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Description: This document details the reporting and analysis plan for the final analysis for AGO-OVAR16/VEG110655, a randomized, double-blinded, placebo-controlled multi-center Phase III study to evaluate efficacy and safety of pazopanib compared to placebo in women who have not progressed after first line chemotherapy for epithelial ovarian, fallopian tube or primary peritoneal cancer.

Subject: Overall survival, Safety

Author's Name, Title and Functional Area:

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			[redacted]	Section 14.1 Table of contents for data display specification

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List of abbreviations

AE	Adverse Event
BP	Blood pressure
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC QLQ-C30	EORTC quality of life questionnaire core 30
EQ-5D	EuroQoL-5D
GSK	GlaxoSmithKline
hr(s)	Hour(s)
HR	Hazard ratio
IDMC	Independent data monitoring committee
IDSL	Integrated data standards library
ITT	Intend-to-treat
MedDRA	Medical dictionary for regulatory activities
Min	Minute(s)
Mg	Milligram(s)
mL	Milliliter(s)
mmHg	Millimeters of mercury (BP)
mRCC	Metastatic renal cell carcinoma
Msec	Millisecond(s)
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PGx	Pharmacogenetics
PK	Pharmacokinetic
PR	Partial response
PT	preferred term
QTc	Heart rate-corrected Q-T interval
QoL	Quality of life
QTcB	Bazett's corrected QT intervals
RAP	Report and analysis plan
RAMOS	Registration and Medication Ordering System
RECIST	Response Evaluation Criteria In Solid Tumors
RS	Raw score
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Stable disease
SI	System independent
SOC	System Organ Classes
TSH	Thyroid-stimulating hormone
µg	Microgram(s)
ULN	Upper limit of normal
WBC	White blood cell(s)

Trademark Information

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

1. introduction

This reporting and analysis plan (RAP) details all planned final analyses for study AGO-OVAR16/VEG110655/PZP034C2301. This is a phase III study to evaluate the efficacy and safety of pazopanib (trademark: Votrient) compared to placebo using a randomized, double-blinded, placebo-controlled, and multi-center design in women with non-bulky, FIGO Stage II-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer that has not progressed after first line chemotherapy.

For further information on the study design, see Protocol Amendment 9, dated May 09, 2016 (GlaxoSmithKline Document Number UM2008/00144/0).

2. Study Objective(s) and Endpoint(s)

2.1. Study Objective(s)

Primary

- To determine whether pazopanib (up to 24 months of pazopanib 800 mg daily) prolongs progression free survival (PFS by RECIST 1.0) compared to placebo in women with non-bulky, FIGO Stage II-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer that has not progressed after first line chemotherapy.

Secondary

The principal secondary objective is:

- To compare overall survival (OS) of patients treated with up to 24 months of pazopanib 800 mg daily to those treated with placebo.

Other secondary objectives are:

To compare the effect of 24 months of pazopanib 800 mg daily versus placebo on

- Safety
- PFS by GCIG criteria
- 3-year PFS (by RECIST) rate
- Quality of life (measured using EORTC QLQ-C30 with the OV-28 module, and EuroQOL EQ-5D)

2.2. Study Endpoint(s)

Primary

- **PFS** is defined as the interval between the date of randomization and the earliest date of either radiological progression or death due to any cause. The primary analysis will be based on the radiological progression per RECIST as determined by the investigator.

Secondary

The principal secondary endpoint:

- **OS** is defined as the time from date of randomization until date of death due to any cause.

Other secondary endpoints:

- **PFS by GCIG Criteria** is defined as the time from randomization to the earliest date of either progression by GCIG criteria or death due to any cause.
- **3-year PFS** is defined as the percentage of subjects who are alive and progression-free (progression defined as radiological progression per RECIST or death due to any cause) at 3 years from randomization.
- **Safety** will include evaluation of AEs and changes from baseline in vital signs, ECGs, and laboratory parameters
- **Quality of life** is measured using the EORTC QLQ-C30 with the OV-28 module, and EuroQOL EQ-5D.

2.3. Statistical Hypotheses

The primary objective of this study is to compare progression free survival (PFS) of pazopanib versus placebo each given for up to 24 months in women with non-bulky Stage II-IV epithelial ovarian (EOC), fallopian tube, or primary peritoneal cancer that has not progressed after first line chemotherapy. For the primary hypothesis, PFS is defined as the interval between the date of randomization and the earliest date of disease progression (as defined by the investigator based on RECIST criteria) or death due to any cause.

The study is designed to provide evidence with regard to PFS to support the null hypothesis H_0: $\lambda = 1$ or to reject it in favor of the alternative hypothesis HA: $\lambda \neq 1$, where λ is the hazard ratio: pazopanib / placebo. While the primary endpoint of the study is PFS, the study will have 80% power to detect a 27% increase in median survival in subjects

who receive pazopanib compared to subjects who receive placebo (49 months vs. 38.5 months).

The study will have more than 90% power to detect a 47% increase in median PFS in subjects who receive up to 24 months of pazopanib compared to subjects who receive placebo (19.8 months vs. 13.5 months) at the time of final PFS analysis.

Confidence intervals will be two-sided and will use 95% confidence levels unless otherwise specified. Two-sided hypotheses will be tested at the 5% significance level unless otherwise specified.

2.4. Pharmacokinetic (PK) and PK/Pharmacodynamic (PD) hypotheses

Not applicable

3. Study Design

For information on the study design, see Protocol (UM2008/00144/0).

4. Planned Analyses

The 3rd interim analysis for futility based on OShas occurred at 80% information fraction (at least 441 OS events). An overall conditional power of 20% served as the boundary for futility. Based on the estimated hazard ratio at the third interim analysis, the futility criteria was met, and the study will be closed (conditional power was <1%).

The main purpose of the final analyses is to report the updated OS results after all patients have completed the end of study visit.

5. Sample Size Considerations

For information on sample size considerations, see Protocol (UM2008/00144/0).

6. Analysis populations

The Intent-to-Treat (ITT) population will comprise all randomized subjects who are not screen failure, i.e. subjects who were screen failure but randomized by mistake and were not treated will not be included. The treatment group assignment will be based on the randomized treatment instead of the actual treatment received. The ITT population will be used for the analysis of efficacy data and summaries of study population.

The All Treated population will comprise all randomized subjects who receive at least one dose of investigational product, and will be based on the actual treatment received if this differs from that to which the subject was randomized. The All Treated population will be used for the analysis of safety data.

It is possible that during the course of the study a subject will only temporarily receive the incorrect treatment, which means the subject will receive incorrect treatment for some time, but not the whole treatment period. Pazopanib subjects who temporarily receive placebo will be treated similarly to subjects with drug interruptions. Placebo subjects who temporarily receive pazopanib will be included in the safety summaries for pazopanib arm.

7. Treatment comparisons

The single treatment comparison will be between pazopanib and placebo. Unless otherwise stated, all efficacy comparisons will be performed using the ITT population and all safety comparisons will be performed using the All Treated population (as defined in Section 6).

7.1. Data Display Treatment and Other Sub-group Descriptors

The following treatment descriptors will be used on all applicable tabulations:

- Pazopanib
- Placebo

8. general considerations for data analyses

8.1. Multicentre Studies

Data from all participating centers will be pooled prior to analysis. Since patient accrual is spread thinly across multiple centers, summaries of data by center would be unlikely to be informative and will not, therefore, be provided.

8.2. Other Strata and Covariates

Prior to randomization, eligible patients are stratified according to the following two stratification factors:

1. First-line treatment outcome:

   a) no evidence of disease [NED] after surgery (or, if unknown, FIGO stage II-IIIA at diagnosis) and NED after chemotherapy and normal Screening CA-125; *versus,*

   b) residual tumor after surgery (or, if unknown residual tumor after initial surgery, FIGO stage IIIB-IV at diagnosis) and NED after chemotherapy and normal Screening CA-125; *versus,*

   c) residual tumor after chemotherapy or elevated Screening CA 125 regardless of tumor status after surgery and FIGO stage at diagnosis

2. Geographic coverage of participating cooperative group: Europe vs Asia vs North America/Australia.

This represents a total of nine (9) sub-strata. Patients in each sub-stratum are then centrally randomized in a 1:1 ratio to receive either 800 mg pazopanib daily dosing or the matching placebo.

The OS analyses will include stratified log rank tests using the above listed stratification factors for a total of nine substrata. In such an analysis, these stratification factors will be adjusted for by including them as covariates in the model. If a sub-stratum is too small, it may be pooled with others. Significance tests will be conducted for the overall pooled analysis population.

The analyses will be performed based on the data collected in the CRF, not the actual assigned stratum at the time of randomization.

8.3. Multiple Comparisons and Multiplicity

No further statistical testing will be performed as this study is closed out due to futility.

9. Data handling conventions

9.1. Premature Withdrawal and Missing Data

Subjects are considered to have completed the study if death occurs. Subjects who withdraw from the study will be included in analyses up to the time of withdrawal, regardless of the duration of treatment.

As the length of treatment for any patient will depend on the efficacy and toxicity of the treatment, the duration of follow-up will vary among patients. Consequently, there will be no imputation for missing data. Where appropriate, available data will be summarized over specified intervals (e.g. from randomization until withdrawal from the study) using suitable summary statistics.

10. Disposition of Subjects

A summary of the number and percentage of subjects who completed the study as well as subjects who withdrew prematurely from the study will be displayed based on the ITT population. Reasons for premature withdrawal will be presented in the order they are displayed in the CRF, which include study closed/terminated, lost to follow-up, investigator discretion, and withdrew consent.

11. Efficacy Analyses

Unless otherwise specified, all the efficacy analyses will be based on the ITT population as defined in Section 6.

11.1. Overall Survival (OS)

OS is defined as the interval between the date of randomization and date of death due to any cause. The length of this interval (in days) is estimated as the date of death minus date of randomization plus 1 day. Subjects who have not died will be censored at the date of last contact (as recorded in the eCRF). Last date of contact will be defined as the maximum date of any visit date, survival follow-up date, or date of study withdrawal. Only patient contacts recorded in the eCRF can be used for the calculation of last date of contact.

OS will be summarized using Kaplan-Meier survival curves, and compared between treatment arms using a stratified log rank test based on the stratification factors defined in Section 8.2. For each Kaplan-Meier analysis the following estimates will also be provided:

The Pike estimator [Berry, 1991] of the treatment hazard ratio based on the corresponding stratified log-rank test statistic will be provided together with a naïve 95% confidence interval. For each treatment group, the Kaplan-Meier estimates for the median OS time, the first and third quartiles will be presented, along with approximate naïve 95% confidence intervals. Brookmeyer-Crowley method [Brookmeyer, 1982] will be used to calculate the confidence intervals.

11.1.1.1. Subgroup analyses of OS

The second interim OS analysis revealed a negative trend for Asian patients with HR: 1.71 (95% CI: 1.01 to 2.89; p=0.047). To better understand whether the negative trend observed in the Asian subgroup at the first two OS interim analyses was due to a true negative treatment effect or it was rather secondary to random variation, a subgroup analysis by region (Asia vs. non-Asia) was performed at the time of third OS interim analysis. A numerical trend was also observed in this third analysis (HR=1.35, 95% CI: 0.87, 2.09 and p=0.181), but not as strong as that in the second analysis. Updated results will be presented at the time of the final analyses. It is important to note that the study was not designed to make definitive conclusions in any of the subgroups including the Asia subgroup. The analysis of OS by the ethnicity subgroups should be considered exploratory in nature.

12. Safety Analyses

Unless otherwise specified, all the safety analyses will be based on the All Treated population. Given all patients were off treatment as of the primary analysis/first OS interim analysis, the only safety analyses to be conducted at the time of third OS interim analysis will be the summary of deaths.

All deaths occurring any time from the time of informed consent to the clinical cut-off date will be summarised based on the number and percentage of subjects. This summary

will classify subjects by time of death relative to the last dose of medication (>28 days or ≤ 28 days) and primary cause of death (disease under study, toxicity or other). The summary will also be provided in the following subgroups:

- Region: Asia vs. Non-Asia.

All deaths will be listed with subject level details. In addition, a listing of adverse events with onset date after the third interim analysis cutoff date (Jan 12th, 2017) will be provided.

13. REFERENCES

Berry et al. (1991), A comparison of two simple hazard ratio estimators based on the logrank test.Statistics in Medicine, 10(5), 749-755.

Brookmeyer, R. And Crowley, J. (1982), A Confidence Interval for the Median Survival Time, Biometrics, 38, 29-41.

GlaxoSmithKline Document Number UM2008/00144/09, protocol, A Phase III Study to Evaluate the Efficacy and Safety of Pazopanib Monotherapy Versus Placebo in Women Who Have not Progressed after First Line Chemotherapy for Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer, **Effective Date:** 09-MAY-2016

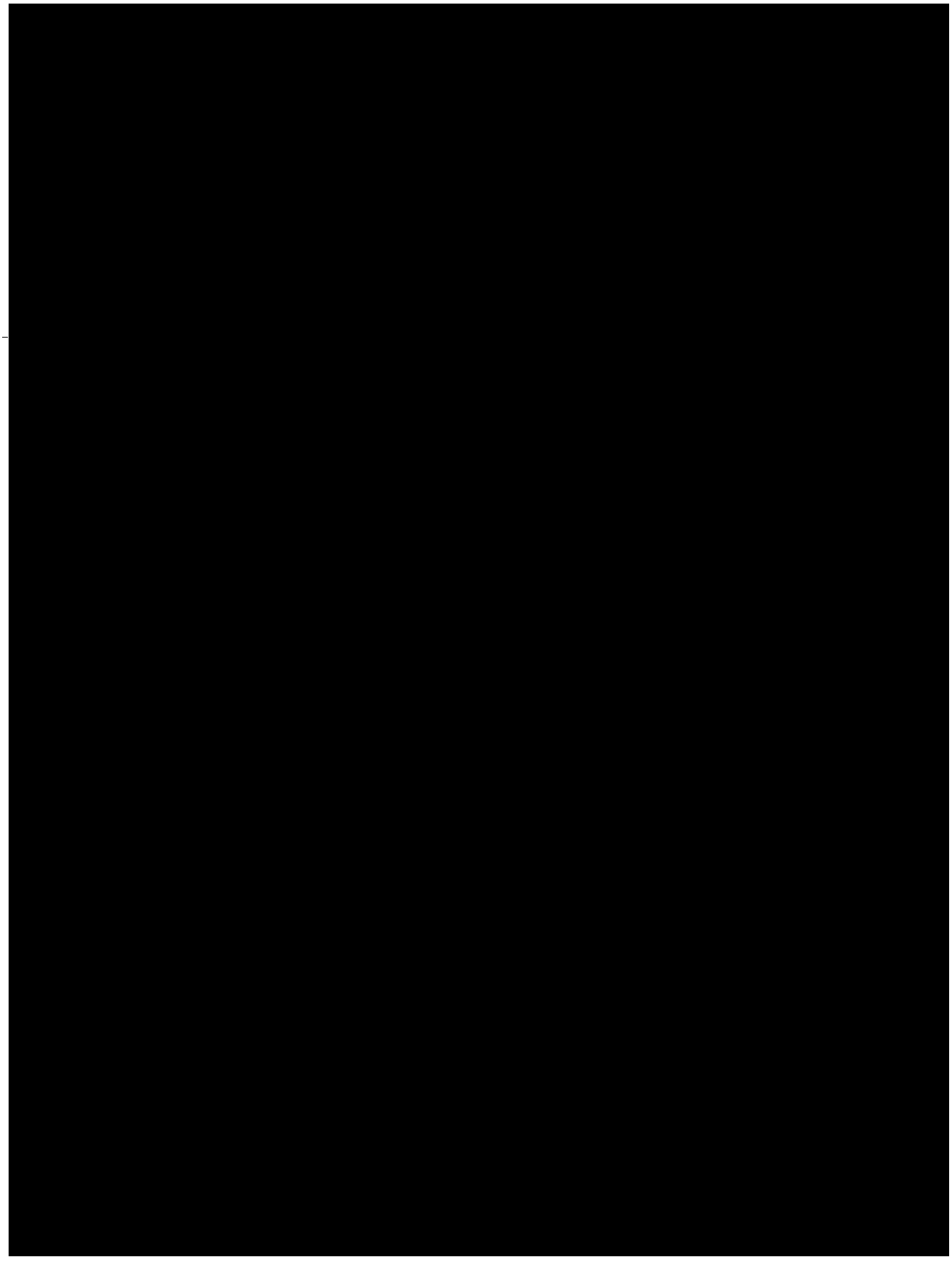
14. Attachments

14.1. Table of Contents for Data Display Specifications

Table Number	Title	Note (output number in SAC reporting effort)
6.1000	Summary of Subject Disposition	6.4000
[redacted]		
7.1000	Statistical Analysis of Overall Survival	7.3000
7.1100	Statistical Analysis of Overall Survival (Asia)	7.3002
7.1200	Statistical Analysis of Overall Survival (Non-Asia)	7.3001
7.3005	Sensitivity Analysis of Overall Survival	7.3000 (see the shells below)
[redacted]		
Figure 7.1000	Kaplan-Meier Curves of Overall Survival	Figure 7.3000
Figure 7.1100	Kaplan-Meier Curves of Overall Survival (Asia)	Figure 7.3000
Figure 7.1200	Kaplan-Meier Curves of Overall	Figure 7.3000

	Survival (Non-Asia)	
8.1000	Summary of Deaths	8.2000
8.1100	Summary of Deaths (Asia)	8.2000
8.1200	Summary of Deaths (Non-Asia)	8.2000
8.3001	On-treatment deaths and serious adverse events by system organ class and preferred term	8.3000 (see the shells below)
8.4001	Non-serious adverse events (threshold = 5%) by system organ class and preferred term	8.4000 (see the shells below)
15.1000	Listing of Adverse Events with Onset Date after Third Interim Analysis Cutoff Date (Jan 12th, 2017)	15.8030
15.2000	Listing of Deaths	15.7180
[redacted]		

NOVARTIS



[redacted]

[redacted]

Table 7.3005 Sensitivity Analysis of Overall Survival

Protocol: AGO-OVAR16/VEG110655
Page 1 of n
Population: Intent-to-Treat
Data as of:

Table 7.3005 Sensitivity Analysis of Overall Survival

	Placebo (N=50)	Pazopanib (N=50)
Number of Patients		
Died (event)	xx (xx%)	xx (xx%)
Censored, follow-up ended	xx (xx%)	xx (xx%)
Censored, follow-up ongoing	xx (xx%)	xx (xx%)
Adjusted Hazard Ratio [1]		
Estimate	xx	
95% CI	(xx,xx)	
Stratified Log-Rank P-Value [1]	xx	
Estimates for overall survival(months) [2]		
1st Quartile	xx	xx
95% CI	(xx, xx)	(xx, xx)
Median	xx	xx
95% CI	(xx, xx)	(xx, xx)
3rd Quartile	xx	xx
95% CI	(xx, xx)	(xx, xx)

[1] The Hazard ratio is estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with pazopanib compared with placebo. Hazard Ratio and P-value from stratified log-rank test are adjusted for the two stratification factors.
[2] Confidence intervals are estimated using the Brookmeyer-Crowley method.
[3] Patients who have missing death dates are treated as have died on the last contact date.

Table 8.3001 On-treatment deaths and serious adverse events by system organ class and preferred term

Protocol: AGO-OVAR16/VEG110655
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Population: All Treated
Data as of:

On-treatment deaths and serious adverse events by system organ class and preferred term

Primary system organ class Preferred term	Placebo N=xxx	Pazopanib N=xxx	All patients N=xxx
Total number of subjects affected			
Subjects affected by serious adverse events / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Number of deaths (all causes)	xx	xx	xx
Number of deaths resulting from adverse events*	xx	xx	xx
Infections and infestations			
Pneumonia			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx	xx/xx	xx/xx
Deaths causally related to treatment/all	xx/xx	xx/xx	xx/xx
Sepsis			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx	xx/xx	xx/xx
Deaths causally related to treatment/all	xx/xx	xx/xx	xx/xx
Investigations			
Platelet count decreased			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx	xx/xx	xx/xx
Deaths causally related to treatment/all	xx/xx	xx/xx	xx/xx
Weight decreased			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx	xx/xx	xx/xx
Deaths causally related to treatment/all	xx/xx	xx/xx	xx/xx
etc.			

*Number of deaths resulting from adverse events corresponds to deaths resulting from serious AE causally related to treatment.
Occurrences causally related to treatment/all: all occurrences are all SAEs occurrences regardless of causality to treatment.
Deaths causally related to treatment/all: all deaths are all SAEs with fatal outcome regardless of causality to treatment.
On-treatment SAEs are included i.e. serious adverse events starting on or

after the day of the first intake of study treatment and no later than 28 days after the last treatment date.
MedDRA version 19.0.

[redacted]

Table 8.4001 Non-serious adverse events (threshold = 5%) by system organ class and preferred term

Protocol: AGO-OVAR16/VEG110655
Page 1 of n
Population: All Treated
Data as of:

Non-serious adverse events (threshold = 5%) by system organ class and preferred term

Primary system organ class Preferred term	Placebo N=xxx	Pazopanib N=xxx	All Patients N=xxx
Total number of subjects affected			
Subjects affected by non-serious adverse events / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Blood and lymphatic system disorders			
Anemia			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Thrombocytopenia			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Infections and infestations			
Pneumonia			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Sepsis			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Investigations			
Platelet count decreased			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Weight decreased			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
etc.			

Total number of subjects affected by non-serious AEs are those subjects who had at least one preferred term that met the threshold criteria.

Preferred terms with a frequency greater than 5% in any treatment arm were printed.
On-treatment AEs are included i.e. adverse events starting on or after the day of the first intake of study treatment and no later than 28 days after the last treatment date.
MedDRA version 19.0.

[redacted]

[redacted]