2%), with almost 2/3 Caucasian (63.7%) and 1/3 Asian (34.4%). Almost all patients (98.2%) had renal cell carcinoma with either clear cell (92.9%) or predominantly clear cell histology (5.3%). Memorial–Sloan Kettering Cancer Center (MSKCC) risk was 'favorable' or 'intermediate' in about 86% of patients and 80% by Heng risk scoring. About 3/4 of patients had a Karnofsky Performance Scale score of 90 or 100. Most patients (83.2%) had undergone a prior nephrectomy.

In the ITT analysis, the median PFS in pazopanib-treated patients was 8.4 months compared with 9.5 months in sunitinib-treated patients. This translated into a non-statistically significant hazard ratio (HR) of 1.05 (95% CI, 0.90 to 1.22). In the PP analysis, the median PFS in pazopanib-treated patients was 8.4 months compared with 10.2 months in sunitinib-treated patients, corresponding to a HR of 1.07 (95% CI, 0.91 to 1.26). Since the upper-bound of the 95% CI in the ITT analysis did not exceed the pre-specified NI margin of 1.25, the non-inferiority hypothesis was confirmed. Non-inferiority in the PP population was not a pre-specified analysis; however, it was noted that the upper bound only slightly exceeded the NI margin of the ITT analysis. Because results from the ITT and PP analyses were not demonstrated to be consistent, one cannot conclude non-inferiority with absolute certainty.

Reasons for excluding patients from the ITT analysis are listed in the table below:

Table 1. Summary of Patients Excluded from Per Protocol Population (ITT Population) – COMPARZ trial[1]

	Pazopanib n=557	Sunitinib n=553
Included in PP population, n (%)	501 (90)	494 (89)
Excluded from PP population, n (%)	56 (10)	59 (11)
Reason for exclusion, n (%)		
Baseline scan performed outside protocol defined time frame	19 (3)	21 (4)
Unreadable baseline scan per the IRC	2 (<1)	1 (<1)
Measurable disease per investigator but non-measurable disease per IRC	20 (4)	24 (4)
Disease histology other than clear cell component	1 (<1)	0
Karnofsky Performance Score < 70	0	1 (<1)
Prior systemic treatment for metastatic disease	1 (<1)	0
Received radiation while on study treatment	3 (<1)	2 (<1)
Radiologic progression recorded, but censored due to extended loss-to-follow-up	1 (<1)	7 (1)
Interruption of study treatment for > 42 days	11 (2)	6 (1)

IRC=Independent Review Committee; **ITT**=intent to treat; **PP**=per protocol

Summary of Outcomes – COMPARZ[18]

	Pazopanib (n=557)	Sunitinib (n=553)
EFFICACY		
Progression-free survival		
IRC-assessed (ITT)		
Median PFS in months (95% CI)	8.4 (8.3, 10.9)	9.5 (8.3, 11.1)
HR (95% CI)	1.05 (0.90, 1.22)[a]	

IRC-assessed (PP)		
Median PFS in months (95% CI)	8.4 (8.3, 10.9)	10.2 (8.3, 11.1)
HR (95% CI)	1.07 (0.91, 1.26)[b]	
Overall survival (ITT)		
Median OS in months (95% CI)	28.4 (26.2, 35.6)	29.3 (25.3, 32.5)
HR (95% CI)	0.91 (0.76, 1.08)	
Overall response rate (ITT), IRC-assessed		
Response rate (CR+PR), n (%)	171 (31)	137 (25)
95% CI	26.9, 34.5	21.2, 28.4
Difference in response [CR+PR], % (95% CI)	6 (0.7, 11.2)	
FACIT-F (ITT)		
Difference in mean change vs. sunitinib (95% CI)	2.32 (1.13, 3.52)	
FKSI-19 (Total score, ITT)		
Difference in mean change vs. Sunitinib (95% CI)	1.41 (0.24, 2.58)	
SQLQ (ITT)		
Difference in mean vs. sunitinib		
Mouth and throat sores	-0.505	
Hand soreness	-0.204	
Foot soreness	-0.267	
CTSQ (ITT)		
Satisfaction with therapy		
Difference in mean vs. sunitinib (95% CI)	3.21 (1.36, 5.06)	
HARMS		
	Pazopanib (n=554)	Sunitinib (n=548)
Dose reductions		
Patients with any dose reductions, n (%)	246 (44)	277 (51)
Patients with ≥1 dose	246 (44)	277 (50)

reductions, n (%)		
Dose interruptions		
Patients with any dose interruption ≥7 days, n (%)	243 (44)	267 (49)
Median duration of dose interruption, days (IQR)	12 (8-14)	14 (11-20)
Adverse events, most common, pazopanib > sunitinib, n (%)		
Diarrhea	348 (63)	315 (57)
Hypertension	257 (46)	223 (41)
ALT increased	171 (31)	97 (18)
Hair color changes	168 (30)	53 (10)
AST increased	148 (27)	98 (18)
Serious adverse events		
Patients with any SAE, n (%)	230 (42)	224 (41)
Most common SAEs, pazopanib > sunitinib, n (%) (ITT, on therapy)		
ALT increased	35 (6)	8 (1)
AST increased	17 (3)	2 (<1)
Patients with fatal SAEs, n (%)	13 (2)	19 (3)
Withdrawals due to adverse events		
Patients with any WDAE, n (%)	135 (24)	112 (20)

CI=confidence interval; **CR**=complete response; **CTSQ**=Cancer Therapy Satisfaction Questionnaire; **FACIT-F**=Functional Assessment of Chronic Illness Therapy – Fatigue; **FKSI-19**=Functional Assessment of Cancer Therapy – Kidney Symptom Index-19; **IQR**=interquartile range; **ITT**=intent to treat; **IRC**=Independent Review Committee; **PP**=per protocol; **PR**=partial response; **SAE**=serious adverse event; **SQLQ**=Supplementary Quality of Life Questionnaire; **WDAE**=withdrawal due to adverse event

[a]Non-inferiority met [b]Non-inferiority analysis was not pre-specified and so non-inferiority could not be confirmed with certainty [c]Adjusted for baseline score

Major limitations and sources of bias for the COMPARZ trial were as follows:

- The conclusion of pazopanib's non-inferiority to sunitinib is based on results from the ITT analysis rather than the more conservative PP analysis. While the upper bound of the 95% CI for the hazard ratio did not exceed the 1.25 NI margin in the ITT analysis, this could not be demonstrated for the PP analysis, as a formal analysis was not conducted. As there could not be consistency demonstrated between the ITT and PP analyses, the results cast some uncertainty around the non-inferiority of pazopanib to sunitinib. In NI trials, the PP analysis is the more conservative analysis and there is a

body of evidence which supports that is the preferred analysis, with confirmatory results in the ITT analysis.[13-15] When results from the ITT and PP analyses are demonstrated to be consistent, one cannot conclude non-inferiority with absolute certainty. Upon review of feedback provided by the manufacturer, it is acknowledged that a body of evidence supports the use of the ITT population as being the primary analysis in non-inferiority trials. However, evidence also supports that analysis be conducted both in the ITT and PP analysis and in the event inconsistent conclusions are demonstrated, the use of the PP population is reasonable.

- The NI margin was established, in part, from sunitinib trial data showing a median PFS of 11 months in sunitinib-treated patients;[1] however, this treatment effect may not be generalizable to 'real-world' practice. In fact, median PFS observed in COMPARZ fell below 11 months in sunitinib-treated patients in both intent-to-treat (ITT) and per-protocol (PP) analyses. Of note, the CGP observed that the overall response rate in the sunitinib group (i.e., 25%) seemed unusually low compared with what would normally be expected in clinical practice. Therefore, there is a potential risk of bias in the trial toward a declaration of non-inferiority.
- Due to higher than anticipated rates of attrition and discordance [between independent review committee (IRC) and investigator assessments], a protocol amendment was filed allowing for the addition of patients from a concurrently running Asian trial (VEG113078) to expand the study population size in COMPARZ. COMPARZ is therefore an amalgam of two studies: Asian trial (VEG113078) and original COMPARZ trial. The population analysis sets are therefore derived from two separate trials instead of one; likewise, Asian patients in COMPARZ do not represent a true subgroup analysis as they were sourced from two separate trials.

PISCES

PISCES[2] (n=168) was a 22-week double-blind, cross-over trial conducted in 40 centres in 5 European countries, which randomized the order of treatment administration according to two periods – SP (sunitinib first then pazopanib) or PS (pazopanib first then sunitinib); a two-week wash-out separated the finish of the first treatment from the start of the next treatment. The primary efficacy outcome of PISCES was to determine which drug was preferred by patients through a questionnaire.

Similar to COMPARZ, PISCES patients had a mean age of about 62 years and were mostly male (67.3%). The majority (93.5%) of patients were Caucasian and about 90% had renal cell carcinoma with clear cell histology; 72.0% of patients had an ECOG score of 0. Like COMPARZ, most patients (88.7%) had previously undergone a nephrectomy. Several imbalances between groups were observed, notably in the proportion of males (PS >SP), those with clear cell histology (SP >PS). Numerical differences were also noted with respect to the number of metastatic sites and nephrectomy status, but the CPG considered these differences trivial.

Patient preference, the primary efficacy outcome, was evaluated through the use of an unvalidated questionnaire.[2] Upon review of feedback provided by the manufacturer, it is noted that the questionnaire validation has since been published; however the validation was not verified as part of this review. Although numerically, the data seemed to show that patients preferred pazopanib over sunitinib treatment in both period 1 and period 2, without questionnaire validation,

it is impossible to state with certainty that these data reflect measurement of treatment preference. HRQOL data were similarly difficult to interpret owing to a lack of questionnaire validation or published information on minimal clinically important differences in the setting of RCC.

Additional major limitations and sources of bias for the PISCES trial were as follows:

- The use of a cross-over design, which assumes disease stability over the period during which the trial is conducted, may have been inappropriate due to possible disease instability:[19]
    - While the number of patients who prematurely discontinued was similar between SP and PS treatment arms in period 1, in period 2, twice the number of patients in the PS group prematurely discontinued compared with the SP group. Premature discontinuations were driven primarily by adverse events in both periods. The manufacturer speculated that the notable difference in discontinuations and adverse events between treatment groups observed in period 2 may have been due to unstable disease, which increases susceptibility to drug-related toxicity.[2]
- Treatment interruptions were not permitted during the trial, thus potentially underestimating toxicity/tolerability profiles. Approximately 20% of patients did not complete period 1, with 10% of patients failing to complete period 1 due to adverse events.[2] By comparison, there were fewer non-completers in period 2 (~7%) and fewer withdrawals due to adverse events (~1%)[2] potentially suggesting that patients most susceptible to treatment-related toxicity were weeded out early.
- For (secondary) HRQOL outcomes, the safety population was used, not the ITT population, which is the analysis set conventionally employed in efficacy analyses. In contrast, the modified ITT was (appropriately) used for analysis of the primary outcome (patient preference). In theory, these two efficacy outcomes should be related, so it is unclear why the population analysis sets used differed.
    - Typically, the ITT population (n= 136) should closely resemble the all-randomized population (n=168), which it does not in this trial. The modified ITT set (n=114), used in the primary analysis, was even smaller in size. Thus, some doubt is cast on how generalizable the results from these ITT and modified ITT analysis sets are.
    - In using the safety set, the definition of which seems to imply that patients may only have received a single dose of study drug, to evaluate HRQOL, it is unclear how reflective these data would be of quality of life in a real-world setting.
- Although the 2-week wash-out period was considered adequate in duration by the CGP, there is a potential risk of unblinding in the case of any lingering treatment-related toxicity (e.g., alopecia). Moreover, subjecting pazopanib-treated patients to a wash-out period at all is not reflective of real-world administration of pazopanib since the drug is taken continuously (i.e., without scheduled interruption).

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

There were no supplemental questions identified for this review.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, maintaining quality of life is an important aspect when consideration is given to treatment. Although there are agents currently available on the Canadian market for the first-line treatment of metastatic renal cell carcinoma, they can cause adverse effects, sometimes significant, in some patients. The side effect profile of pazopanib may differ from the currently available agents for metastatic RCC. Patients and their families expressed a strong need for choice, flexibility, and access to the most appropriate first-line treatment for each individual patient.

PAG Input

Input on the pCODR review of the original pazopanib (Votrient) mRCC review was obtained from all nine of the provinces (Ministries of Health and/or cancer agencies) participating in pCODR. The PAG input from the original pazopanib submission was reviewed again and PAG members had confirmed the original PAG input as sufficient for the resubmission. From a PAG perspective, sunitinib is considered the most relevant comparator and PAG indicated it would be important to be aware of any differences between pazopanib and sunitinib with respect to side effect profile and treatment outcomes. Given this, PAG considered that the relative cost and cost-effectiveness of sunitinib and pazopanib was a very important factor

2.2 Interpretation and Guidance

Burden of Renal Cell Carcinoma

Kidney cancer accounts for approximately 3% of malignant diseases in Canada with approximately 90-95% being renal cell carcinomas (RCC). An estimated 5600 new cases (all stages) will be diagnosed in 2012 with approximately 1700 deaths reported highlighting the unfavourable prognosis of this disease and the need for effective therapy.[4] Males are more frequently affected with a predominance of 1.8 to 1. Kidney cancer rates rose nearly 3% per year for males since 2003.[4] The peak incidence of kidney cancer is among individuals aged between 50-70 years. The estimated 5 year survival across all stages is 67% but the prognosis for patients with metastatic disease remains dismal and only very few survive

longer than five years. Surgery remains the only curative treatment option and metastatic patients are generally considered incurable.

Treatments for Renal Cell Carcinoma

The management of metastatic renal cell carcinoma has undergone significant change in the past five to eight years. Based largely on an increasing understanding of the disease biology and better activity than older immunotherapy agents like interferon and IL-2, targeted agents such as the small molecule tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib), the mTOR inhibitors (everolimus and temsirolimus) and the monoclonal antibody bevacizumab have evolved as the new standard therapies for the treatment of metastatic kidney cancer.[5-12]

Sunitinib, a small molecule tyrosine kinase inhibitor, is considered standard first-line therapy in Canada. Sunitinib blocks vascular-endothelial growth factor (VEGF) receptor types 1, 2, 3, platelet-derived growth factor (PDGF) receptors alpha and beta, c-kit and FLT-3. Sunitinib demonstrated a median progression free survival of 11 months versus 5 months ($P < 0.001$) and a median overall survival of 26.4 months versus 21.8 months ($P = 0.051$) in the pivotal randomized controlled trial in which it was compared with interferon.[7] None of the currently available systemic treatment options for metastatic disease however (including targeted therapy, immunotherapy (cytokines) or conventional chemotherapy) is considered curative and all of these therapies are associated with various degrees of side effects. Thus, there remains a need for novel therapies in the treatment of metastatic RCC, which have increased efficacy or have an improved toxicity profile.

Pazopanib is a new small molecule tyrosine kinase inhibitor, which inhibits a broad spectrum of tyrosine kinases including VEGF receptors 1–3, PDGF receptors alpha and beta, and c-Kit. However, the spectrum, selectivity and potency of different kinase inhibitors vary which may explain differences in the safety profile of these agents. Pazopanib was initially approved based on the Study VEG105192, which randomized pazopanib versus placebo in either previously untreated or cytokine pretreated patients. Pazopanib demonstrated a superior and significant improvement in the primary study endpoint of median progression free survival with a median PFS of 9.2 months versus 4.2 months [HR = 0.46 $P < 0.0001$] for the entire patient population and a median PFS in the treatment-naïve population of 11.1 months vs. 2.8 months [HR = 0.40; $p< 0.0001$].[10] Based on these results, pazopanib is considered an alternative to sunitinib as standard therapy in the first-line setting.

No direct comparison study exists between first-line options apart from the herein discussed COMPARZ study. Given the mechanism of action and proposed indication of first-line therapy, sunitinib is the most valid comparator for pazopanib. No randomized phase III data exist for sorafenib in the first-line setting and the combination of bevacizumab/interferon has never been approved in Canada.

COMPARZ Study

The COMPARZ study was designed as a non-inferiority study with progression-free survival as the primary endpoint. The non-inferiority boundary was set to 1.25, which allowed a maximum accepted PFS difference of 2 months.

The validity of PFS as the primary endpoint for RCC trials has been repeatedly discussed. However, clinically PFS is a very important objective in itself since a period without tumour progression is often associated with a good quality of life for patients. In addition, observational data suggests an association between PFS and overall survival.[20] With the

availability of various active therapies and the option of crossover within the trials, overall survival has become a difficult endpoint for first-line trials in metastatic RCC. Almost all large randomized RCC studies to date examining targeted agents have used PFS as the primary endpoint.[7-10]

Patient Populations

The patient populations in the COMPARZ study and the previously conducted pazopanib versus placebo (Study VEG105192) and sunitinib versus interferon studies were comparable, with the exception that a higher proportion of MSKCC poor risk patients and a slightly lower number of patients with prior nephrectomy (approx. 5% less) were recruited to the COMPARZ study as compared to the two other studies. [7-10]

All studies excluded patients with non-clear cell histology and required either clear cell or predominantly clear cell histology.

Several issues have been raised regarding the generalization and applicability of these results to patients with non-clear cell carcinoma, and patients with poor performance status.

- Similar to the other two studies, COMPARZ included only patients with clear cell carcinoma or a clear cell component. Histology plays a significant role in RCC treatment selection and outcome. About 80% of RCCs are of clear-cell histology, whereas 20% are classified as non-clear cell cancers including papillary, sarcomatoid, chromophobe subtypes amongst others. Importantly, only clear cell RCCs are associated with defects in the von Hippel-Lindau (VHL) gene which appear to drive tumor progression in these patients. Approximately 80% of patients with sporadic (noninherited) clear cell RCC acquire defects of both alleles of the VHL gene with resulting dysfunction of the VHL protein. The VHL protein functions as a tumour suppressor and the VHL protein plays a pivotal role in the control of neo-angiogenesis. Loss of VHL gene function results in enhanced secretion of VEGF, PDGF, and creation of the vascular phenotype characteristic of clear cell RCC. All targeted agents available to date are interfering with the angiogenesis pathway either by inhibiting the vascular-endothelial growth factor (VEGF) receptor (sunitinib, sorafenib), VEGF (bevacizumab) or the mTOR pathway (everolimus, temsirolimus). No data are available for pazopanib in non-clear cell cancers, although other TKI's have demonstrated some activity in non-clear cell carcinomas.
- Treatment for patients with poor performance status (ECOG ≥ 2) remains a challenge. The very vast majority of patients included in these 2 studies presented with an ECOG performance status of 0 and 1 and the efficacy and, most importantly, tolerability of pazopanib (and sunitinib) in patients with a performance status ≥ 2 remains somewhat uncertain. The requirement of a performance status of 0 or 1 also lead to the inclusion of mostly good and intermediate risk patients according to the MSKCC classification, albeit in COMPARZ a higher number of poor risk patients were included (12%) as compared to the previous pazopanib study (3%) and the sunitinib study (6%). Hence, the interpretation of the results in poor risk patients remains difficult.

Effectiveness

PFS was the primary endpoint of the COMPARZ study. Pazopanib demonstrated non-inferiority based on the "intention-to-treat" analysis with a median PFS of 8.4 months compared with 9.5 months in sunitinib-treated patients [HR 1.05 (95% CI, 0.90 to 1.22)]. Both PFS curves were virtually overlapping indicating a very similar effect. Noninferiority

was not a pre-specified analysis and not confirmed in the "per-protocol" analysis [median PFS 8.4 months for pazopanib compared with 10.2 months in sunitinib-treated patients (HR 1.07 (95% CI, 0.91 to 1.26)]. Overall, ITT-based PFS was shorter than in previously reported randomized trials. A number of factors may account for that such as the inclusion of a higher percentage of poor risk patients as compared to previous trials. However, it is re-assuring that the overall survival was similar to the OS reported previously.

Overall survival was similar in both groups with an OS for pazopanib of 28.4 months (95% CI: 26.2-35.6 months) and 29.3 months (95% CI: 25.3-32.5 months) in the sunitinib group ($p > 0.05$). Albeit cross comparisons of trials are to be interpreted with caution, it is re-assuring that the OS results were comparable with the OS result from the previous phase III sunitinib trial (26.4 months) and slightly better than for the previous pazopanib trial (22.9 months). However, OS can be substantially influenced by the availability of subsequent therapies.

Response rates were lower (31% for pazopanib and 25% for sunitinib) than described in previous trials, in particular for sunitinib. Tumor assessments were performed every 6 weeks which may have resulted in a lower sunitinib response rate since some patients progress during the 2 week break on the 4 weeks on/2 weeks off schedule. In general, objective response rate is not a very reliable indicator of clinical benefit.

Tumour response rates and tumour progression were reviewed by an independent review committee and compared to investigator assessments. There was a higher than anticipated drop-out rate and discordance between the independent review committee and investigators in adjudicating outcomes. Hence, COMPARZ amended its protocol to include all 183 patients randomized to a concurrently running Asian trial (VEG113078) of similar design in order to increase its sample size.

Overall, these clinical data with an ITT non-inferiority in PFS and similar OS suggest that pazopanib represents an alternative option to sunitinib for first-line therapy in metastatic RCC patients.

Safety

Almost all patients in both group experienced an adverse event of any grade. The most frequent adverse events related to either pazopanib or sunitinib treatments were diarrhoea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes. The frequency of dose reductions and dose delays was similar in the two treatment groups as was the frequency of dose discontinuation, indicating that both, pazopanib and sunitinib are important treatment options in the first line setting.

While the toxicity profile of both agents was qualitatively similar, there are some important differences including the frequency of side effects. The adverse event rates for pazopanib, in particular for important side effects such as dyspepsia, mucositis/stomatitis, fatigue, hand-foot syndrome, myelosuppression and altered taste were lower than for sunitinib while pazopanib treated patients experienced significantly more hepatotoxicity. Mucositis, fatigue and in particular hand-food syndrome are amongst the most frequent TKI-related adverse events e.g. sunitinib related side effects leading to dose reductions or dose delays and may frequently interfere substantially with treatment administration, patients' quality of life and subsequently optimal outcomes.

Due to these lower rates of certain frequent and clinically relevant side effects, pazopanib represents an attractive alternative for elderly patients, patients with pre-existing skin conditions, and in particular patients who wish to have a low risk for these side effects or patients who become intolerant of sunitinib in the absence of tumor progression. It is of

utmost importance for patients to be able to stay on one class of drugs e.g. TKIs as long as they benefit.

Of note, in contrast to sunitinib and sorafenib, no cardiotoxicity has yet been reported with pazopanib and preclinical studies suggest differences in effects on myocardium and mitochondria between pazopanib and sunitinib. This makes pazopanib an attractive alternative to sunitinib in patients with pre-existing heart disease.

Quality of life analysis also favoured pazopanib and showed significant advantages for pazopanib, which appear clinically relevant. It is important to note that the quality of life questionnaires used in COMPARZ were not available for validation during the review and hence were interpreted with caution. In addition, quality of life was measured on day 28 of sunitinib dosing, which is in general the time of the worst toxicity from sunitinib and could bias the data against sunitinib. Nevertheless, a significant benefit was observed in favour of pazopanib. This is also corroborated by the PISCES study, which was a randomized patient preference study. Despite a number of methodological issues such as the lack of published information on minimal clinically important differences in the setting of RCC, the study suggests patient preference for pazopanib.

Comments on Methodology:

ITT versus PP analysis:

The study achieved non-inferiority in the primary endpoint PFS based on the ITT analysis but not based on the PP analysis. A lack of demonstrable concordance between the results of the ITT and PP analyses casts some uncertainty around the non-inferiority of pazopanib to sunitinib. While ideally both ITT and PP should be considered and positive for greatest certainty, there is no clear consensus amongst statisticians which population is the more important one. The requirement for demonstrating non-inferiority for both, ITT and PP, does not necessarily guarantee the validity of a non-inferiority conclusion and it is important to assess the reasons for the exclusion of patients.[16] The majority of patients were excluded from the PP analysis for reasons of the baseline scan being performed outside the 4 week window prior to treatment start and due to the lack of measurable disease. The exclusions were equally distributed between the 2 treatment groups. It is unlikely that these exclusions would have biased the trial towards noninferiority.

Ten and eleven percent of patients were excluded from the PP analysis in the pazopanib and sunitinib group, respectively. The decrease in power for PP due to these withdrawals may have impacted results and power may not have been sufficient to prove noninferiority in the PP analysis.

Schedule of assessments:

Both, schedule of quality of life assessments and the response assessments appear to have disadvantaged sunitinib. Sunitinib toxicity is generally at its worst at the 4 week mark, just prior to the 2 week break. Other assessment points may have been associated with a smaller difference in quality of life. Similarly, measuring objective response at 6 weeks may artificially lower the response rate of sunitinib since some patients have clinically asymptomatic progression during the 2 week break.

Evidence Gaps

A number of gaps were identified when reviewing the evidence for pazopanib:

- No evidence exists whether one of the 2 drugs is superior or whether they are equivalent.
- No data exist for the use of pazopanib in the adjuvant setting after curative resection of the primary tumour. A randomized study in this setting is currently ongoing. At the present time, none of the approved agents should be given in this setting outside of clinical trials.
- As well, no randomized data exist for the sequential use of pazopanib as second or third line option after failure of other anti-angiogenic therapies. Sunitinib, sorafenib, and pazopanib appear to work through the same pathway (VEGF receptor inhibition) to inhibit angiogenesis. It is currently unknown whether resistance to sunitinib or sorafenib will confer similar resistance to pazopanib. Few small phase II and retrospective studies suggest activity of pazopanib after sunitinib but this observation needs confirmation in a larger randomized trial and thus, the use of pazopanib in this setting outside of clinical trials remains experimental.
- Similarly, no randomized data exist for pazopanib in non-clear cell carcinomas. The most often recommended treatment for these patients is temsirolimus due to the inclusion of non-clear cell carcinoma patients in the pivotal phase III study. Other targeted therapies such as sunitinib or everolimus are currently being tested within prospective trials.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to pazopanib in the treatment of advanced and metastatic RCC based on the previous pCODR assessment of the randomized controlled trial, Study VEG105192,[17] and based on the two studies included in the systematic review, COMPARZ and PISCES. VEG105192 demonstrated a clinically and statistically significant benefit in progression-free survival for pazopanib compared with placebo, while COMPARZ and PISCES demonstrated noninferiority of pazopanib to sunitinib based on ITT analysis as well as important differences in clinically meaningful side effects.

In making this conclusion, the Clinical Guidance Panel also considered that:

- The original pCODR review of pazopanib,[17] based on Study VEG105192 found that there was a clinically and statistically significant benefit in progression-free survival for pazopanib compared with placebo.
- COMPARZ supports the use of pazopanib in patients with clear cell histology or clear cell component and good performance status (ECOG 0 and 1).
- While significant advances have been achieved in recent years in the treatment of metastatic kidney cancer, it remains an incurable disease. Approximately one quarter of patients with RCC present with metastases at diagnosis and at least one half of all patients will eventually develop advanced disease.
- Limited treatment options exist for patients with metastatic RCC. Sunitinib has been the only drug approved and funded in most provinces for patients with good performance status and/or good or intermediate risk disease. While sunitinib, the

current standard first-line option in Canada for the vast majority of patients, is an effective therapy, it is also associated with a number of substantial side effects, including hypertension, fatigue, diarrhoea and hand-foot syndrome, all of which can greatly impact a patient's quality of life, optimal administration of therapy and subsequent outcomes.

- Pazopanib was well tolerated with an overall low incidence of grade 3 and 4 toxicity. The most frequent adverse events related to pazopanib treatment were diarrhea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes and these were manageable in the majority of patients. COMPARZ demonstrated a lower incidence of certain toxicities, such as hand-foot syndrome, with pazopanib as compared to sunitinib.
- Pazopanib is a clinically useful treatment option for patients with advanced or metastatic disease because it has a more favourable toxicity profile in certain clinically meaningful side effects compared with other tyrosine kinase inhibitors such as sunitinib or sorafenib and, demonstrates noninferior efficacy by ITT analysis.
- Oncologists should have the option to choose between pazopanib and sunitinib in order to allow optimal treatment of patients with a maximum treatment effect. Toxicity interfering with delivery of either drug should not be considered failure to VEGF TKI and an opportunity to switch to the other drug should be allowed as long as there is no tumor progression. Ideally patients deserve an optimised exposure to a VEGF TKI such as sunitinib or pazopanib before being deemed resistant. This data and toxicity profile allows two appropriate drugs to achieve this clinical benefit

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Cancers of the kidney account for approximately 3% of all cancers in Canada. An estimated 5,600 new cases of kidney cancer and 1,700 deaths from kidney cancer are expected in 2012.[4] About 90% of kidney cancers consist of RCC, which are genetically and histologically distinctly different from carcinomas of the renal pelvis. About 80% of them are of clear-cell histology, whereas 20% are classified as non-clear cell cancers including papillary, sarcomatoid, chromophobe subtypes amongst others.

Approximately 75% of patients with RCC have localized disease (confined to the kidney/extensive growth in the area of the kidney but no distant metastases) at the time of diagnosis. About 25% of RCCs are metastatic at the time of diagnosis and approximately 30-50% of patients, who are initially diagnosed with localized disease, will eventually relapse and metastasize.[21]

The most important prognostic factor for outcome is tumour stage. Survival rates in localized stages range from 70-90% for smaller tumours (stages I and II) but drop significantly in localized but more extensive tumours (stage III) with survival rates of 50-60%. Patients with metastatic disease are rarely cured.

Metastatic RCC is considered refractory to conventional cytotoxic chemotherapy as well to conventional radiation. Historically, immunotherapy (cytokines) was the treatment of choice in the metastatic setting although only a small group of patients derived meaningful benefit from it. In the era of immunotherapy, median overall survival across all metastatic patients was in the range of 12-14 months.[22-24]

Several prognostic factors have been identified in patients with metastatic disease dividing metastatic patients into a favourable, intermediate and poor risk group. The most commonly used classification is the MSKCC model which includes the presence or absence of five distinct risk factors (performance status, lactate dehydrogenase, corrected calcium, hemoglobin, and time from diagnosis to treatment). This classification has been used in a number of clinical studies and is used by many in clinical practice to select patients.[25,26]

An increased understanding of RCC biology and the development of new therapeutic agents (targeted therapies / antiangiogenic agents), in particular in the clear-cell subtype, have resulted in the availability of several new treatment options for patients with advanced or metastatic RCC. Clear-cell carcinomas are characterized by the presence of inactivating mutations in the von-Hippel-Lindau gene. Loss of functional VHL protein results in the activation of pro-angiogenic and growth factor pathways via constitutive stabilization of the alpha subunits of a group of transcriptionally active proteins called the hypoxia-inducible factors (HIF). HIF plays a central role in renal tumor genesis by acting as a transcription factor for genes that are involved in angiogenesis, tumor cell proliferation, cell survival and progression, metastatic spread, apoptosis and glucose metabolism. The phosphatidylinositol-3 kinase (PI3K)-AKT-mTOR signal transduction pathway is also involved in controlling HIF.[27] Elucidation of the VHL/HIF pathway has led to the successful evaluation and regulatory approval of agents targeting the VEGF and mTOR axes.

Targeted therapies have a distinct mechanism of action, fundamentally different from classic chemotherapy and are also associated with a different toxicity profile.

The RCC treatment landscape has changed significantly over the past years and continues to evolve rapidly but RCC therapy continues to be a major challenge. While these therapies are active in clear cell RCC, the vast majority of tumours eventually become treatment refractory through different, as yet poorly understood, mechanisms.

3.2 Accepted Clinical Practice

Surgery with complete removal of the tumour remains the mainstay of therapy in localized or locally advanced stages. There is currently no role for adjuvant or neoadjuvant therapy.

Until the introduction of targeted therapies, immunotherapy (cytokines) with low dose interferon-α, low dose interleukin-2 or high dose interleukin-2 represented the standard of care for patients with metastatic clear-cell RCC. Although these agents have been helpful for a small group of patients, the majority of patients derive no benefit or the clinical benefit was very modest and achieved at the expense of significant toxicity.[22,24]

Targeted therapies have replaced immunotherapy as standard treatment for patients with metastatic disease and today, high-dose interleukin-2 is only considered for a highly selected, very small subgroup of patients while low-dose interferon and interleukin-2 as single agents are no longer recommended at all.[28]

There are currently three different classes of agents, small molecule tyrosine kinase inhibitors such as sunitinib or sorafenib, inhibitors of mTOR (mammalian target of rapamycin) such as temsirolimus or everolimus and the monoclonal antibody bevacizumab in clinical use for the treatment of clear-cell RCC. All these agents interfere with the VEGF pathway, which plays a crucial role in tumour angiogenesis. Tyrosine kinase inhibitors block the intracellular domain of the VEGF receptor, while bevacizumab binds VEGF and mTOR inhibitors interfere with mTOR, which is key regulator within cells.

Sunitinib is an oral tyrosine kinase inhibitor with activity against VEGF receptor types 1, 2, 3, PDGF receptors alpha and beta, c-kit and FLT-3. In the pivotal phase III trial examining treatment-naive patients with metastatic RCC, there was a statistically significant difference in PFS in patients treated with sunitinib versus interferon (11 vs. 5 months) with a hazard ratio of 0.42 ($P < 0.001$).[7] In addition, this was the first trial to demonstrate a median overall survival of more than 2 years in patients with metastatic RCC patients. These results served as the basis for introducing sunitinib as a reference first-line standard of care.

Sorafenib is also an oral tyrosine kinase inhibitor with activity against VEGFR-2, VEGFR-3, PDGF-beta, Flt-3, RAF-kinase and c-Kit. Based on the results of the TARGET trial, which randomized patients after failure of cytokine therapy to either sorafenib or placebo and demonstrated superiority in PFS, sorafenib was approved for the treatment of advanced RCC.[9] Sorafenib is considered a treatment option in metastatic RCC, although its use has substantially decreased due to the decreased use of cytokines and the lack of robust randomized data in the first-line setting.[29]

The mTOR inhibitor temsirolimus, given intravenously once a week, was tested in a randomized trial which included only poor risk patients according to the MSKCC and Cleveland Clinic criteria. In this trial, temsirolimus demonstrated superior overall survival outcomes as compared to interferon alone or the combination of both drugs.[5] Temsirolimus is considered a standard treatment option for patients with poor risk criteria.

Everolimus, an oral mTOR inhibitor is considered a standard treatment for patients who have failed first-line therapy with tyrosine kinase inhibitors. Everolimus demonstrated a significant PFS benefit in a randomized phase III trial which compared everolimus to placebo in patients with failure to at least one prior line of tyrosine kinase therapy.[6]

Bevacizumab was tested in combination with interferon versus interferon alone within 2 randomized trials. Both trials demonstrated a significant PFS benefit for the bevacizumab combination group.[11,12] Based on these results the combination has been approved for the treatment of advanced RCC in Europe, the US and other countries. The combination has not been filed for approval in Canada yet.

Pazopanib is also an oral tyrosine kinase inhibitor with activity against VEGF receptor types 1, 2, 3, PDGF receptors alpha and beta and c-kit. Pazopanib was initially approved for use in metastatic RCC based on results from a randomized phase III study in 435 patients with mRCC who had received no more than one prior cytokine therapy. Patients were randomly assigned to receive either pazopanib or placebo. Pazopanib was associated with a statistically significant improvement in PFS [median PFS 9.2 versus 4.2 months, hazard ratio 0.46, 95% confidence interval (CI) 0.34–0.62, P<0.0001], as well as a significantly higher ORR (30 versus 3%, P<0.0001).[30] No statistically significant differences in overall survival were observed in this study, certainly related to the frequent and often early crossover of patients, the availability of other targeted agents at the time of progression and the prolonged application of targeted agents in "placebo" patients after progression on placebo.[10] In the current treatment landscape, sunitinib is considered the reference standard for first-line therapy of patients with good or intermediate risk according to the MSKCC classification and considered a treatment option for poor risk patients with good performance status. Pazopanib is considered an alternative to sunitinib as first line therapy for good and intermediate risk patients. However, until recently comparative studies between sunitinib and pazopanib have been lacking.

Sorafenib is listed as a first-line option in most clinical practice guidelines although no randomized phase III data exist in treatment-naïve patients.

Temsirolimus is considered the standard therapy for patients with poor risk criteria.[13] No standard second line therapy exists for patients after failure of first-line temsirolimus.

Everolimus is considered standard second line therapy after failure of first line tyrosine kinase inhibitor therapy.[6,8]

There is no standard third or subsequent line therapy due to the lack of randomized trials.

In today's clinical practice, these agents are sequenced, meaning if one line of therapy fails, it is replaced by another agent. The most commonly used standard sequence in Canada consists of sunitinib as first-line therapy followed by everolimus as second-line therapy.

Combinations of these agents are not considered clinically relevant at the present time and for the most part have been shown to be associated with intolerable side effects.

The use of tyrosine kinase inhibitors is limited by their toxicity which includes fatigue, hand-foot syndrome, hypertension, hypothyroidism, diarrhea, and mucositis as the clinically most relevant. Side effect management is an important part in the overall treatment strategy.[31]

Another limitation is the development of resistance to therapy. Eventually almost all patients progress and require a switch to a different therapy.

Pazopanib is also being evaluated as second-line therapy in metastatic RCC patients previously treated with VEGF-targeted therapy in a single arm phase II study (NCT00731211).

3.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of pazopanib for patients with the following criteria:[10,30]

- Metastatic or advanced, inoperable renal cell carcinoma
- Clear cell histology or clear cell component
- Treatment-naïve patients (first line therapy) or patients after failure of cytokine therapy

Currently, no clinically useful and reliable biomarkers exist for the prediction of response and/or benefit.

3.4 Other Patient Populations in Whom the Drug May Be Used

Pazopanib has also been approved for the treatment of patients with soft-tissue sarcoma who have prior received chemotherapy for metastatic disease or who have relapsed within 12 months after adjuvant chemotherapy.

In most jurisdictions, including Canada and the European Union, pazopanib has been approved for first-line treatment or treatment of patients who previously had failed cytokines. In the US, pazopanib is approved for the treatment of advanced RCC without indicating line of therapy.

Apart from first-line therapy or second-line therapy after cytokine failure, pazopanib may be used in clinical practice as second-line or third-line therapy after failure of another tyrosine kinase inhibitor and/or mTOR inhibitor. Emerging data suggest activity for re-challenging patients with same class agents in later line of therapy.

There is a large randomized study currently ongoing which examines the role of pazopanib in the adjuvant setting after curatively intended resection (NCT01235962, Study VEG113387).

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Kidney Cancer Canada, provided input on the pazopanib resubmission for metastatic renal cell carcinoma (RCC). In July 2011, Kidney Cancer Canada provided input to pCODR for the review of pazopanib. Input from Kidney Cancer Canada for the review of the pazopanib resubmission was based on the input previously provided and included additional market access information.

Kidney Cancer Canada conducted both a qualitative in-depth study using telephone interviews and a quantitative online survey to gather information about the patient and caregiver experience with the drug under review. There were a total of 6 respondents to the telephone interview conducted by Kidney Cancer Canada. An online survey was hosted by the Canadian Cancer Action Network and consisted of two separate parts. Part one of the survey (120 respondents) collected information regarding patient experience with kidney cancer as well as their view on future drug therapies. Part two of the survey (6 respondents) collected information from patients and caregivers having direct experience with pazopanib. Based on both sources of patient information, 11 unique respondents were identified as having direct experience with pazopanib.

From a patient perspective, maintaining quality of life is an important aspect when consideration is given to treatment. Although there are agents currently available on the Canadian market for the first-line treatment of metastatic renal cell carcinoma, they can cause adverse effects, sometimes significant, in some patients. The side effect profile of pazopanib may differ from the currently available agents for metastatic RCC. Patients and their families expressed a strong need for choice, flexibility, and access to the most appropriate first-line treatment for each individual patient.

Please see below for a summary of specific input received from the patient advocacy group.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Renal Cell Carcinoma

Patients with early stage kidney cancer often have no symptoms and as a result, many cases are diagnosed when the cancer has already metastasized. Patients with metastatic RCC can experience many symptoms, including shortness of breath, coughing, fatigue, severe abdominal or back pain, or bone pain/fractures often involving the pelvis, femur or spine.

There is no cure for metastatic RCC and there are limited treatment options. Patients have found hope in the development of new targeted therapies that shrink tumors and stop the progression of their cancer, sometimes for long periods of time. Without treatment alternatives, patients face disease progression including worsening of symptoms such as increasing shortness of breath, severe bone pain and fatigue. Depending upon the site of untreated metastases, patients may suffer from seizures, spinal compression leading to paralysis and painful bone fractures often requiring orthopedic surgery.

From a patient perspective, quality of life while living with metastatic RCC is one of the most important considerations. Treatment options that reduce worsening of disease, pain, and fatigue can lead to maintaining or resuming normal daily activities. Comments from a survey of patients with metastatic RCC highlighted that, in addition to the physical impact, the emotional and mental impact of cancer can be significant.

4.1.2 Patients' Experiences with Current Therapy for Metastatic Renal Cell Carcinoma

Current first-line therapies for metastatic RCC include sunitinib, temsirolimus (poor prognosis) and cytokine treatments such as interleukin-2 or interferon-alpha. Across Canada, patients are frequently prescribed sunitinib as first-line therapy. Although sunitinib and other tyrosine kinase inhibitors are considered effective in significantly delaying progression, each has associated side effects which some patients, in varying degrees, find difficult to manage. Depending on the individual patient, other concurrent health issues and the kidney cancer symptoms, the treatment's side effects have a significant impact on 'quality of life' and daily activities of patients and caregivers.

Comments from survey respondents currently receiving sunitinib therapy highlighted the impact of sunitinib side effects including fatigue, nausea, vomiting, and hand/foot syndrome. Patients noted that additional medications were sometimes required to control sunitinib side effects, e.g. antihypertensive for elevated blood pressure, antacids for acid reflux and thyroid hormones for thyroid dysfunction.

While patients are aware of and have direct experience with the serious side effects of current therapies, the survey results indicate that a moderate majority is willing to accept side effects and the serious risks associated with a future, new drug such as pazopanib. Given that metastatic RCC is a life-threatening cancer, patients are willing to accept a higher level of risk even if the treatment is not curative and the benefits are projected to be short-term.

It is the opinion of Kidney Cancer Canada, that the need for individualized choice in first-line therapy is not being met in Canada. If first-line options or choices were available, patients and oncologists would be able to individualize treatment plans to the characteristics of their tumours, contraindications and lifestyle enabling each individual patient the best possible quality of life.

Some qualities that patients are looking for in a new therapy include:

- **Individualized Therapy:** Patients feel that the need for individualized choice in first-line therapy is currently not being met in Canada for metastatic RCC, unlike for other cancers.
- **Quality of Life:** When considering a new drug treatment, survey respondents placed a very strong emphasis and importance on quality of life.
- **Choice**: Patients placed a very high significance on having a choice with their doctors in selecting which drug is better suited for their circumstances.

4.1.3 Impact of Metastatic Renal Cell Carcinoma and Current Therapy on Caregivers

Patient advocacy group input indicated that the impact of kidney cancer on caregivers is significant. Caregivers provide supportive care to the patient in managing adverse side effects, providing emotional support and assuming additional unpaid work duties in the home. A caregiver's paid work; community and social involvement are affected by the physical requirements, time commitments, and emotional stress of caring for a patient.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Pazopanib

Patients without direct experience with pazopanib seek individualized choice in treatment that would offer disease control and improve quality of life while offering ease of use relative to other treatments. While sunitinib will remain a viable option for many patients, pazopanib could provide an additional option for patients and their oncologists. Both treatments have different toxicity profiles.

Similar to other therapies, pazopanib has risks and known side effects. Management of side effects may require intervention of health care professionals and caregivers similar to other Health Canada approved therapies for metastatic RCC. An indication of prior liver impairment (moderate to severe) would prevent a patient from receiving pazopanib and patients will require close monitoring of liver function during pazopanib treatment to allow the oncologist to lower dosage or stop treatment as necessary. One patient that commented on pazopanib disclosed that liver toxicity became an issue with their pazopanib therapy and they were required to discontinue use.

As an oral therapy, pazopanib is not administered in a hospital or cancer care centre and allows the patient ease of use. In addition, as pazopanib is administered daily, it might make it easier for patients and caregivers to follow the administration schedule, without keeping track of the weeks on/off therapy associated with other treatments.

Canadian patient experience with pazopanib is limited as Canadian patients were not involved in the pivotal Phase III trial. However, a limited number of patients have had access through subsequent trials or a Patient Assistance Program from the manufacturer. While these patients experienced side effects with pazopanib, the side effects were quite different when compared to other tyrosine kinase inhibitors, such as less severe/no hand/foot syndrome. Pazopanib survey respondents indicated that with respect to their experience with this drug, their quality of life was reasonably good.

Patients receiving pazopanib indicated that it had shrunk their tumours and seemed to have an important role in PFS. Patients indicated that they expect pazopanib to change their long-term health and well-being by providing PFS in managing kidney cancer.

4.3 Additional Information

- **Provincial Reimbursement Delays post pCODR Recommendation**

Kidney Cancer Canada understands that, at the time of the first pCODR recommendation for pazopanib, no one could have anticipated the delays and barriers to access that may have resulted from the wording of an “intolerant to” recommendation. Kidney Cancer Canada hoped that provincial drug plans would interpret the pCODR recommendation with some flexibility. Instead, access to pazopanib across Canada has been difficult for patients and variable between provinces with the potential for life-threatening consequences for frail and elderly patients for whom pazopanib as a first-line treatment might offer an improved quality of life. Some provinces have taken up to a year to deliberate, debate and interpret how to measure “intolerance to sunitinib”. Patients in many provinces have had no choice in first-line treatment and in other provinces patients have suffered side effects in an attempt to qualify for another choice.

- **Additional Definitions of Eligibility, Proof of Intolerance Applied Across Canada**

Kidney Cancer Canada states that additional layers of eligibility, proof, and paperwork have been placed between the expert oncologist and their patient. In some provinces oncologists must prove that a patient has taken an acceptable dosage over 'x 'cycles, and that the toxicities are deemed to be significant before a patient can access the drug that could allow an improved quality of life. Patients' whose disease progress on the prior course of sunitinib are not eligible to switch to the first –line treatment that they and their oncologist had selected at the outset.

- **Lack of Medical Evidence for Prior Treatment and Intolerance Condition**

Kidney Cancer Canada is very concerned that the 'intolerance' condition, as applied to kidney cancer patients, falls outside the boundaries of evidence-based care.

Kidney cancer specialists have to prove that they have given an adequate dosage for a sufficient duration as determined differently by each individual jurisdiction. For frail and elderly patients, for whom pazopanib may have offered easier tolerability, the requirement to prove toxicity from another drug first impedes access to "the right drug for the right patient" and does harm to overall patient care.

For an advanced cancer such as mRCC for which there are limited funded lines of treatments (two), patients have been forced to "burn through" one treatment line just to access the desired treatment. Following disease progression, patients may find that access to a proven second-line treatment may not be possible (post-sunitinib and post-pazopanib). Access to a clinical trial may be denied based upon prior use of two lines of therapy. Many second-line trials allow the use of one, but not two prior systemic treatments. Patients who have taken both sunitinib and pazopanib will have an exceptionally difficult time getting any subsequent treatment.

For some patients, down-dosing the prerequisite course of sunitinib from 50 mg to 37.5 to 25 mg in an attempt to manage toxicity is known to reduce the efficacy of that treatment. Forcing oncologists to down-dose sunitinib or determine "an effective dose" (without evidence of disease progression) prior to and in order to obtain access to pazopanib is an unacceptable hurdle and carries the risk of adversely affecting health outcomes.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for pazopanib for metastatic RCC. PAG includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the pCODR review of the original pazopanib (Votrient) mRCC review was obtained from all nine of the provinces (Ministries of Health and/or cancer agencies) participating in pCODR. The PAG input from the original pazopanib submission was reviewed again and PAG members had confirmed the original PAG input as sufficient for the resubmission. From a PAG perspective, sunitinib is considered the most relevant comparator and PAG indicated it would be important to be aware of any differences between pazopanib and sunitinib with respect to side effect profile and treatment outcomes. Given this, PAG considered that the relative cost and cost-effectiveness of sunitinib and pazopanib was a very important factor and that comparative data between the two drugs would be most relevant.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

Sunitinib was identified by PAG as the most relevant comparator to pazopanib in the first-line treatment of metastatic RCC and it was noted that sunitinib is funded in many jurisdictions for this indication. Therefore, PAG considered it important to identify any differences in effectiveness, side effects or costs which would make one drug more favourable over the other. PAG indicated that comparative data between pazopanib and sunitinib would be useful to identify any differences but noted that if only placebo-controlled trials for either drugs was available, this may be a barrier. PAG indicated that if the two drugs were determined to have similar clinical effects then the relative costs of pazopanib and sunitinib would a key consideration.

5.2 Factors Related to Patient Population

PAG noted that as metastatic RCC affects a relatively small patient population, there may be a small number of patients accessing pazopanib when considering budget impact, which may be an enabler for jurisdictions if implementing a funding recommendation.

PAG noted that if pazopanib were available, in addition to current therapies such as sunitinib or everolimus, there may sequential use of pazopanib and other agents used to treat metastatic RCC. This may be a barrier to implementation as it could potentially increase costs to the drug program. Therefore, PAG would be interested to know if there is evidence available to support sequential use of pazopanib and other agents in metastatic RCC.

PAG noted that pazopanib could be used in other clinical settings, such as the adjuvant treatment of metastatic RCC; therefore, evidence to support use of pazopanib in these settings may be needed if funding were to be provided for this population.

5.3 Factors Related to Accessibility

PAG input considered that both pazopanib and sunitinib are oral agents that can be given in the community setting without the need for chemotherapy unit resources or the patient having to travel for treatment. This would be beneficial for patients in less central or rural areas.

Pazopanib and sunitinib do not require access to other concomitant drug therapies and specialized molecular tests are not required for a patient to be considered a candidate for pazopanib therapy.

PAG input noted that in some jurisdictions oral therapies are funded under their provincial drug plans and that not all provincial drug plans cover the entire patient population, which may be a barrier to access. Therefore, patients who are not covered under the provincial drug plan would have to receive funding for pazopanib from a private drug plan or pay out of pocket for treatment.

PAG recognized that the same accessibility issues apply to both pazopanib and sunitinib; therefore, when compared with sunitinib, there are no enablers or barriers to access.

5.4 Factors Related to Dosing

PAG noted that there are differences between pazopanib and sunitinib with respect to dosage and schedule that may affect the feasibility of implementing a funding recommendation.

Pazopanib is given in a continuous daily fashion whereas treatment with sunitinib requires a two-week break in therapy during each cycle. PAG input considered that diagnostic scans to assess the effectiveness of metastatic RCC therapy must not be performed during the two week break period with sunitinib, which may cause scheduling issues in cancer treatment centers. PAG observed that this would be an enabler to the use of pazopanib as there is no break period in its treatment schedule.

PAG also noted that patient compliance with pazopanib may be affected by the greater pill burden required, which may impact the effectiveness of pazopanib and be a barrier to implementation. The recommended dosage of pazopanib is 800 mg daily taken as 4 x 200mg tablets. This differs from sunitinib which can be dosed as a single 50 mg tablet. However, given that pazopanib is taken in a continuous daily fashion without a need for treatment breaks, there is a possibility that compliance could be enhanced. Information on patient compliance may be useful to jurisdictions.

In addition, jurisdictions have observed dose de-escalations with sunitinib treatment and have considered that this may occur with pazopanib, as well, therefore, evidence available on the effectiveness of pazopanib at lower doses would be of interest to jurisdictions.

5.5 Factors Related to Implementation Costs

Other than drug costs, additional implementation costs were not identified for pazopanib.

5.6 Other Factors

No other input was provided by PAG although it was noted that some jurisdictions will have to decide whether pazopanib should be funded under the provincial drug program or specific Cancer Care Programs.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of pazopanib on patient outcomes compared to standard therapies in the treatment of patients with advanced RCC who have received no prior systemic therapies or who have received prior treatment with cytokines.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those highlighted in bold. Protocol amendments made after the review protocol was finalized are listed below Table 2.

Table 2. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCT	Patients with advanced renal cell carcinoma who have received no prior systemic therapies or who have received prior treatment with cytokines for metastatic disease Subgroup by ethnicity	Pazopanib (oral) as monotherapy at recommended 800 mg once daily	Targeted therapies for advanced RCC (i.e., VEGF inhibitors, mTOR inhibitors) • Sunitinib • Sorafenib • Bevacizumab + interferon	• Progression-free survival • Overall survival • Response rate • **QoL** • **Patient preference** • SAE • AE (**hand-foot syndrome, fatigue, mucositis/ stomatitis, diarrhea, hypertension**) • WDAE

AE=adverse events; **mTOR**=mammalian target of rapamycin; **QoL**=quality of life; **RCT**=randomized controlled trial; **SAE**=serious adverse events; **WDAE**=withdrawal due to adverse events; **VEGF**=vascular endothelial growth factor

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 1) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's

MeSH (Medical Subject Headings), and keywords. The main search concept was pazopanib or Votrient.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was an update of the literature search conducted for the original Votrient pCODR review, which was not limited by publication year. The search was also limited to English documents. The search is considered up to date as of June 6, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Cancer Trials - canadiancancertrials.ca) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the most recent meetings, proceeding after the original Votrient review. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

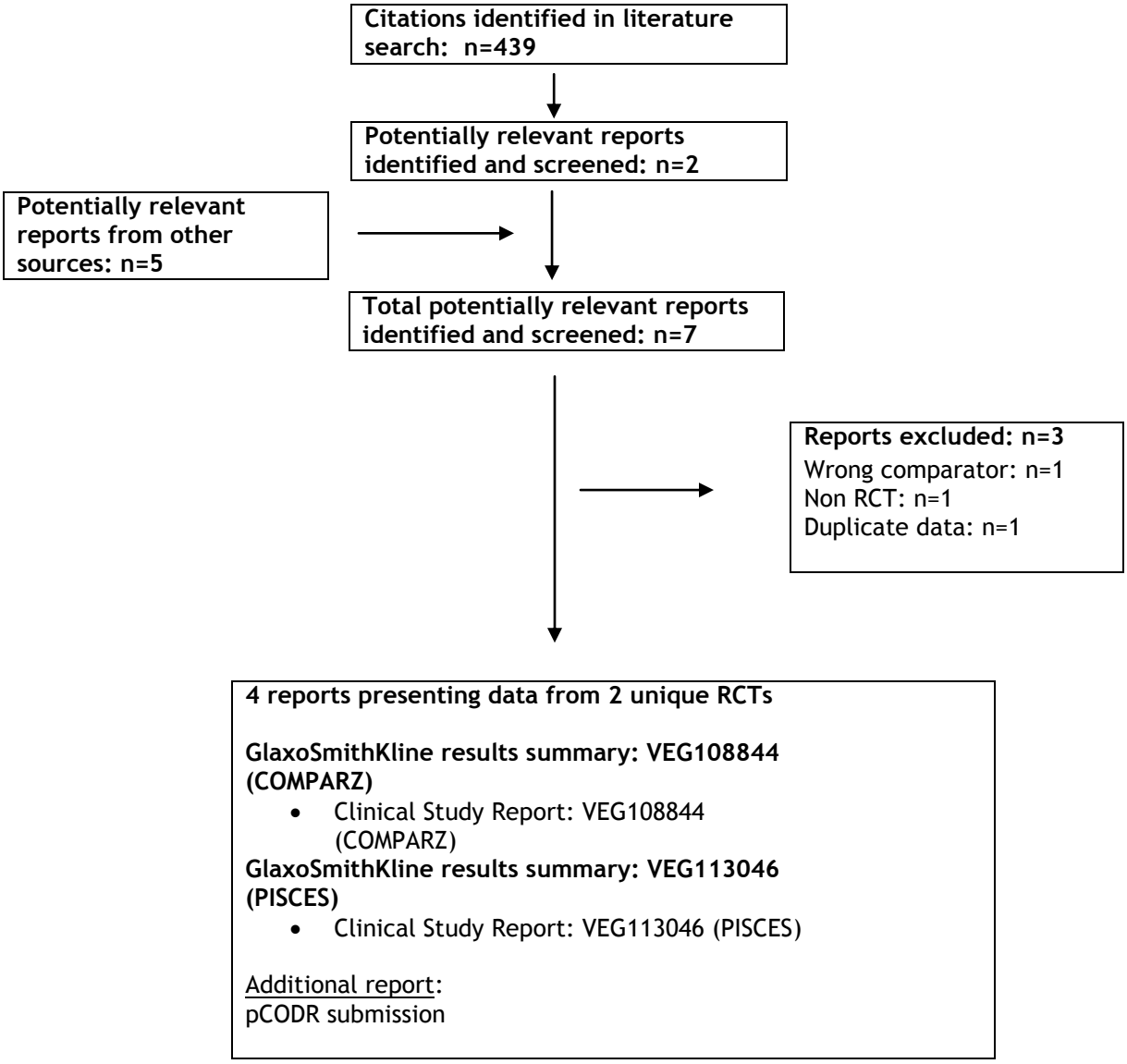
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 439 potentially relevant reports identified, 2 studies were included in the pCODR systematic review [1,2] and 3 studies were excluded. Studies were excluded for the following reasons: duplicate data,[32] comparator (placebo) was not relevant,[33] publication was a review article not a trial.[34]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Two trials were included in this systematic review: COMPARZ,[1] an open-label, randomized, active-controlled, parallel arm, non-inferiority trial and PISCES,[2] a double-blind, randomized, cross-over trial. Both trials were multicentre-multinational and manufacturer-funded; only COMPARZ, however, included Canadian centres. Detailed trial characteristics for COMPARZ and PISCES are summarized below in Table 3 and Table 4.

1.1.1.1 Table 3. Summary of Trial characteristics of the included Study[1]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
COMPARZ 210 centres in 14 countries in Europe, Asia, and North America (including Canada) August 14, 2008 to May 21, 2012[a] Open-label, active-controlled, parallel-group, phase III, non-inferiority RCT (1:1) stratified by KPS (70-80 vs 90-100), LDH (≤1.5 vs >1.5 ULN) previous nephrectomy (yes vs no) n= 1110[b] (randomized) n= 1110[b] (ITT) n= 995[b] (PP) n= 1102[b] (Safety analysis) Funded by: GlaxoSmithKline	• Men and women aged ≥ 18 years old • Diagnosis of RCC (clear cell) • No prior systemic therapy for advanced or metastatic RCC • Locally advanced or metastatic (Stage IV) disease • Measurable disease (by RECIST v1.0 criteria) • KPS ≥70 • Adequate organ system functions **Exclusion criteria:** • History of another malignancy[d] • History or evidence of CNS metastases[e] • Poorly controlled hypertension[f] • Cardiovascular disease • History of CVA or TIA within past 12 months • History of PE or untreated DVT within past 6 months[g] • Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels	Pazopanib 800 mg once daily continuously or sunitinib 50 mg once daily in 6-week cycles (4 weeks on, 2 weeks off) *Note:* Treatment interruption or dose adjustment[c] was permitted in case of adverse events	Primary • PFS Secondary • OS • ORR (CR or PR), time to and duration of response • HRQoL • Safety

CNS=central nervous system; **CR**=complete response; **CVA**=cerebrovascular accident; **DVT**=deep venous thrombosis; **HRQoL**=health-related quality of life; **ITT**=intention to treat; **KPS**=Karnofsky Performance Scale; **LDH**=lactate dehydrogenase; **ORR**=overall response rate; **OS**=overall survival; **PE**=pulmonary embolism; **PFS**=progression-free survival; **PP**=per protocol; **PR**=partial response; **RECIST**= Response Evaluation Criteria in Solid Tumours; **RCC**=renal cell carcinoma; **RCT**= randomized controlled trial; **TIA**=transient ischemic attack; **ULN**=upper limit of normal

1.1.1.1 Table 3. Summary of Trial characteristics of the included Study[1]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**

[a]Cut-off date for primary endpoint
[b]Includes 183 patients from VEG113078
[c]Up to two dose reductions or ≤2 weeks treatment interruption were permitted.
[d]Patients who had another malignancy and had been disease-free for 3 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated *in situ* carcinoma were eligible.
[e]Subjects with previously-treated CNS metastases (surgery ± radiotherapy, radiosurgery, or gamma knife) and with all 3 of the following criteria were eligible:

- Asymptomatic AND
- No evidence of active CNS metastases for ▫6 months prior to enrollment AND
- No requirement for steroids or enzyme-inducing anticonvulsants.

[f]Initiation or adjustment of antihypertensive medication(s) was permitted prior to study entry. Blood pressure must be re-assessed on 2 occasions that were separated by a minimum of 1 hour. The mean SBP/DBP values from each blood pressure assessment (mean of 3 values at each assessment) must be <150/90 mmHg in order for a subject to be eligible for the study.
[g]Subjects with recent DVT who have been treated with therapeutic anticoagulating agents for at least 6 weeks are eligible.

1.1.1.2 Table 4. Summary of Trial characteristics of the included Study[2]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
PISCES 40 centres in 5 countries (France, Italy, UK, Germany, Finland) May 17, 2010 to Oct 19, 2011[a] Randomized (1:1), double-blind, cross-over trial stratified by ECOG performance status (0 vs 1) and number of metastatic sites (≤1 vs ≥2) n=168 (randomized) n=136 (ITT) n= 114 (Modified ITT) n=166 (Safety analysis) Funded by:	• No prior systemic therapy for advanced or metastatic RCC; receipt of adjuvant cancer vaccine was permitted • Locally advanced or metastatic (Stage IV) RCC of any histology, or non-measurable disease if metastases confirmed • Male or female patients ≥18 years old • ECOG ≤1 **Exclusion criteria:** [insert text] • Poor MSKCC risk group • History of another malignancy (exceptions: disease-free for 3 years; completely resected non-melanomatous skin cancer; successfully treated *in situ* carcinoma)	Pazopanib 800 mg once daily continuously for 10 weeks or sunitinib 50 mg once daily for 4 weeks followed by matching placebo for 2 weeks then sunitinib 50 mg once daily for another 4 weeks; a 2-week wash-out occurred between treatments in which no treatments were taken in either arm *Note:* Dose adjustment[b] and early cross-over[c] were permitted in case of adverse events, but treatment interruptions were not.	Primary • Patient preference (questionnaire) Secondary • Primary reasons for patient preference (questionnaire) • QOL (fatigue-FACIT-F, EuroQoL EQ-5D) • Time to dose modification

1.1.1.2 Table 4. Summary of Trial characteristics of the included Study[2]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
GlaxoSmithKline			

ECOG=Eastern Cooperative Oncology Group; **FACIT-F**=Functional Assessment of Chronic Illness Therapy-Fatigue; **ITT**=intention to treat; **MSKCC**=Memorial Sloan-Kettering Cancer Center; **PP**=per protocol; **QOL**=quality of life; **RCC**=renal cell carcinoma; **RCT**= randomized controlled trial

[a]On-going trial; cut-off date for primary endpoint
[b]Up to two dose reductions were permitted.[2] This was accomplished using a stepwise approach where one less capsule was taken at each step with monitoring for approximately 10-14 days at each dose level. If toxicity did not abate, the drug may have been discontinued and the patient crossed over early to the second treatment; in the case of crossing over early, the patient would immediately proceed to a 2-week washout period before beginning the second treatment.[3]
[c]Patients were able to cross over earlier than 10 weeks if an AE necessitated immediate dose interruption or was not resolving despite dose reductions.

a) Trials

A total of two trials, both sponsored by the Submitter, were identified for inclusion into the systematic review: COMPARZ[1] and PISCES[2]. COMPARZ (n=1110) was an open-label, active-controlled, parallel-group, Phase III randomized trial conducted in 210 centres in 14 countries (including Canada) while PISCES (n=168) was a randomized, double-blind, cross-over trial conducted in 40 centres 5 European countries. Both trials compared pazopanib 800 mg with sunitinib 50 mg once daily. COMPARZ was designed to test the non-inferiority of pazopanib compared with sunitinib on progression-free survival while PISCES aimed to determine which drug was preferred by patients through a questionnaire. PISCES randomized the order of treatment administration according to two periods – SP (sunitinib first then pazopanib) or PS (pazopanib first then sunitinib); a two-week wash-out separated the finish of the first treatment from the start of the next treatment.

b) Populations

COMPARZ

COMPARZ comprised a total of 1110 randomized patients. Following higher than anticipated rates of drop-out and discordance between the independent review committee and investigators in adjudicating outcomes, COMPARZ amended its protocol to include all 183 patients randomized to a concurrently running Asian trial (VEG113078) of similar design in order to increase its sample size.[1] COMPARZ patients had a mean age of about 61 years, were mostly male (73.2%), with almost 2/3 Caucasian (63.7%) and 1/3 Asian (34.4%). Almost all patients (98.2%) had renal cell carcinoma with either clear cell (92.9%) or predominantly clear cell histology (5.3%). Memorial–Sloan Kettering Cancer Center (MSKCC) risk was 'favorable' or 'intermediate' in about 86% of patients and 80% by Heng risk scoring. About 3/4 of patients had a Karnofsky Performance Scale score of 90 or 100. Most patients (83.2%) had undergone a prior nephrectomy. Baseline characteristics were well balanced between groups.[1] (Table 5)

PISCES

PISCES randomized 168 patients in total. Similar to COMPARZ, PISCES patients had a mean age of about 62 years and were mostly male (67.3%). The majority (93.5%) of patients were Caucasian and about 90% had renal cell carcinoma with clear cell histology; 72.0% of patients had an ECOG score of 0. Like COMPARZ, most patients (88.7%) had previously undergone a nephrectomy. Several imbalances between groups were observed, notably in the proportion of males (PS >SP), those with clear cell histology (SP >PS). Numerical differences were also noted with respect to the number of metastatic sites and nephrectomy status, but the CPG considered these differences trivial.[2]

Table 5. Baseline characteristics (ITT Population) – COMPARZ trial[1]

Variable	Pazopanib n=557	Sunitinib n=553
Age (years)		
Mean (SD)	60.9 (10.9)	61.2 (11.0)
Median (min-max)	61.0 (18-88)	62.0 (23-86)
Sex, n (%)		
Male	398 (71.5)	415 (75.0)
Race, n (%)		
White	349 (62.7)	358 (64.7)
Asian	194 (34.8)	188 (34.0)
Other	13 (2.3)	6 (1.1)
Region, n (%)		
North America (Canada, USA)	195 (35.0)	187 (33.8)
Asia (China, Japan, Korea, Taiwan)	188 (33.8)	179 (32.4)
European Union (Germany, Ireland, Italy, The Netherlands, Spain, Sweden, UK)	153 (27.5)	157 (28.4)
Primary tumor type, n (%)		
Renal cell	557 (100)	553 (100)
Time since initial diagnosis (days)		
Median[a] (IQR)	206.0 (51.0-1064.0)	229.0 (51.0-984.0)
Stage, n(%)		
I	2 (<1)	0
II	0	5 (<1)
III	8 (1)	9 (2)
IV	546 (98)	539 (97)
Missing	1 (<1)	0
Histology, n (%)		
Clear cell	522 (94)	509 (92)
Predominantly clear cell	27 (5)	32 (6)
Other	8 (1)	11 (2)
Measurable disease at baseline (IRC assessed), n (%)		
Yes	543 (97)	538 (97)
No	11 (2)	12 (2)
Missing	3 (<1)	3 (<1)
Number of organs involved, n (%)[18]		

Variable	Pazopanib n=557	Sunitinib n=553
1	117 (21)	108 (20)
2	204 (37)	204 (37)
≥3	235 (42)	241 (44)
MSKCC risk category, n (%)		
Favorable	151 (27)	152 (27)
Intermediate	322 (58)	328 (59)
Poor	67 (12)	52 (9)
Unknown	17 (3)	21 (4)
Heng risk category, n (%)		
Favorable	142 (25)	137 (25)
Intermediate	299 (54)	308 (56)
Poor	106 (19)	94 (17)
Unknown	10 (2)	14 (3)
Karnofsky Performance Scale, n (%)		
70 or 80	141 (25)	130 (24)
90 or 100	416 (75)	423 (76)
Prior nephrectomy, n (%)		
With prior nephrectomy[b]	459 (82)	465 (84)
Without prior nephrectomy	98 (18)	88 (16)
Baseline levels of LDH, n (%)		
>1.5 x ULN	40 (7)	29 (5)
≤1.5 x ULN	517 (93)	524 (95)

IQR=interquartile range; **IRC=**independent review committee; **MSKCC=**Memorial-Sloan Kettering Cancer Center; **SD=**standard deviation;

[a]pazopanib, n=533; sunitinib, n=529

[b]Includes 7 nephrectomies reported as non-cancer related surgeries

Note: Australia not included due to small sample size.

Table 6. Baseline characteristics (All Randomized Population) – PISCES trial[35]

Variable	SP N= 82	PS N= 86
Age (years)		
Mean Age, years (SD)	62.1 (9.56)	62.2 (11.35)
Sex, n (%)		
Males	52 (63.4)	61 (70.9)
Race, n (%)		
N	76[a]	83[b]
White	74 (97)	83 (100)
African American/ African heritage	1 (1)	0
Central/South Asian heritage	1 (1)	0
ECOG, n(%)		
ECOG 0	61 (74)	60 (70)
ECOG 1	21 (26)	26 (30)
Histology, n (%)		
Clear cell	76 (93)	75 (87)
Measurable disease, n (%)		
Yes	75 (91)	80 (93)
Number of metastatic sites, n (%)		
0 and 1	23 (28)	20 (23)
>=2	58 (71)	65 (76)
Missing	1 (1)	1 (1)
Nephrectomy, n (%)		
With prior nephrectomy	70 (85)	79 (92)

PS = Pazopanib 800 mg once daily orally followed by a 2-week Wash-out Period then sunitinib 50 mg once daily orally
SP = Sunitinib 50 mg once daily orally followed by a 2-week Wash-out Period then pazopanib 800 mg once daily orally
[a]Six subjects had missing race in the SP arm
[b]Three subjects had missing race in the PS arm

c) Interventions

The following comparators were identified in the systematic review protocol: sunitinib, sorafenib, and bevacizumab + interferon. However, only the COMPARZ and PISCES trials comparing pazopanib with sunitinib met the inclusion criteria; no other trials comparing pazopanib with either of the two other comparators of interest were identified. Both sunitinib and pazopanib are dosed orally once daily; however, sunitinib is administered in 6-week cycles (4 weeks on-treatment and 2 weeks off-treatment) while pazopanib is administered continuously (i.e., without treatment interruption). In both COMPARZ and PISCES, pazopanib was dosed at 800

mg once daily while sunitinib was dosed at 50 mg once daily; dose adjustment was permitted in case of toxicity. Concomitant supportive medications were permitted during both trials; however, in COMPARZ, concomitant anticancer treatments (medical, surgical, radiologic) for RCC were not allowed while in PISCES, neither concomitant anticancer treatments, palliative radiotherapy nor strong CYP3A4 inhibitors were permitted.[1,2]

d) Patient Disposition

COMPARZ

The Intention-to-treat (ITT) population comprised all randomized patients from the original population of study VEG108884 and the substudy VEG113078 according the treatment to which the patients were randomized. The Per-protocol (PP) population was similar to the ITT population, comprising the subset of ITT patients who did not have any major protocol deviations. The safety population comprised all randomized patients from the original population of study VEG108884 and the substudy VEG113078 according to the actual treatment received, and who received at least one dose of study treatment.[18] (Table 7)

In COMPARZ, 557 patients were randomized to pazopanib and 553 to sunitinib; these patients also comprised the ITT analysis set. The per-protocol analysis set comprised 501 (89.9%) pazopanib-treated patients and 494 (89.3%) sunitinib-treated patients; the most common reasons for exclusion from the PP analysis were the baseline scan being performed outside of the protocol-defined time frame (3.4% vs 3.8%, respectively) and discordance occurring between the investigator and independent review committee (i.e., measurable disease per investigator but non-measurable disease per IRC, 3.6% vs 4.3%, respectively). The safety set consisted of 554 (99.5%) patients in the pazopanib arm compared with 548 (99.1%) in the sunitinib arm. A similar proportion of patients discontinued treatment whether taking pazopanib [486 (87.3%)] or sunitinib [483 (87.3%)]. The most common reason for discontinuing treatment was disease progression (51.7% vs 54.6%, respectively) followed by adverse events (23.0% vs 18.4%, respectively). (Table 8)

Table 7: Patient Disposition – COMPARZ trial[18]

	Pazopanib	Sunitinib
Screened, n	1403[1]	
Randomized, n (%)[1]	557	553
ITT analysis set	557	553
PP analysis set	501	494
Safety analysis set	554	548
Discontinued, n (%)	486 (88)	483 (88)
Reasons for discontinuing treatment:		
• Disease progression (including death due to disease progression), n (%)	288 (52)	302 (55)

	Pazopanib	Sunitinib
• Adverse events, n (%)	128 (23)	102 (19)
• Protocol deviation, n (%)	4 (<1)	6 (1)
• Lost to follow-up, n (%)	1 (<1)	0
• Investigator decision, n (%)	28 (5)	36 (7)
• Decision by subject or proxy, n (%)	37 (7)	37 (7)

ITT=intent to treat; **PP**=per protocol

Table 8. Summary of Patients Excluded from Per Protocol Population (ITT Population) – COMPARZ trial[1]

	Pazopanib n=557	Sunitinib n=553
Included in PP population, n (%)	501 (90)	494 (89)
Excluded from PP population, n (%)	56 (10)	59 (11)
Reason for exclusion, n (%)		
Baseline scan performed outside protocol defined time frame	19 (3)	21 (4)
Unreadable baseline scan per the IRC	2 (<1)	1 (<1)
Measurable disease per investigator but non-measurable disease per IRC	20 (4)	24 (4)
Disease histology other than clear cell component	1 (<1)	0
Karnofsky Performance Score < 70	0	1 (<1)
Prior systemic treatment for metastatic disease	1 (<1)	0
Received radiation while on study treatment	3 (<1)	2 (<1)
Radiologic progression recorded, but censored due to extended loss-to-follow-up	1 (<1)	7 (1)
Interruption of study treatment for > 42 days	11 (2)	6 (1)

IRC=Independent Review Committee; **ITT**=intent to treat; **PP**=per protocol

PISCES

The All Randomized Population comprised all randomized patients regardless of whether they received a dose of study treatment. The Intention-to-treat (ITT) population comprised all randomized patients who received at least one dose of either study treatment from each period. The Modified ITT population comprised all randomized patients who received at least one dose of either study treatment from each period and who did not have documented progression after period 1 and who completed the patient preference questionnaire. The Modified ITT population was the primary analysis population. The Safety population comprised all randomized patients who received at least one dose of either study treatment.[35] (Table 9)

In PISCES, 82 patients were randomized to sunitinib-pazopanib (SP) and 86 to pazopanib-sunitinib (PS). The ITT set consisted of 32 (19.0%) fewer patients than the randomized set: 68 (82.9%) in the SP group and 68 (79.1%) in the PS group. The modified ITT set consisted of 60 (73.2%) patients in the SP group and 54 (62.8%) in the PS group. The safety analysis set comprised 80 (97.6%) SP patients and 86 (100%) PS patients. In period 1, a similar number of patients discontinued prematurely in the SP [21 (25.6%)] and PS [19 (22.1%)] groups; in period 2, however, the discontinuation rate was twice as high in the PS [28 (41.2%)] group compared with the SP [14 (20.6%)] group. In both periods, the primary reason for discontinuation was adverse event: in period 1, 15 (18.3%) SP patients compared with 12 (14.0%) PS patients were prematurely discontinued due to adverse events; in period 2, twice the number of PS patients [21 (30.9%)] compared with SP patients [10 (14.7%)] prematurely discontinued due to adverse events. (Table 10)

Table 9. Patient Disposition – PISCES[2]

Populations	Number (%) of patients	
	SP	PS
All randomized	82 (100)	86 (100)
ITT	68 (83)	68 (79)
Modified ITT	60 (73)	54 (63)
Safety	80 (98)	86 (100)
Open-label pazopanib	39 (48)	45 (52)

ITT=intent to treat; **PS**=pazopanib 800 mg once daily orally followed by a 2-week wash-out period then sunitinib 50 mg once daily orally; **SP**=sunitinib 50 mg once daily orally followed by a 2-week wash-out period then pazopanib 800 mg once daily orally

Table 10. Summary of Study Treatment Status (All Randomized Population) – PISCES[2]

Period		No. (%) of Patients	
		SP N=82	PS N=86
		Sunitinib	**Pazopanib**
	Completion status		
	Entered	82 (100)	86 (100)
	Completed[a,b]	61 (74)	67 (78)[c]
Period 1	Prematurely discontinued	21 (26)	19 (22)[c]
	Primary reason for discontinuation		
	Disease progression (including death due to disease progression)	2 (2)	3 (3)[d]
	Adverse event	15 (18)	12 (14)
	Protocol deviation	0	1 (1)
	Investigator discretion	0	1 (1)
	Decision by patient or proxy	4 (5)	2 (2)
		Sunitinib	**Pazopanib**
	Completion status		
	Entered	68 (100)	68 (100)
	Completed[a,b]	54 (79)[e]	40 (59)
Period 2	Prematurely discontinued	14 (21)[e]	28 (41)
	Primary reason for discontinuation		
	Disease progression (including death due to disease progression)	2 (3)[e]	5 (7)
	Adverse event	10 (15)	21 (31)
	Protocol deviation	1 (1)	0
	Investigator discretion	1 (1)	1 (1)
	Decision by patient or proxy	0	1 (1)

a. Patients who completed all 10 weeks of the period and did not discontinue study treatment prematurely

b. Based on investigator assessment

c. Two patients (Patients 253 and 370) were recorded as prematurely discontinued from the study; however, exposure data indicated that both patients had completed all 10 weeks of Period 1 treatment. Both patients are included in the table as completed.

d. Patient 78 had the primary reason for discontinuation recorded as disease progression; however, there was no scan or a response assessment to support disease progression

e. Two patients (Patients 36 and 214) were recorded as prematurely discontinued from the study; however, both patients had completed all 10 weeks of Period 2 treatment and are included in the table as completed.

e) Limitations/Sources of Bias

COMPARZ

- Progression-free survival (PFS) was the primary efficacy outcome and the basis for the non-inferiority (NI) margin determination. However, PFS may not be a valid surrogate marker for overall survival (OS) in RCC.
    - The conclusion of pazopanib's non-inferiority to sunitinib is based on results from the ITT analysis rather than the more conservative PP analysis. While the upper bound of the 95% CI for the hazard ratio did not exceed the 1.25 NI margin in the ITT analysis. The PP analysis was not pre-specified and NI could not be confirmed. The lack of demonstrable consistency between the results of the ITT and PP analyses casts some uncertainty around the non-inferiority of pazopanib to sunitinib. Upon review of feedback provided by the manufacturer, it is acknowledged that a body of evidence supports the use of the ITT population as being the primary analysis in non-inferiority trials. However, evidence also supports that analysis be conducted both in the ITT and PP analysis and in the event inconsistent conclusions are demonstrated, the use of the PP population is reasonable. [13-15]
    - The NI margin was established, in part, from sunitinib trial data showing a median PFS of 11 months in sunitinib-treated patients;[1] however, this treatment effect may not be generalizable to 'real-world' practice. In fact, median PFS observed in COMPARZ fell below 11 months in sunitinib-treated patients in both intent-to-treat (ITT) and per-protocol (PP) analyses. Of note, the CGP observed that the overall response rate in the sunitinib group (i.e., 25%) seemed unusually low compared with what would normally be expected in clinical practice. Therefore, there is a potential risk of bias in the trial toward a declaration of non-inferiority when sunitinib may not be as effective as was assumed.
- Due to higher than anticipated rates of attrition and discordance [between independent review committee (IRC) and investigator assessments], a protocol amendment was filed allowing for the addition of patients from a concurrently running Asian trial (VEG113078) to expand the study population size in COMPARZ. COMPARZ is therefore an amalgam of two studies: Asian trial (VEG113078) and original COMPARZ trial. The population analysis sets are therefore derived from two separate trials instead of one; likewise, Asian patients in COMPARZ do not represent a true subgroup analysis as they were sourced from two separate trials.
- A methodologically weaker open-label design was chosen for comparing pazopanib and sunitinib instead of a double-blind design, which was used in PISCES.

- The Clinical Guidance Panel noted that the timing of Health-Related Quality of Life (HRQoL) assessment corresponded to the time at which peak treatment-related toxicity may be most likely to occur in sunitinib-treated patients, thus potentially making pazopanib treatment appear more favourable compared with sunitinib.
    - Health-Related Quality of Life (HRQoL) was also not assessed in half [183 (16.5%)] of the Asian patients [378 (34.1%)] included in COMPARZ (n=1110); this was due to HRQOL not being assessed as an outcome in VEG113078, from which these 183 patients were drawn.[32]
- Since it is recognized that Asian patients respond differently to tyrosine kinase inhibitor treatment than non-Asians, the trial ideally would have stratified patients at the outset according to being Asian or non-Asian to enable proper treatment comparisons by subgroup instead of relying on inconclusive exploratory analyses.
- Women were underrepresented in the trial, comprising just over 1/4 of the study population.

PISCES

- The use of a cross-over design, which assumes disease stability over the period during which the trial is conducted, may have been inappropriate due to possible disease instability:[19]
    - While the number of patients who prematurely discontinued was similar between SP and PS treatment arms in period 1, in period 2, twice the number of patients in the PS group prematurely discontinued compared with the SP group. Premature discontinuations were driven primarily by adverse events in both periods. The manufacturer speculated that the notable difference in discontinuations and adverse events between treatment groups observed in period 2 may have been due to unstable disease, which increases susceptibility to drug-related toxicity.[2]
- The patient preference questionnaire used to assess the primary outcome was acknowledged by the manufacturer to not be a validated questionnaire.[2] This questionnaire has subsequently been published. However, the questionnaire was not available for the pCODR review and as a result was not assessed for validity.
- Treatment interruptions were not permitted during the trial, thus potentially underestimating toxicity/tolerability profiles. Approximately 20% of patients did not complete period 1, with 10% of patients failing to complete period 1 due to adverse events.[2] By comparison, there were fewer non-completers in period 2 (~7%) and fewer withdrawals due to adverse events (~1%)[2] potentially suggesting that patients most susceptible to treatment-related toxicity were weeded out early.
- A two-sided alpha of 0.10/90% CI was used in the trial, increasing the chance of finding a difference between treatments when one does not exist. (Type I error) Ideally, a two-sided alpha of 0.05/95% CI would have been used to minimize the risk of a Type I error.

- For (secondary) HRQOL outcomes, the safety population was used, not the ITT population, which is the analysis set conventionally employed in efficacy analyses. In contrast, the modified ITT was (appropriately) used for analysis of the primary outcome (patient preference). In theory, these two efficacy outcomes should be related, so it is unclear why the population analysis sets used differed.
    - Typically, the ITT population (n= 136) should closely resemble the all-randomized population (n=168), which it does not in this trial. The modified ITT set (n=114), used in the primary analysis, was even smaller in size. Thus, some doubt is cast on how generalizable the results from these ITT and modified ITT analysis sets are.
    - In using the safety set, the definition of which seems to imply that patients may only have received a single dose of study drug, to evaluate HRQOL, it is unclear how reflective these data would be of quality of life in a real-world setting.
- The derivation of the sample size is not described, other than to say it was based on 50% of patients preferring one drug, 30% preferring the other drug, and 20% having no preference.[2]
- Although the 2-week wash-out period was considered adequate in duration by the CGP, there is a potential risk of unblinding in the case of any lingering treatment-related toxicity (e.g., alopecia). Moreover, subjecting pazopanib-treated patients to a wash-out period at all is not reflective of real-world administration of pazopanib since the drug is taken continuously (i.e., without scheduled interruption).

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Results are presented according to the hierarchy of outcomes established in the systematic review protocol (section 6.2.1). The data cut-off dates for the primary outcome in COMPARZ was May 21, 2012;[1] for PISCES, the cut-off date was October 19, 2011.[2]

Only COMPARZ assessed efficacy outcomes of progression-free survival, overall survival, and response rate; both COMPARZ and PISCES report health-related quality of life data.

COMPARZ

A summary of the trial results for COMPARZ are presented in

Table 11. *Summary of Outcomes – COMPARZ*[18]

	Pazopanib (n=557)	Sunitinib (n=553)
EFFICACY		
Progression-free survival		
IRC-assessed (ITT)		
Median PFS in months (95% CI)	8.4 (8.3, 10.9)	9.5 (8.3, 11.1)
HR (95% CI)	1.05 (0.90, 1.22)[a]	
IRC-assessed (PP)		
Median PFS in months (95% CI)	8.4 (8.3, 10.9)	10.2 (8.3, 11.1)
HR (95% CI)	1.07 (0.91, 1.26)[b]	
Overall survival (ITT)		
Median PFS in months (95% CI)	28.4 (26.2, 35.6)	29.3 (25.3, 32.5)
HR (95% CI)	0.91 (0.76, 1.08)	
Overall response rate (ITT), IRC-assessed		
Response rate (CR+PR), n (%)	171 (31)	137 (25)
95% CI	26.9, 34.5	21.2, 28.4
Difference in response [CR+PR], % (95% CI)	6 (0.7, 11.2)	
FACIT-F (ITT)		
Difference in mean change vs. sunitinib (95% CI)	2.32 (1.13, 3.52)	
FKSI-19 (Total score, ITT)		
Difference in mean change vs. Sunitinib (95% CI)	1.41 (0.24, 2.58)	
SQLQ (ITT)		
Difference in mean vs. sunitinib		
Mouth and throat sores	-0.505	
Hand soreness	-0.204	
Foot soreness	-0.267	
CTSQ (ITT)		
Satisfaction with therapy		

Difference in mean vs. sunitinib (95% CI)	3.21 (1.36, 5.06)	
HARMS		
	Pazopanib (n=554)	Sunitinib (n=548)
Dose reductions		
Patients with any dose reductions, n (%)	246 (44)	277 (51)
Patients with ≥1 dose reductions, n (%)	246 (44)	277 (50)
Dose interruptions		
Patients with any dose interruption ≥7 days, n (%)	243 (44)	267 (49)
Median duration of dose interruption, days (IQR)	12 (8-14)	14 (11-20)
Adverse events, most common, pazopanib > sunitinib, n (%)(ITT, on therapy)		
Diarrhea	348 (63)	315 (57)
Hypertension	257 (46)	223 (41)
ALT increased	171 (31)	97 (18)
Hair color changes	168 (30)	53 (10)
AST increased	148 (27)	98 (18)
Serious adverse events		
Patients with any SAE, n (%)	230 (42)	224 (41)
Most common SAEs, pazopanib > sunitinib, n (%)		
ALT increased	35 (6)	8 (1)
AST increased	17 (3)	2 (<1)
Patients with fatal SAEs, n (%)	13 (2)	19 (3)
Withdrawals due to adverse events		
Patients with any WDAE, n (%)	135 (24)	112 (20)

CI=confidence interval; **CR**=complete response; **CTSQ**=Cancer Therapy Satisfaction Questionnaire; **FACIT-F**=Functional Assessment of Chronic Illness Therapy – Fatigue; **FKSI-19**=Functional Assessment of Cancer Therapy – Kidney Symptom Index-19; **IQR**=interquartile range; **ITT**=intent to treat; **IRC**=Independent Review Committee; **PP**=per protocol; **PR**=partial response; **SAE**=serious adverse event; **SQLQ**=Supplementary Quality of Life Questionnaire; **WDAE**=withdrawal due to adverse event

[a]Non-inferiority met [b]Non-inferiority analysis was not pre-specified and so non-inferiority could not be confirmed with certainty [c]Adjusted for baseline score

Progression-free survival

Progression-free survival (PFS) was the primary efficacy outcome in COMPARZ, as assessed by the independent review committee (IRC). In the ITT analysis, the median PFS in pazopanib-treated patients was 8.4 months compared with 9.5 months in sunitinib-treated patients. This translated into a non-statistically significant hazard ratio (HR) of 1.05 (95% CI, 0.90 to 1.22). In the PP analysis, the median PFS in pazopanib-treated patients was 8.4 months compared with 10.2 months in sunitinib-treated patients, corresponding to a HR of 1.07 (95% CI, 0.91 to 1.26) which was not statistically significant. Since the upper-bound of the 95% CI in the ITT analysis did not exceed the pre-specified NI margin of 1.25, the non-inferiority hypothesis was confirmed; however, non-inferiority could not be confirmed in the PP analysis since the upper-bound of the 95% confidence interval exceeded 1.25. (Table 12)

In the systematic review protocol, ethnicity was identified as a subgroup of interest. However, for PFS, subgroup analyses by ethnicity were limited to White versus Japanese patients. The results from a subgroup analysis performed on 707 White patients supported the results from the main analysis (HR $\pm$ standard error: 1.04 $\pm$ 0.10).[1] No separate subgroup analysis was reported for Japanese patients.[1]

Table 12: Progression-free survival – COMPARZ[18]

	Pazopanib (n=557)	Sunitinib (n=553)
IRC-assessed (ITT)		
Number died (event)	21 (4)	28 (5)
Number progressed	315 (57)	295 (53)
Number censored, follow-up ended	156 (28)	168 (30)
Number censored, follow-up ongoing	65 (12)	62 (11)
Median PFS in months (95% CI)	8.4 (8.3, 10.9)	9.5 (8.3, 11.1)
HR (95% CI)	1.05 (0.90, 1.22)[a]	
IRC-assessed (PP)[b]		
Median PFS in months (95% CI)	8.4 (8.3, 10.9)	10.2 (8.3, 11.1)
HR (95% CI)	1.07 (0.91, 1.26)[c]	
Investigator-assessed (ITT)		
Median PFS in months (95% CI)	10.5 (8.3, 11.1)	10.2 (8.3, 11.1)
HR (95% CI)	1.00 (0.86, 1.15)[a]	

CI=confidence interval; **IRC**=Independent Review Committee; **PP**=per protocol; **ITT**=intention-to-treat

[a]Non-inferiority met; [b]pazopanib n=501, sunitinib n=494; [c]Non-inferiority not met

Overall survival

Overall survival (OS) was a secondary endpoint in COMPARZ. It was defined as the interval between the date of randomization and the date of death due to any cause.[1] OS was estimated based on 502 deaths: 250 (45%) in the pazopanib group and 252 (46%) in the sunitinib group.[1] The median OS in pazopanib-treated patients was 28.4 months compared with 29.3 months in sunitinib-treated patients corresponding to a non-statistically significant HR of 0.91 (95% CI, 0.76 to 1.08).(Table 13) No subgroup analyses were performed for OS.

Table 13. Overall survival (ITT) – COMPARZ[18]

	Pazopanib (n=557)	Sunitinib (n=553)
Number died, n (%)	250 (45)	252 (46)
Number censored, follow-up ended	36 (6)	42 (8)
Number censored, follow-up ongoing	271 (49)	259 (47)
Median OS in months (95% CI)	28.4 (26.2, 35.6)	29.3 (25.3, 32.5)
HR (95% CI)	0.91 (0.76, 1.08)	

CI=confidence interval; **ITT**=intention-to-treat; **OS**=overall survival

Overall response rate

The overall response rate (ORR) consisted of complete or partial responses (CR+PR). In the IRC-assessed ITT analysis, there was a greater overall response rate in pazopanib-treated [171 (31%)] compared with sunitinib-treated [137 (25%)] patients [response difference: 6% (95% CI, 0.7 to 11.2%)]. (Table 14)

The manufacturer stated that the difference in ORR between groups was driven by a higher ORR in Asian patients. In a subgroup analysis of Asian patients, ORR was 36% (95% CI, 28.8% to 42.5%) in pazopanib-treated patients compared with 21% (95% CI, 14.7% to 26.6%) in sunitinib-treated patients. In White patients, the ORR was 29% (95% CI, 23.9% to 33.4%) in pazopanib-treated patients compared with 26% (95% CI, 21.7% to 30.8%) in sunitinib-treated patients.[1] The results of this subgroup analysis should be interpreted with caution as these were exploratory analyses conducted without adjustments for multiple statistical testing; consequently, the risk for committing a Type I statistical error is increased.

Table 14. Overall response rate (ITT) – COMPARZ[18]

ORR (ITT)	IRC-assessed		Investigator-assessed	
	Pazopanib (n=557)	Sunitinib (n=553)	Pazopanib (n=557)	Sunitinib (n=553)
Best response, n (%)				
CR	1 (<1)	3 (<1)	3 (<1)	8 (1)
PR	170 (31)	134 (24)	183 (33)	152 (27)
SD[a]	216 (39)	242 (44)	231 (41)	239(43)
PD	97 (17)	105 (19)	78 (14)	93 (17)
Unknown	73 (13)	69 (12)	62 (11)	61 (11)
Response rate (CR+PR), n (%)	171 (31)	137 (25)	186 (33)	160 (29)
95% CI	26.9, 34.5	21.2, 28.4	29.5, 37.3	25.2, 32.7
Difference in response (CR+PR), %	6		4	
95% CI for difference	0.7, 11.2		-1.0, 9.9	

CI=confidence interval; **CR**=complete response; **ITT**=intention-to-treat; **ORR**=overall response rate; **PD**=progressive disease; **PR**=partial response; **SD**=stable disease

[a]In order to qualify as a best response of SD, a response of SD had to be observed at week 12 or later.

Health-Related Quality of Life

Health-related quality of life (HRQoL) was studied as a secondary endpoint through a series of self-reported questionnaires. These consisted of the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), Functional Assessment of Cancer Therapy – Kidney Symptom Index-19 (FKSI-19), Supplementary Quality of Life Questionnaire (SQLS), and the Cancer Therapy Satisfaction Questionnaire (CTSQ). These questionnaires are described in Table 15 below.

Table 15. Minimal Clinically Important Differences for Quality of Life Tools Used to Assessed Cancer

Citation	Sample Population	*QoL Tool* and Subscales	MCID
Cella et al.[36]	Sample 1* Sample 2† Sample 3‡	***FACT/FACIT*** Fatigue Scale FACT-G total score FACT-An total score Trial Outcome Index-Fatigue Trial Outcome Index-Anemia	 3.0 4.0 7.0 5.0 6.0
Cella et al.[37]	Diagnosis of advanced or recurrent kidney cancer (cancer that had spread outside the kidney), ≥ 18 yrs, speak, read and write English, no current diagnosis of psychosis or dementia	***FKSI*** FKSI-15 FKSI-10	 3-5 (range) 2-4 (range)
Cella et al.[38]	Physician sample† Patient sample†	***FKSI-DRS***	2-3 (range)
Reddy et al.[39]	194 Palliative care cancer patients (treated with methylphenidate and/or donepezil or placebo) experiencing CRF; ESAS min. score 4 for 4 days, MMSE of ≥ 24, hemoglobin > 10g/dL, no history of seizures, no major contraindications to methylphenidate/ donepezil or other medications for fatigue	***ESAS***** ***FACIT-F***	Reduction in 4 points Reduction in 10 points
Trask et al.[40]	Cancer patients (including breast, colorectal, lung cancer, or melanoma), ≥ 18 yrs, who had received in the last 6 months or were currently receiving more than one cycle of chemo, biological, or hormonal therapy	***CTSQ*** ET domain SWT domain FSE domain	 8.3 5.9 10.3
Yost et al.[41]***	N/A***	***FACT-G*** Physical Well-Being Emotional Well-Being Social/Family Well-Being Functional Well-Being ***FACT-An*** Fatigue Subscale TOI-Fatigue TOI- Anemia	3-7 (range) 2-3 (range) 2-3 (range) 2-3 (range) 2-3 (range) 7 (range) 3-4 (range) 5 (range) 6 (range)

CRF = cancer-related fatigue; **CTSQ** = Cancer Therapy Satisfaction Questionnaire; **ESAS** = Edmonton Symptom Assessment System; **ET** = Expectations of Therapy; **FACIT** = Functional Assessment of Chronic Illness Therapy; **FACT** = Functional Assessment of Cancer Therapy; **FACT-An** = Functional Assessment of Cancer Therapy-Anemia; **FACIT-F** = Functional Assessment for Chronic Illness Therapy-Fatigue; **FACT-General** = Functional Assessment of

Cancer Therapy**-General; FKSI-15** = Functional Assessment of Cancer Therapy-Kidney Symptom Index-15 index; **FKSI-10** = Functional Assessment of Cancer Therapy-Kidney Symptom Index-10 abbreviated options; **FKSI-DRS** = Functional Assessment of Cancer Therapy—Kidney Symptom Index- Disease-Related Symptoms; **FSE** = Feelings about Side Effects**; MCID** = Minimal Clinically Important Difference; **QoL** = quality of life; **SWT** = Satisfaction with Therapy; **TOI** = Trial Outcome Index; **yrs** = years

*Sample 1: 50 mixed diagnosis cancer patients currently receiving treatment.

†Sample 2: 131 mixed-diagnosis cancer patients participating in a longitudinal observational study of fatigue and quality of life during chemotherapy.

‡Sample 3: 2,402 mixed-diagnosis cancer patients enrolled in an open-label, non-randomized, community-based clinical trial evaluating the effectiveness, safety, and clinical outcome of a treatment for anemia in cancer patients.

†Physician sample: Experts who treat kidney cancer.

↑Patient Sample: 141 patients with kidney cancer.

**Investigators studied the clinically important difference in CRF using the patients' perception of benefit, as measured by the global benefit score (GBS).

***Summarizes established MCIDs for FACIT Scales and Subscales.

FACIT-F

The adjusted mean change scores for FACIT-F worsened in both pazopanib (-4.7) and sunitinib (-7.0) groups from baseline to 6 months, though less so in pazopanib-treated patients [difference: 2.32 (95% CI, 1.13 to 3.52)]. (Table 16) Though statistically significant, the clinical meaningfulness of the difference is uncertain as the minimal clinically importance difference (MCID) has not been determined in the setting of RCC; in a sample of mixed cancer diagnoses, an MCID of 3.0 has been reported.

Table 16. FACIT-F: Summary of analysis of change from baseline over 6 months (ITT) – COMPARZ[18]

	Pazopanib (n=557)	Sunitinib (n=553)
N	377	403
Adjusted mean change[a]	-4.7	-7.0
Difference in mean change vs. sunitinib	2.32	
95% CI for treatment difference	1.13, 3.52	

CI=confidence interval; **FACIT-F=**Functional Assessment of Chronic Illness Therapy – Fatigue

Note: A negative change from baseline represented a worsening of condition. Higher scores represented better health. A positive difference indicates that pazopanib scores were better.

[a]Adjusted for baseline score

FKSI-19

The adjusted mean change scores for FKSI-19 showed a worsening over 6 months from baseline in both groups in all but the DRS-E domain; however, only the difference in mean change scores for DRS-P and TSE domains and total domain score reached statistical significance, showing less worsening in disease and treatment-related symptoms in pazopanib-treated patients compared with sunitinib-treated patients.(Table 17) However, the changes were small and below the range considered clinically important in the FKSI-15 (range: 3-5) and FKSI-10 (range: 2-4); no MCID information is available for the FKSI-19, however.

Table 17. FKSI-19: Summary of analysis of change from baseline over 6 months (ITT) – COMPARZ[18]

FKSI-19 Domain	Adjusted mean[a] for pazopanib (n=557)	Adjusted mean[a] for sunitinib (n=553)	Difference in Mean vs. sunitinib	95% CI for treatment difference
n	377	408	1.41	0.24, 2.58
Total	-5.1	-6.5		
n	378	407	0.78	0.09, 1.48
DRS-P	-2.7	-3.5		
n	370	402	-0.05	-0.17, 0.07
DRS-E	0.4	0.5		
n	351	382	0.31	0.03, 0.60
TSE	-2.1	-2.4		
n	378	403	0.31	-0.06, 0.67
FWB	-0.9	-1.2		

CI=confidence interval; **DRS-P**=Disease Related Symptoms – Physical; **DRS-E**= Disease Related Symptoms – Emotional; **FKSI-19**=Functional Assessment of Cancer Therapy – Kidney Symptom Index-19; **FWB**=Functional Well Being; **TSE**=Treatment Side Effects

Note: A negative change from baseline represented a worsening of condition. Higher scores represented better health. A positive difference indicates that pazopanib scores were better.

[a]Adjusted for baseline score

SQLQ

The difference in adjusted mean change scores from baseline to 6 months suggested numerically that pazopanib treatment may be associated with less soreness or limitations of the mouth and throat, hand (soreness only), or foot compared with sunitinib. However, these changes were small and more importantly, the manufacturer noted that the SQLQ had not been validated at the time of the study or had an MCID established, so the meaningfulness of these data was uncertain at the time of this review.[1]

Table 18. SQLQ[a]: Summary of analysis of change from baseline over 6 months (ITT) – COMPARZ[18]

SQLQ item	Mean change[a] for pazopanib (SD) (n=557)	Mean change[a] for sunitinib (SD) (n=553)	Difference in Mean vs. sunitinib
n	215	194	-0.505
Mouth and throat soreness	0.391 (0.714)	0.896 (0.806)	

SQLQ item	Mean change[a] for pazopanib (SD) (n=557)	Mean change[a] for sunitinib (SD) (n=553)	Difference in Mean vs. sunitinib
n	219	195	-0.204
Hand soreness	0.249 (0.617)	0.453 (0.650)	
n	217	195	-0.267
Foot soreness	0.272 (0.833)	0.539 (0.774)	

SD=standard deviation; **SQLQ**=Supplementary Quality of Life Questionnaire

Note: A positive mean change from baseline represented a worsening of condition. A negative difference indicates that pazopanib scores were better. This questionnaire was added after the VEG108844 study began, so some subjects were missing scores at baseline and some of the other early time points. Subjects missing baseline scores were excluded from the analyses.

[a]Adjusted for baseline score. Change from baseline was computed for all subjects as their average post-baseline scores through week 24 minus their baseline score.

Table 19. SQLQ Limitations: Summary of analysis of change from baseline over 6 months (ITT) – COMPARZ[18]

SQLQ item	Adjusted mean[a] for pazopanib (n=557)	Adjusted mean[a] for sunitinib (n=553)	Difference in Mean vs. sunitinib	95% CI for treatment difference
n	196	185	0.94	0.60, 1.28
Limitations due to mouth and throat soreness	-0.7	-1.6		
n	190	180	0.65	0.13, 1.17
Limitations due to foot soreness	-1.0	-1.7		

SQLQ=Supplementary Quality of Life Questionnaire

Note: A negative mean change from baseline represented a worsening of condition. A positive difference indicates that pazopanib scores were better. This questionnaire was added after the VEG108844 study began, so some subjects were missing scores at baseline and some of the other early time points. Subjects missing baseline scores were excluded from the analyses.

[a]Adjusted for baseline score. Change from baseline was computed for all subjects as their average post-baseline scores through week 24 minus their baseline score.

CTSQ

A statistically significant difference in adjusted mean change scores from baseline to 6 months favoring pazopanib was shown for two of the three domains - feelings about side effects and satisfaction with therapy. (

Table 20) Though MCIDs specific for RCC have not been established, the differences observed fell below MCIDs established for other types of cancer. (Table 15)

Table 20. CTSQ: Summary of analysis over first 6 months (ITT) – COMPARZ[18]

CTSQ domain	Adjusted mean[a] for pazopanib (n=557)	Adjusted mean[a] for sunitinib (n=553)	Difference in Mean vs. sunitinib	95% CI for treatment difference
n	414	421	1.41	-1.17, 3.99
Expectations of therapy	73.1	71.6		
n	401	413	8.50	5.69, 11.31
Feelings about side effects	65.5	57.0		
N	408	417	3.21	1.36, 5.06
Satisfaction with therapy	83.3	80.1		

CTSQ=Cancer Therapy Satisfaction Questionnaire

Note: Higher scores represent better health. A positive difference indicates that pazopanib scores were better.

[a]Adjusted for baseline score

PISCES

The following outcomes of interest identified in the systematic review protocol are presented below from the PISCES trial: patient preference (primary efficacy outcome), and health-related quality of life (HRQoL) as assessed by the FACIT-F, SQLS, and the EuroQol EQ-5D questionnaires.

Patient preference

Patient preference, the primary efficacy outcome, was evaluated through the use of an unvalidated questionnaire.[2] Although numerically, the data seem to show that patients preferred pazopanib over sunitinib treatment in both period 1 and period 2, (Table 21) without prior questionnaire validation, it is impossible to state with certainty that these data reflect measurement of treatment preference. Notwithstanding this important limitation, the manufacturer stated that a period effect was observed,[2] which would have the consequence of reducing the size of the difference observed in an adjusted analysis.

Table 21. Primary Analysis – Patient Preference[a] (Modified ITT Population Primary Analysis Population) – PISCES trial[35]

	SP N=60	PS N=54	Total N=114
Subject Preference, n (%)			
Sunitinib	19 (32)	6 (11)	25 (22)
Pazopanib	37 (62)	43 (80)	80 (70)
No preference	4 (7)	5 (9)	9 (8)
90% CI for pazopanib preference	62.3, 77.2		
90% CI for sunitinib preference	15.7, 29.3		
Difference (%) in (pazopanib vs. sunitinib)[b]	49.26		
90% CI for difference	37.0, 61.5		
p-value[c]	<0.001		

CI = confidence interval; PS=pazopanib 800 mg once daily orally followed by a 2-week wash-out period then sunitinib 50 mg once daily orally; SP=sunitinib 50 mg once daily orally followed by a 2-week wash-out period then pazopanib 800 mg once daily orally
[a]This analysis was unadjusted for the randomization strata
[b]The estimated treatment difference is adjusted for sequence effects
[c]The two-sided p-value was calculated from Prescott's test

FACIT-F

The adjusted mean change scores for FACIT-F worsened from baseline to 6 months in both the SP and PS groups during both periods, with period 2 showing a statistically significant treatment difference in mean change scores favoring pazopanib [difference: 4.36 (90% CI, 1.74 to 6.99)]. (Table 22) Likewise, the cross-over analysis showed a small but statistically significant treatment difference in mean scores favoring pazopanib [difference: 2.49 (90% CI, 1.17 to 3.82)]. (Table 23) Though statistically significant, the clinical meaningfulness of these differences is uncertain as the minimal clinically important difference (MCID) has not been determined in the setting of RCC; in a sample of mixed cancer diagnoses, an MCID of 3.0 has been reported.

Table 22. Health-related QoL - FACIT-Fatigue Change from Baseline Analysis (Safety Population) – PISCES trial[35]

Change from Baseline[a] to:	Arm	n[b]	Adjusted Mean[c]	SE of Adjusted Mean	Difference vs. Control	90% CI for Treatment Difference	p-value for Treatment Difference
Average Period 1	SP	77	-4.4	0.9	-0.19	(-2.28, 1.9)	0.881
	PS	79	-4.6	0.89			
Average Period 2	SP	63	-3.3	1.13	4.36	(1.74, 6.99)	0.007
	PS	65	-7.7	1.11			

SE = standard error; **CI** = confidence interval
PS = Pazopanib 800 mg once daily orally followed by a 2-week Wash-out Period then sunitinib 50 mg once daily orally
SP = Sunitinib 50 mg once daily orally followed by a 2-week Wash-out Period then pazopanib 800 mg once daily orally
[a]Change from Baseline was calculated for all subjects as their average post-Baseline fatigue score within each period minus their period-specific Baseline score. For Period 1, Baseline was the Period 1 predose assessment and for Period 2, Baseline was the Wash-out assessment.
[b]Number of subjects included in the analysis
[c]Adjusted for Baseline score.
Note: A negative change from Baseline represented a worsening of condition.

Table 23. Health-related QoL - FACIT-Fatigue Cross-over Analysis (Safety Population) – PISCES trial[35]

Treatment[a]	n[b]	Mean[c]	Treatment Difference[d]	SE of Treatment Difference	90% CI for Treatment Difference	p-value for Treatment Difference
Pazopanib	131	38.1	2.49	0.80	(1.17, 3.82)	0.002
Sunitinib	131	35.6				

SE = standard error; **CI** = confidence interval
[a]Subjects had to complete assessments in both treatment periods to be included in this analysis
[b]Number of subjects included in the analysis
[c]The mean fatigue score was computed for all subjects as their average post-Baseline fatigue score within each period averaged over periods
[d]The treatment difference was an estimate of the mean pazopanib minus mean sunitinib responses. The estimated treatment difference, confidence interval, and p-value were adjusted for period and sequence effects in the analysis of variance model
Note: Higher scores represented better health

SQLQ

The adjusted treatment difference in mean scores suggested that, numerically, pazopanib treatment may be associated with less soreness or limitations of the mouth and throat, hand (soreness only), or foot compared with sunitinib. However, these changes were small and more importantly, the manufacturer noted that the SQLQ had not been validated at the time of study or had an MCID established, so the clinical meaningfulness of these data was uncertain at the time of this review.[1](Table 24 and Table 25)

Table 24. SQLQ Cross-over Analysis (Safety Population) – PISCES trial[35]

Treatment	n[a]	Mean[b]	Treatment Difference[c]	SE of Treatment Difference	90% CI for Treatment Difference	p-value for Treatment Difference
Worst Mouth and Throat Soreness Scores						
Pazopanib	131	0.40	-0.38	0.056	(-0.47, -0.29)	<0.001
Sunitinib	131	0.78				
Worst Hand Soreness Scores						
Pazopanib	131	0.21	-0.08	0.035	(-0.14, -0.02)	0.026
Sunitinib	131	0.29				
Worst Foot Soreness Scores						
Pazopanib	129	0.36	-0.16	0.055	(-0.25, -0.07)	0.005
Sunitinib	129	0.52				

SE = standard error; **CI** = confidence interval
[a]Number of subjects included in the analysis
[b]The mean soreness score was calculated for all subjects as their average post-Baseline soreness score within each period averaged over periods. A score of 0 was best and 3 was worst.
[c]The treatment difference was an estimate of mean pazopanib minus mean sunitinib responses. The estimated treatment difference, CI, and p-value were adjusted for period and sequence effects in the analysis of variance model. A negative treatment difference indicated pazopanib treatment was better.

Table 25. SQLQ Limitations (Safety Population) – PISCES trial[35]

Treatment	n[a]	Mean[b]	Treatment Difference[c]	SE of Treatment Difference	90% CI for Treatment Difference	p-value for Treatment Difference
Limitations due to Mouth and Throat Soreness Scores						
Pazopanib	126	14.32	0.6	0.154	(0.34, 0.85)	<0.001
Sunitinib	126	13.72				
Limitations due to Foot Soreness Scores						
Pazopanib	129	13.82	0.58	0.189	(0.27, 0.89)	0.003
Sunitinib	129	13.24				

SE = standard error; **CI** = confidence interval
[a]Number of subjects included in the analysis
[b]The mean soreness score was calculated for all subjects as their average post-Baseline soreness score within each period averaged over periods. A score of 15 was best and 0 was worst.
[c]The treatment difference was an estimate of mean pazopanib minus mean sunitinib responses. The estimated treatment difference, confidence interval, and p-value were adjusted for period and sequence effects in the analysis of variance model. A positive treatment difference indicated pazopanib treatment was better.

EQ-5D

The EQ-5D data were collected for descriptive purposes only to support the submitted health economic model. No statistical comparisons were performed.[2,3]

Table 26. EQ-5D Thermometer & Utility Scores (Safety Population) – PISCES trial[35]

	Arm	N	Visit	n	Mean	SD	Median	Min.	Max.
Thermometer score	SP	80	Period 1 pre-dose	74	75.7	17.65	80.0	27	100
			Wash-out	60	74.4	16.76	79.5	30	100
			Period 2 Week 10	51	71.3	16.19	70.0	45	100
	PS	86	Period 1 pre-dose	79	74.8	18.54	80.0	0	100
			Wash-out	63	69.8	19.94	75.0	10	100
			Period 2 Week 10	45	65.1	22.55	70.0	20	100
Utility score	SP	80	Period 1 pre-dose	76	0.7625	0.25331	0.7960	-0.016	1.000
			Wash-out	61	0.8103	0.20776	0.8480	-0.003	1.000
			Period 2 Week 10	52	0.7487	0.21324	0.7780	0.088	1.000
	PS	86	Period 1 pre-dose	81	0.7664	0.22946	0.7960	-0.016	1.000
			Wash-out	67	0.7595	0.26826	0.7960	-0.016	1.000
			Period 2 Week 10	47	0.6325	0.29635	0.6910	-0.181	1.000

SD = standard deviation
Note: Higher scores represent better health
EuroQoL EQ-5D: The EQ-5D was assessed in this study at Baseline, wash-out, and end of Period 2. The median time from last dose of treatment in Period 1 until Wash-out EQ-5D completion was 14 days for both arms for the end of Period 1 assessment, which makes interpretation of the results of end of Period 1 difficult and Period 1 vs. 2 highly problematic since the end of Period 2 assessment was done immediately after the end of Period 2.

Harms Outcomes

Dose reductions or modifications

COMPARZ

The proportion of patients who experienced any reduction in dose was numerically higher in sunitinib-treated [277 (51%)] compared with pazopanib-treated [246 (44%)] patients; a majority of patients experienced one or two dose reductions regardless the treatment assignment, but was numerically higher in sunitinib-treated (47%) compared with pazopanib-treated (41%) patients. (Table 27)

Table 27. Summary of dose reductions, delays, or interruptions, and escalations (Safety population) – COMPARZ[1]

	Pazopanib (n=554)	Sunitinib (n=548)
Patients with any reduction, n (%)	246 (44)	277 (51)
Total number of dose reductions	379	413
Number of dose reductions, n (%)		
0	308 (56)	270 (49)
1	147 (27)	161 (29)
2	78 (14)	101 (18)
3 or more	21 (4)	15 (3)
Not evaluable[a]	0	1 (<1)

[a]Not evaluable means the patient did not receive any drug in any succeeding time period after the first dose.

Similarly, there was a higher proportion of sunitinib-treated [267 (49%)] than pazopanib-treated [243 (44%)] patients who experienced any dose interruption lasting at least 7 days. More sunitinib-treated (13%) than pazopanib-treated (8%) patients experienced three or more dose interruptions lasting 7 days or longer. The median duration of dose interruption was 12 days (IQR: 8-14) in pazopanib-treated patients compared with 14 days (IQR: 11-20) in sunitinib-treated patients.

Table 28. Summary of dose interruptions of at least 7 days (Safety population) – COMPARZ[1]

	Pazopanib (n=554)	Sunitinib (n=548)
Patients with any dose interruption ≥ 7 days, n (%)	243 (44)	267 (49)
Total number of dose interruptions ≥ 7 days	482	611
Number of dose interruptions ≥ 7 days, n (%)		
0	311 (56)	280 (51)
1	138 (25)	135 (25)
2	61 (11)	61 (11)
≥3	44 (8)	71 (13)
Not evaluable[a]	0	1 (<1)
Duration of interruption (days)		
N	482	611
7-14, n (%)	367 (76)	310 (51)
>14, n (%)	115 (24)	301 (49)
Median	12	14
IQR	8-14	11-20

IQR=interquartile range

[a]Not evaluable means the patient did not receive any drug in any succeeding time period after the first dose.

PISCES

The proportion of patients who experienced any reduction in dose was numerically higher in sunitinib-treated [30 (20%)] compared with pazopanib-treated [20 (13%)] patients; a majority of patients did not experience a dose reduction, with a slightly higher proportion in the pazopanib group (87%) compared with the sunitinib group (80%). Dose interruptions – a protocol violation – occurred more often in sunitinib-treated (12%) than pazopanib-treated (6%) patients.

Table 29. Dose Reductions and Interruptions (Safety Population) – PISCES trial[35]

	Pazopanib N=153	Sunitinib N=148
Dose Reduction[a]		
Subjects with any dose reduction, n (%)	20 (13)	30 (20)
Total number of dose reductions	33	49
Number of dose reductions, n (%)		
0	133 (87)	118 (80)
1	8 (5)	16 (11)
2	11 (7)	10 (7)
≥3	1 (<1)	4 (3)
Reasons for reduction[b], n (%)		
N	33	49
Adverse event	33/33 (100)	46/49 (94)
Subject non-compliance	0/33	0/49
Other	0/33	3/49 (6)
Dose Interruption[a]		
Subjects with any dose interruption, n (%)	9 (6)	18 (12)
Reasons for interruption, n (%)		
N	9	19
Adverse event	3 (33)	12 (63)
Subject non-compliance	0	2 (11)
Other	6 (67)	5 (26)

[a]Subjects were recorded under the treatment they were receiving at the time the dose reduction or interruption was reported
[b]Subjects may have been counted multiple times in the same 'reason' row if the subject had multiple reductions for the same reason
Note: The manufacturer stated that there was no difference in the median time to dose modification (dose reduction) between treatment arms (3.7 weeks, sunitinib vs. 4.0 weeks, pazopanib)

Adverse events

COMPARZ

Of the most frequent adverse events reported, the following were numerically more common with pazopanib than sunitinib treatment: diarrhea (63% vs. 57%), hypertension (46% vs. 41%), ALT increased (31% vs. 18%), hair color changes (30% vs. 10%), and AST increased (27% vs. 18%). There were no differences between treatment groups in the frequency of nausea, decreased appetite, or vomiting. Fatigue, hand-foot syndrome, dysgeusia, stomatitis, thrombocytopenia, and neutropenia were more common with sunitinib than pazopanib treatment. (Table 30)

Table 30. Ten most frequent adverse events - COMPARZ[18]

	Pazopanib (n=554)	Sunitinib (n=548)
Most frequent AEs – on therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	552 (>99)	544 (>99)
Diarrhea	348 (63)	315 (57)
Fatigue	302 (55)	344 (63)
Hypertension	257 (46)	223 (41)
Nausea	247 (45)	250 (46)
Decreased appetite	207 (37)	202 (37)
ALT increased	171 (31)	97 (18)
Hair color changes	168 (30)	53 (10)
HFS	163 (29)	275 (50)
Vomiting	155 (28)	146 (27)
AST increased	148 (27)	98 (18)
Dysgeusia	143 (26)	198 (36)
Stomatitis	77 (14)	150 (27)
Thrombocytopenia	57 (10)	185 (34)
Neutropenia	62 (11)	149 (27)

AE=adverse event; **ALT**=alanine aminotransferase; **AST**=aspartate aminotransferase; **HFS**=palmar-plantar erythrodysesthesia syndrome;

PISCES

Of the most frequent adverse events reported, only diarrhea (42% vs. 32%) was numerically more common with pazopanib than sunitinib treatment. Although no formal statistical analysis was conducted in a pre-specified way, there were no notable differences between treatment groups in the frequency of nausea, fatigue, hypertension, decreased appetite, vomiting, or hair color changes. Dysgeusia, hand-foot syndrome, asthenia, mucosal inflammation, dyspepsia, and stomatitis were more common with sunitinib than pazopanib treatment. (Table 31)

Table 31. Most Frequent Adverse Events – On-Therapy (Safety Population) – PISCES trial[35]

Most Frequent 10 Adverse Events in each Treatment Group	No. (%) of Subjects	
	Pazopanib N=153	Sunitinib N=148
Subjects with any AE(s)	148 (97)	147 (>99)
Diarrhea	64 (42)	47 (32)
Nausea	50 (33)	44 (30)
Fatigue	44 (29)	44 (30)
Dysgeusia	25 (16)	40 (27)
Hypertension	35 (23)	38 (26)
Palmar-plantar erythrodysesthesia syndrome	25 (16)	38 (26)
Asthenia	25 (16)	35 (24)
Mucosal inflammation	24 (16)	32 (22)
Decreased appetite	31 (20)	28 (19)
Dyspepsia	16 (10)	23 (16)
Stomatitis	7 (5)	23 (16)
Vomiting	22 (14)	24 (16)
Hair color changes	26 (17)	20 (14)

Serious adverse events

COMPARZ

The frequency of serious adverse events was similar whether treated with pazopanib (42%) or sunitinib (41%). Of the most frequent serious adverse events reported, ALT increased (6% vs. 1%) and AST increased (3% vs. <1%) were numerically more common with pazopanib than sunitinib treatment. Although no formal statistical analysis was conducted in a pre-specified way, there were no notable differences between treatment groups in the frequency of anemia, dehydration, diarrhea, acute renal failure, fatigue, and pleural effusion. Pyrexia, thrombocytopenia, and platelet count decreased were more common with sunitinib than pazopanib treatment.

Table 32. Serious adverse events in ≥2% patients regardless of treatment - COMPARZ[18]

	Pazopanib (n=554)	Sunitinib (n=548)
Patients with any SAE[a], n (%)	230 (42)	224 (41)
Patients with fatal SAEs, n (%)	13 (2)	19 (3)
ALT increased	35 (6)	8 (1)
AST increased	17 (3)	2 (<1)
Anemia	8 (1)	9 (2)
Dehydration	8 (1)	11 (2)
Diarrhea	5 (<1)	10 (2)
Pyrexia	5 (<1)	14 (3)
Renal failure acute	4 (<1)	9 (2)
Thrombocytopenia	4 (<1)	24 (4)
Fatigue	3 (<1)	12 (2)
Pleural effusion	1 (<1)	11 (2)
Platelet count decreased	0	9 (2)

ALT=alanine aminotransferase; **AST**=aspartate aminotransferase; **SAE**=serious adverse event

[a]Includes both fatal and non-fatal SAEs

PISCES

The frequency of serious adverse events was similar whether treated with pazopanib (20%) or sunitinib (24%). Of the most frequent serious adverse events reported, only a slight numerical imbalance was noted in the frequency of thrombocytopenia, which seemed to occur more often in sunitinib (2%) than pazopanib-treated (0%) patients. (Table 33)

Table 33. Serious Adverse Events - On-Therapy (Safety Population) – PISCES trial[35]

Subjects with SAEs - includes both fatal and non-fatal events	**Pazopanib N=153 n (%)**	**Sunitinib N=148 n (%)**
Subjects with any SAEs	30 (20)	35 (24)
Anemia	2 (1)	3 (2)
Asthenia	0	1 (<1)
Diarrhea	1 (<1)	0

Subjects with SAEs - includes both fatal and non-fatal events	Pazopanib N=153 n (%)	Sunitinib N=148 n (%)
Dizziness	1 (<1)	0
Dyspnea	0	1 (<1)
Fatigue	2 (1)	3 (2)
General physical health deterioration	0	3 (2)
Infection	0	2 (1)
Hemorrhage intracranial	0	1 (<1)
Hemiparesis	0	1 (<1)
Mucosal inflammation	0	1 (<1)
Nausea	1 (<1)	0
Performance status decreased	0	1 (<1)
Pyrexia	0	1 (<1)
Sinusitis	0	1 (<1)
Stomatitis	0	1 (<1)
Vomiting	1 (<1)	1 (<1%)
Hepatic SAEs		
Alanine aminotransferase increased	3 (2)	2 (1)
Aspartate aminotransferase increased	2 (1)	0
Blood bilirubin increased	1 (<1)	0
Gamma-glutamyltransferase increased	1 (<1)	0
Hepatic function abnormal	1 (<1)	0
Hepatotoxicity	0	1 (<1)
Cardiovascular and Pulmonary SAEs		
Acute myocardial infarction	1 (<1)	1 (<1)
Atrial flutter	1 (<1)	0
Hypertension	3 (2)	2 (1)
Myocardial ischemia	1 (<1)	0
Pleural effusion	1 (<1)	2 (1)
Pulmonary embolism	1 (<1)	0
Transient ischemic attack	2 (1)	0
Hematologic SAEs		
Thrombocytopenia	0	3 (2)
Epistaxis	0	2 (1)
Hematoma	0	1 (<1)
Neutropenic infection	0	1 (<1)
Pancytopenia	0	1 (<1)

Subjects with SAEs - includes both fatal and non-fatal events	Pazopanib N=153 n (%)	Sunitinib N=148 n (%)
Subjects with fatal SAEs		
Subjects with any fatal SAEs	2 (1)	2 (1)
Dyspnea	0	1 (<1)
General physical health deterioration	0	1 (<1)
Infectious peritonitis	1 (<1)	0
Respiratory failure	1 (<1)	0

Manufacturer stated - Note: Subjects were counted in the denominator for each treatment to which they were exposed. The death was only counted under the treatment that the subject was exposed to most recently before death.

- An AE which spans more than one period was considered to be an AE for the treatment period under which it started as well as the treatment period in which it may have increased in grade.
- There was only one label for serious/non-serious, and action taken with respect to AE as well as relationship to treatment for the entire event.
- Once an event became serious in any of the periods, the entire event was labeled serious regardless of the treatment.
- It was only possible to note that an SAE was related to a study treatment (Yes/No), but it was not possible to designate which treatments the SAE was related to (Pazopanib/Sunitinib).
- Therefore, only the AE safety table regardless of causality is included here
    - In the SAE safety table, in some instances, relationship to the treatment is attributed to both treatments

Withdrawals Due to Adverse Events

COMPARZ

Withdrawals due to adverse events (WDAEs) occurred in 135 (24%) of pazopanib-treated patients and 112 (20%) of sunitinib-treated patients. In pazopanib-treated patients, increased ALT (3%) and AST (2%), and proteinuria (2%) were most commonly reported while in sunitinib-treated patients, fatigue (2%) was the most commonly reported AE leading to withdrawal. (Table 34)

Table 34. Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study Occurring in ≥1% of Patients in Either Treatment Arm (Safety Population) – COMPARZ[1]

Preferred Term	Pazopanib, n (%) N=554	Sunitinib, n (%) N=548
Patients with any event	135 (24)	112 (20)
ALT increased	19 (3)	3 (<1)
AST increased	10 (2)	1 (<1)
Proteinuria	13 (2)	6 (1)
Fatigue	7 (1)	13 (2)
Hepatotoxicity	6 (1)	0
Diarrhea	4 (<1)	6 (1)

ALT=alanine aminotransferase; **AST**=aspartate aminotransferase

Note: Events occurring in ≥0.5% to <1% of patients are rounded to 1% and included in this table. This table includes 7 patients that had AEs leading to withdrawal from the study, but did not have AEs leading to permanent discontinuation of study drug.

PISCES

Withdrawals due to adverse events (WDAEs) occurred in 25 (16%) of pazopanib-treated patients and 38 (26%) of sunitinib-treated patients. In pazopanib-treated patients, increased ALT (3%) and AST (2%), fatigue (2%), and vomiting (2%) were most commonly reported while in sunitinib-treated patients, fatigue (3%) and thrombocytopenia (2%) were the most commonly reported AEs leading to withdrawal.

Table 35. Summary of Adverse Events in ≥2 Patients Leading to Permanent Discontinuation of Investigational Product (Safety Population – Randomized Phase) – PISCES[2]

Adverse Event[a,b] Preferred Term	Number of Patients (%)	
	Pazopanib N=153	Sunitinib N=148
Any event	25 (16)	38 (26)
Fatigue	3 (2)	5 (3)
Thrombocytopenia	0	3 (2)
Increased ALT	4 (3)	2 (1)
Asthenia	0	2 (1)
Dyspnea	0	2 (1)
Epistaxis	0	2 (1)
Hypertension	0	2 (1)
Pleural effusion	0	2 (1)
Diarrhea	2 (1)	1 (<1)
Vomiting	3 (2)	1 (<1)
Increased AST	3 (2)	0
Transient ischemic attack	2 (1)	0

ALT=alanine aminotransferase; **AST**=aspartate aminotransferase

a. An adverse event (AE) which spanned more than one period was considered to be an AE for each period during which the AE increased in grade. There was only one action with respect to study treatment recorded for the whole event. As such it was not always possible to determine which period treatment was discontinued due to the AE.
b. AEs are sorted in descending order based on the incidence on sunitinib treatment.

6.4 Ongoing Trials

No additional on-going and/or unreported trials were identified that would have been included had they been completed.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Genitourinary Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on pazopanib (Votrient) for mRCC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The submitter, as the primary data owner, did not agree to the disclosure of some clinical information and this has been redacted from this publicly available Guidance Report until October 4, 2013 or notification from the manufacturer, whichever is earlier.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Genitourinary Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **Embase** 1974 to Present, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	Searches	Results
1	(votrient* or pazopanib* or GW786034* or GW-786034* or GW780604 or GW-780604).ti,ab.	1011
2	*pazopanib/	356
3	1 or 2	1040
4	3 use oemezd	669
5	(votrient* or pazopanib* or GW786034* or GW-786034* or GW780604 or GW-780604).ti,ab,ot,sh,hw,rn,nm.	2578
6	444731-52-6.rn.	1885
7	5 or 6	2578
8	7 use pmez	409
9	4 or 8	1078
10	remove duplicates from 9	728
11	exp animals/	35528275
12	exp animal experimentation/ or exp animal experiment/	1700582
13	exp models animal/	1094567
14	nonhuman/	4065738

15	exp vertebrate/ or exp vertebrates/	34606674
16	animal.po.	0
17	or/11-16	36712983
18	exp humans/	27415480
19	exp human experimentation/ or exp human experiment/	324418
20	human.po.	0
21	or/18-20	27417557
22	17 not 21	9297013
23	10 not 22	709
24	limit 23 to english language	652
25	limit 24 to yr="2011 -Current"	417

2. Literature search via PubMed

Search History

Search	Query	Items found
#3	Search **#1 AND #2**	22
#2	Search **publisher[sb]**	426348
#1	Search **"pazopanib" [Supplementary Concept] OR votrient* OR pazopanib* OR GW786034* OR GW-786034* OR GW780604 OR GW-780604 OR 444731-52-6[rn]**	408

3. Cochrane Central Register of Controlled Trials (Central)

Search for trials. Issue 5, 2013

Search History

Search	Query	Results
#1	"votrient* or pazopanib* or GW786034* or GW-786034* or GW780604 or GW-780604 or 444731-52-6	33
#2	MeSH descriptor: [Carcinoma, Renal Cell] explode all trees	422
#3	renal or kidney* or hypernephroid or collecting duct or nephroid or grawitz	35781
#4	cancer* or carcinoma* or neoplasm* or lymphoma* or tumor* or tumour* or oncolog* or malignan* or sarcoma* or metasta* or adenocarcinoma* or pyelocarcinoma*	90800
#5	#1 and (#2 or (#3 and #4))	19

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: (Votrient OR pazopanib) AND ("renal cell" OR kidney)

Select international agencies including:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Search terms: (Votrient OR pazopanib) AND ("renal cell" OR kidney)

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search terms: (Votrient OR pazopanib) AND (renal cell OR kidney)) / last 5 years

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