NI PASS PROTOCOL

TITLE:	**BELOVA: A NON-INTERVENTIONAL STUDY TO COLLECT DATA ON THE SAFETY AND EFFICACY OF FRONTLINE BEVACIZUMAB TREATMENT IN FIGO STAGE IV OVARIAN CANCER PATIENTS ⩾ 70 YEARS.**
PROTOCOL NUMBER:	ML29515
VERSION NUMBER:	5.0
AUTHOR:	[redacted]
EU PAS REGISTER NUMBER:	ENCEPP/SDPP/13849
ACTIVE SUBSTANCE:	L01XC07: bevacizumab
STUDIED MEDICINAL PRODUCT:	Bevacizumab (AVASTIN)
PRODUCT REFERENCE NUMBER:	EU/1/04/300/001 – 100 mg/4 ml vial EU/1/04/300/002 – 400 mg/16 ml vial
PROCEDURE NUMBER:	Not Applicable
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	Safety and efficacy data of frontline bevacizumab treatment in FIGO stage IV ovarian cancer patients ⩾ 70 years.
COUNTRY OF STUDY POPULATION:	Belgium

MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
MAH CONTACT PERSON:	[redacted], [redacted].
DATE FINAL:	13 October 2016

PROTOCOL FINALIZATION SIGNATURE PAGE

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DATE FINAL:	13 October 2016

This protocol was finalized on the date shown above.

[redacted]	14/10/2016
[redacted] (Medical manager)	Date
QPPV or Deputy's Name	Date

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MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom

I agree to conduct the study in accordance with the current protocol.

_____

Treating Physician's Name (print)

_____ _____

Treating Physician's Signature Date

Please return the signed original of this form to the contact provided below. Please retain a copy for your study files.

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CD	compact disc
CGA	comprehensive geriatric assessment
CI	confidence interval
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
PRO	patient-reported outcome
FDA	Food and Drug Administration
G-GGT	gamma glutamyl transferase
GPP	Good Pharmacoepidemiological Practice
GVP	EU Guideline on Good Pharmacovigilance Practices
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
LDH	lactatdehydrogenase
LPLA	last patient, last assessment
LPLV	last patient, last visit
NCI	National Cancer Institute
PDS	Pharma Development Safety
QPPV	Qualified Person for Pharmacovigilance
RBC	red blood cell
SAE	Serious adverse event
SDV	Source data verification
SPC	Summary of Product Characteristics

Abbreviation	Definition
STIAMP	Suspected Transmission of Infectious Agent by Medicinal Product
ULN	upper limit of normal
WBC	white blood cell

2. RESPONSIBLE PARTIES

Country Medical Manager

[redacted]

Country Medical Unit Manager

[redacted]

Coordination Principal Investigator

[redacted]

Scientific Committee

The Belgium and Luxembourg Gynaecological Oncology Group – BGOG

Scientific Committee

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BGOG@engot.eu

Study Management

[redacted]

Statistics – Clinical Report

[redacted]

Pharmacovigilance

[redacted]

3. SYNOPSIS

TITLE:	**BELOVA: A NON-INTERVENTIONAL STUDY TO COLLECT DATA ON THE SAFETY AND EFFICACY OF FRONTLINE BEVACIZUMAB TREATMENT IN FRONTLINE FIGO STAGE IV OVARIAN CANCER PATIENTS ⩾ 70 YEARS.**
PROTOCOL NUMBER:	**ML29515**
VERSION NUMBER:	5.0
DATE OF SYNOPSIS:	13 October 2016
EU PAS REGISTER NUMBER:	ENCEPP/SDPP/13849
STUDIED MEDICINAL PRODUCT:	Bevacizumab (AVASTIN)
INTERNATIONAL MEDICAL DIRECTOR:	[redacted]
MAIN AUTHOR:	[redacted]
PHASE:	IV, non-interventional study
INDICATION:	Epithelial ovarian, fallopian tube and primary peritoneal cancer (defined as ovarian cancer)
MARKETING AUTHORIZATION HOLDER:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom

Rationale and Background

Due to ageing of the Western countries' population, the number of older patients with cancer is expected to increase within the coming decades.

In Belgium, approximately 900 patients are diagnosed with ovarian cancer annually and according to the Belgian Cancer Registry, in 2011, 46% of patients diagnosed with ovarian cancer were over 70 years old.

Bevacizumab is currently indicated in frontline in combination with carboplatin/paclitaxel based on 2 large randomized phase III studies, GOG-0218 and ICON7. Based on the subgroup analysis of these trials it seems that the treatment combinations are feasible in selected elderly patients.

In GOG-0218, the risk of progression or death was lower in patients older than 70 treated with carboplatin/paclitaxel and bevacizumab followed by bevacizumab for up to a maximum of 15 months compared to patients treated with carboplatin/paclitaxel and placebo, followed by placebo for max. 15 months (HR=0.678). This was consistent to the reduction in risk seen in the entire ITT population where the hazard rate was 0.717 (Burger, presentation ASCO 2010).

In the ICON7 trial, the risk of progression or death was lower in patients older than 70 treated with carboplatin/paclitaxel and bevacizumab followed by bevacizumab for up to a maximum of 12 months compared to patients treated with carboplatin/paclitaxel only with a HR=0.82. Again in this study, the reduction in risk was comparable to that of the whole ITT population where the HR was 0.81 (Perren, ESMO 2010).

These trials, however, only included a minority of the actual elderly population. In the 2 frontline phase III studies, GOG-0218 and ICON7, respectively 17% and 10% were 70 years or older.

Research Question and Objectives

Despite the high incidence of ovarian cancer in the elderly population, older patients are usually underrepresented in clinical trials. One has to be cautious to extrapolate the results of these trials to the general senior adult population. Consequently it is difficult to reach evidence-based clinical recommendations which apply to the treatment of the older population.

The purpose of this study is to evaluate the safety and efficacy in the frontline treatment of ovarian cancer in a wider selection of patients ⩾70 years old in a routine clinical practice in Belgium. Bevacizumab will be used as described in the summary of product characteristics, in combination with carboplatin/paclitaxel followed by bevacizumab as maintenance.

The primary endpoint of this study will be safety. The secondary endpoints will be PFS, ORR, treatment duration and as an adjunct to the general and cancer-specific clinical and diagnostic examinations, comprehensive geriatric assessment (CGA) will be used to evaluate Avastin treatment in elderly patients. The principal areas of focus of the CGA include the patient's functional, physical, mental, emotional, pharmacotherapeutic, and socioeconomic status.

Objectives

The primary objective for this study is as follows:

- To evaluate the safety and tolerability of bevacizumab in the frontline treatment of elderly FIGO stage IV ovarian cancer patients.

The secondary objectives for this study are as follows:

To describe:

- The key demographic characteristics and medical history of the elderly population receiving bevacizumab
- The clinical efficacy measured by progression free survival, defined as time from start of bevacizumab treatment until progression or death from any cause, whichever comes first.
- The Objective Response Rate
- The Comprehensive Geriatric Assessments evolution
- The dosage, schedule of bevacizumab and the chemotherapies used in combination with bevacizumab for the treatment of elderly ovarian cancer patients

Study Design

Description of Study

This is a multi-center, non-interventional, post-authorization study to collect safety and efficacy data on the use of bevacizumab in FIGO stage IV ovarian cancer patients ⩾ 70 years.

Dosing and treatment duration are at the discretion of the investigator in accordance with the local labeling and reimbursement.

Patients will be followed from start of bevacizumab treatment until progression or death from any cause, whichever comes first.

The recruitment is planned to last for about 3 years. The study will continue until the last patient has had disease progression or died, whichever comes first.

Start Date of Study

April 2015

End Date of Study

Based on the average PFS reported in the pivotals studies, the end of the trial is expected 12 months after last patient first visit.

Population

Patients aged ⩾70 years and diagnosed with FIGO stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer for who it is decided to administer frontline chemotherapy with bevacizumab can be included in this study, after signing the informed consent form.

Patients must meet the following criteria for study entry:

- Initially diagnosed with frontline FIGO stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer
- aged ⩾70 years
- have signed the written informed consent and received a copy.
- No treatment with any other investigational agent within 28 days or 2 investigational agent half-lives (whichever is longer) prior to enrolment in this study.

Patients who meet any of the following criteria will be excluded from study entry:

- Contraindications, warnings and precautions for use as specified in the bevacizumab SmPC.

Variables

Primary Variables

The primary variables for this study are as follows:

Safety and tolerability of bevacizumab as part of the frontline treatment of elderly patients with epithelial ovarian, fallopian tube or primary peritoneal cancer.

This means that we will collect all reports of serious adverse events (SAEs), adverse events of special interest (AESI) and non-serious AEs. For adverse events of special interest, the time to first incidence of the AE will be analysed.

The following AESIs will be collected:

- Hypertension
- Proteinuria
- GI perforation
- Wound healing complications
- Thromboembolic events (ATE and VTE)
- Bleeding
- Congestive Heart Failure (CHF)
- Fistulae
- Reversible Posterior Leukoencephalopath Syndrome (RPLS)

Secondary Variables

The secondary variables for this study are as follows:

- The key demographic characteristics and medical history of the elderly population receiving bevacizumab
- Clinical Efficacy measured by
    - Progression free survival, defined as time from start of bevacizumab treatment until progression or death from any cause, whichever comes first.
    - Objective Response Rate, defined as the rate of Complete Responses (CR) or Partial Rasponses (PR) as best overall response under treatment

Tumor assessment will be based according to routine institutional clinical practice: radiographic assessment [through RECIST criteria (version 1.1) or other

interpretation criteria non-standardized, non-quantitative criteria)] or other assessment (e.g. clinical criteria).

- Comprehensive Geriatric Assessments evolution
- The dosage, schedule of bevacizumab and the chemotherapies used in combination with bevacizumab for the treatment of elderly ovarian cancer patients

Data Sources

The following data will be collected:

At baseline:

- Date of informed consent to the study
- Date of birth, height and weight, performance status
- Blood pressure, urine dipstick value
- Ca-125 level (if known)
- Tumour history; date of first diagnosis of ovarian cancer, any previous treatment for OC (incl. neo-adjuvant chemotherapy)
- Surgery for OC; staging, postoperative residual tumour, histology and grade
- Gastrointestinal involvement with tumour (if known) and previous GI surgery
- Relevant medical history; hypertension and its previous/current treatment, cardiovascular history, bleeding disorders, recent major surgery, concomitant medications
- Comprehensive Geriatric Assessment evaluation

During the treatment phase:

- Patient weight and ECOG performance status
- Blood pressure, urine dipstick value recorded
- Any abnormal blood pressure or urine dipstick values recorded since last visit
- Ca-125 level (if measured)
- Type of chemotherapy, dosages and dates
- Dosage and dates of administration of bevacizumab
- Modification to chemotherapy and bevacizumab treatment (action taken, date when modified/stopped and reason)
- Interventions undertaken to address abnormal Blood pressure, urine protein, AEs
- Routine tumor assessment (CR/PR/SD/Not Evaluable, date of response to therapy if any, date of disease progression if any)
- Concomitant medications
- All (S)AEs
- Limited Comprehensive Geriatric Assessment after chemotherapy just before the first monotherapy cycle of Avastin and after 10 months of bevacizumab treatment

End of Treatment Assessment:

- Patient weight and performance status
- Blood pressure, urine dipstick value
- Any abnormal blood pressure or urine dipstick values recorded since last visit
- Ca-125 level (if measured)
- Date of and reason for final bevacizumab administration
- Interventions undertaken to address abnormal Blood pressure, urine protein, AEs

- Routine tumor assessment (CR/PR/SD/Not Evaluable, date of response to therapy if any, date of progression if any)
- Date and cause of death, if death occurred before end of bevacizumab treatment
- Concomitant medications
- Persisting (S)AEs
- Limited Comprehensive Geriatric Assessment

Collection of adverse events:

Adverse events will be collected until at least 28 days after the last administration of bevacizumab. Related SAEs need to be collected until 6 months after last dose. AESIs should be reported if they start up to 6 months after last dose. SAEs & AESIs should be followed up to final resolution.

Follow-up period

Patient information will be recorded at 6 and 12 months after the end of bevacizumab treatment. The following information will be collected;

- Patient status; progression-free, progressed etc
- Basic information on further anti-tumour therapy; type of therapy and dates
- Date of disease progression and/or death

Data collection may be prospective or retrospective from patient records with timings determined by routine standard of care at each center.

SPECIAL PROTOCOL ASSESSMENTS (e.g. QoL)

Patients included in the study will be asked to undergo a comprehensive geriatric assessment.

The geriatric assessment is a multidimensional, multidisciplinary diagnostic instrument designed to collect data on the medical, psychosocial and functional capabilities and limitations of elderly patients.

The geriatric assessment differs from a standard medical evaluation in a way that it focuses on elderly individuals with complex problems and it emphasizes functional status and quality of life.

The geriatric assessment consists of a questionnaire which effectively addresses many areas of geriatric care that are crucial to the successful treatment and prevention of disease and disability in older people.

The completion of this questionnaire does not make the study interventional.

The geriatric assessment will be integrated as part of the CRF.

Study Size

We plan to enroll100 patients with age ≥ 70.

This sample size was not based on a formal calculation but mainly driven by feasibility and a reasonable width of a 95% confidence interval for the rate of AEs and SAEs.

Assuming that a total of 100 patients included in the study, the following can be expected:

- for an observed proportion of 99% of patients presenting at least one AE (all grades) during the study (GOG-0218), the 95% confidence interval ('Agresti-Coull') around this proportion will extend between 94% and 100%

- for an expected proportion of 95% of patients presenting at least one severe AE (grade 3 to 5) during the study (GOG-0218), the 95% confidence interval ('Agresti-Coull') around this proportion will extend between 89% and 98%

- for an observed proportion of 97% of patients presenting at least one AE of Special Interest (all grades) during the study (GOG-0218), the 95% confidence interval ('Agresti-Coull') around this proportion will extend between 91% and 99%

- for an expected proportion of 90% of patients presenting at least one severe AE of Special Interest (grade 3 to 5) during the study (GOG-0218), the 95% confidence interval ('Agresti-Coull') around this proportion will extend between 82% and 95%

Following the small sample size of this study and no specified method used to compare with the overall population exposed to Avastin, the results of the study will be purely descriptive. (Cfr. 8.7 data analysis)

Data Analysis

This non-interventional, exploratory, non-comparative study aims primarily to describe and estimate treatment data rather than to test pre-specified statistical hypotheses. Statistical analyses will be performed primarily for descriptive and estimation purposes. However, statistical models and tests may be used to explore interesting aspects of the data. Unless otherwise specified, all statistical hypotheses will be tested at the 5% significance level against two-sided alternatives, and corresponding 95% confidence intervals will be reported as appropriate.

Analysis of Primary Variables

The primary analysis of the safety endpoints will be undertaken once all patients have completed the study. The incidence of AEs and SAEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

Summaries will include the incidence of AEs and SAEs, AEs leading to premature discontinuation of study treatment, and specific cardiac AEs and SAEs. Summaries will include frequency counts and percentages (with 95% confidence interval according to ‘Agresti-Coull’ method) and time to first onset of selected AEs.

Analysis of Secondary Variables

The analysis of secondary variables will be undertaken once all patients have completed the study.

Demographic and disease characteristics and other background information will be summarized by means of descriptive statistics.Kaplan-Meier estimates will be provided for time-to-event variables.

Standard descriptive statistics will be used for quantitative and categorical variables.

Rates and proportions will be associated with a 95% confidence interval according to ‘Agresti-Coull’ method (95% CI).

Kaplan-Meier estimates and Kaplan-Meier Curve will be provided for time-to-event variables (PFS). If possible, the median survival time will be reported with its 95% confidence interval based on the nonparametric Brookmeyer and Crowley method.

Details will be described in the statistical analysis plan that will be finalized before data base lock.

Interim Analyses

An interim analysis that included summaries of baseline characteristics for all 100 patients will be presented.

Milestones

Planned study milestones are given in the following table.

Milestone	Planned Date
Protocol approval by an IRB/EC	Feb 2015
Start of data collection	Apr 2015
End of data collection	Jul 2019
Study progress report 1	Not Applicable
Study progress report 2	Not Applicable
Study progress report 3	Not Applicable
Interim report 1	Sept 2018
Interim report 2	Not Applicable
Interim report 3	Not Applicable
Registration in the EU PAS register	21 Jun 2016
Final report of study results	Jul 2020
{Any other important timeline in the conduct of the study}	Not Applicable

Start Date of Study:

The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database. The start date is April 2015.

End and length of Study

The end of the study will be the date from which the last information of the last subject is recorded in the study database. Based upon the planned enrolment period of 3 years and expected FU period of 12 months the study end is expected in July 2019.

DATA COLLECTION OVERVIEW (AS PER STANDARD OF CARE)

	Study entry[1]	Baseline, before start of bevacizumab therapy	During bevacizumab therapy[2]	End of bevacizumab therapy	Follow-up, 6 & 12 months after end of bevacizumab
Informed Consent	X				
Date of birth		X			
Height		X			
Weight		X	X	X	
ECOG Performance Status		X	X	X	
Blood pressure		X	X	X	
Dipstick Urinalysis		X	X	X	
Ca-125 (if measured)[3]		X	X	X	
Ovarian cancer history		X			
Ovarian cancer surgery		X			
GI involvement		X			
Medical History		X			
Concomitant Medication		X	X		
Disease assessment[4]		X	X	X	X
Comprehensive Geriatric Assessment[5]		X	X	X	X
Chemotherapy administration		X (if chemotherapy started before bevacizumab)	X (up to a max. of 6 cycles of chemotherapy)	X (if applicable)	
Avastin administration			X		
Adverse Events			X	X	
Interventions for AEs			X	X	
Survival status			X	X	X
Reason for stopping Avastin				X	

[1]Study entry is at time of informed consent, this may occur before or after first bevacizumab administration, but must be after the decision to initiate bevacizumab therapy. [2]Timing of visits determined by routine clinical practice at each center [3]Ca-125 measurement not mandatory, record only if measured in routine clinical care. [4] Assessment according to local standard of care (e.g. clinical examination or ultrasound or CT-scan). [5] CGA will be performed at baseline, limited CGA will be performed after chemotherapy has ended just before the first cycle of bevacizumab monotherapy, 10 months after start of bevacizumab treatment and 15 months after start of bevacizumab treatment or at progression of disease whichever comes first.

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Authorization Holder or designee.

Protocol amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Site Operations Representative or contact information).

Protocol amendments/updates so far: see table below

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	14/01/2016	All, new template is used	New template	Safety requirements
2	03/03/2016	Exclusion criteria	“No” treatment with any other investigational agent	Typo
3	13/10/2016	Milestones	Updated milestones	Adapt timelines recruitment/minor changes to wording

5. MILESTONES

Study milestones are given in the following table.

Milestone	Planned Date
Start of data collection	Apr2015
End of data collection	Jul 2019
Study progress report 1	Not Applicable
Study progress report 2	Not Applicable
Study progress report 3	Not Applicable
Interim report 1	Sept 2018
Interim report 2	Not Applicable
Interim report 3	Not Applicable
Registration in the EU PAS register	21 June 2016
Final report of study results	Jul 2020
{Any other important timeline in the conduct of the study}	Not Applicable

6. RATIONALE AND BACKGROUND

6.1 STUDY RATIONALE

Due to ageing of the Western countries' population, the number of older patients with cancer is expected to increase within the coming decades.

Ageing is a highly individualized process and all the changes involved in this process cannot be predicted just on the basis of chronological age.

The older population is hugely complex and very fit patients in their eighties and nineties are mixed up with frail individuals in their seventies; the former deserving aggressive state-of-the-art cancer treatments, the latter only requesting an adaption on their physical/mental capability or even palliative management aimed at improving their quality of life.

As a consequence, it is clear that there is an emerging need for developing tools to better evaluate a patient's 'biological' or 'functional age' rather than chronological age. (Pallis et al. 2012)

According to the National Comprehensive Cancer Network (NCCN) guidelines, Comprehensive Geriatric Assessment (CGA) should be a key part of the treatment approach for vulnerable and frail older patients with cancer. The CGA is a means of assessing physiologic age and provides an assessment of functional reserve independent of chronological age. Its use is advocated by geriatric oncologists to uncover predictors of functional decline, frailty, and mortality, which vary among patients of comparable age. (NCCN guidelines 2014)

More than half of all patients diagnosed with ovarian cancer are older than age 65 years. This ratio is also expected to increase in the coming decades as our population ages and life-expectancy improves. (Tew et al. 2013)
According to the Belgian Cancer registry, in 2011, 46% of all new diagnoses were in women over 70 years. (Belgian Cancer Registry, 2014)

Older patients with ovarian cancer are less likely to be offered standard cancer treatments, have poorer outcomes and develop higher toxicity to treatment. In addition, advancing age is considered a risk factor for survival of ovarian cancer. Reasons for this may be numerous, and theoretically could include: more aggressive cancer with advanced age, inherent resistance to chemotherapy, individual patient factors such as multiple concurrent medical problems, and physician and healthcare biases toward elderly, which lead to inadequate surgery, less than optimal chemotherapy and poor enrollment in clinical trials. (Tew et al. 2013)

Also in ovarian cancer, a comprehensive geriatric assessment is needed to evaluate the benefit-risk ratio for patients and determine which patient will be able to benefit from the combination of invasive surgery, chemotherapy and biological treatment.

To the extent of our knowledge, no prospective study examining the use of bevacizumab for the frontline treatment of elderly patients with stage IV ovarian cancer exists.

- For information on the condition under observation please refer to the most recent version of the SPC

In the treatment of advanced ovarian cancer, the combination of carboplatin/paclitaxel and bevacizumab is considered a standard treatment option (Stuart et al. 2010; Ledermann et al. 2013) based on the 2 large randomized phase III studies, GOG-0218 and ICON7. And evidence from subgroup analysis of these trials suggests that the treatment combinations are also feasible in selected elderly patients.

In GOG-0218, the risk of progression or death was lower in patients older than 70 treated with carboplatin/paclitaxel and bevacizumab followed by bevacizumab for up to a maximum of 15 months compared to patients treated with carboplatin/paclitaxel and placebo, followed by placebo for max. 15 months (HR=0.678). This was consistent to the reduction in risk seen in the entire ITT population where the hazard rate was 0.717. (Burger et al. 2011)

In the ICON7 trial, the risk of progression or death was lower in patients older than 70 treated with carboplatin/paclitaxel and bevacizumab followed by bevacizumab for up to a maximum of 12 months compared to patients treated with carboplatin/paclitaxel only with a HR=0.82. Again in this study, the reduction in risk was comparable to that of the whole ITT population where the HR was 0.81. (Perren et al. 2011)

These trials, however, only included a minority of the actual elderly population. In the 2 frontline phase III studies, GOG-0218 and ICON7, respectively 17% and 10% were 70 years or older.

Additionally, no specific safety data analysis was done in these subgroups of patients, so one has to be cautious to extrapolate the results of these trials to the general senior adult population. Consequently, it is difficult to reach evidence-based clinical recommendations which apply to the treatment of the older population.

- For information on bevacizumab (Avastin) please refer to the most recent version of the SPC.

6.2 BACKGROUND ON OVARIAN CANCER

6.2.1 Epidemiology of ovarian cancer

Epithelial ovarian cancer and related malignancies (primary peritoneal carcinoma, fallopian tube carcinoma) represent the fifth most common cause of cancer-related death among women in Europe and the United States. (Globocan 2008; Siegel et al, 2011)

Ovarian cancer (OC) alone is the fourth most common cause of cancer-related death in women with an estimated 200,000 cases and 125,000 deaths annually worldwide. It is also the gynecological malignancy with the highest mortality rate. (Chan et al, 2006)

In Belgium in 2008, 869 patients were newly diagnosed and 653 women died from this neoplasm. (Belgian Cancer Registry, 2014)

Epithelial ovarian cancer is primarily a disease of older women. According to the Belgian Cancer registry, in 2011, 46% of all new diagnoses were in women over 70 years. (Belgian Cancer Registry, 2014)

6.2.2 Natural history of ovarian cancer

Despite improvements in the treatment of ovarian cancer, increases in overall survival (OS) have been modest and as such, mortality remains high. (Belgian Cancer Registry, 2014; Engel et al. 2002)

Ovarian cancer is often asymptomatic in early stages; consequently, patients typically have late stage disease at diagnosis, contributing to the high mortality rate. (Tate et al. 2009)

Approximately 70% of patients will present at advanced stage, and 26% of patients in Belgium will only be diagnosed when the tumor has spread to other organs at FIGO stage IV. (Belgian Cancer Registry, 2014)

The optimal frontline treatment for these patients involves the appropriate integration of surgery and chemotherapy mostly consisting of carboplatinum and paclitaxel. (Bookman et al. 2003)

However, disease recurs in most patients within five years of diagnosis and more than half of all patients die within 5 years of diagnosis. (Pfisterer et al. 2006; Harries et al. 2002)

Major trials published over the past 15 years reported that the median progression-free survival (PFS) for patients with advanced disease ranges between 16 and 23 months while the median OS is within 31 and 65 months. (International Collaborative Ovarian

Neoplasm Group (ICON)-3; Armstrong et al. 2006; McGuire et al. 1996; Muggia et al. 2000; Piccart et al. 2000 ; Ozols et al. 2003 ; du Bois et al 2003.)
Since the introduction of platinum-based chemotherapy and the addition of paclitaxel further advances in treatment have been modest. Addition of a third chemotherapeutic agent has failed to improve efficacy in numerous trials and this strategy has been largely abandoned. In this regard, molecular targeted therapeutic agents herald a new era for cancer treatment. In the setting of epithelial ovarian cancer, a growing body of evidence supports the use of anti-angiogenic agents in combination with chemotherapies. (Spannuth et al. 2008)

6.3 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) composed of human IgG1 framework regions and antigen-binding complementary determining regions from a murine monoclonal antibody (muMAb VEGF A.4.6.1) that blocks the binding of human VEGF to all VEGF-A receptors.

Bevacizumab has been evaluated in numerous phase I to IV trials in a variety of solid tumors as monotherapy and in combination with chemotherapy. The combination of bevacizumab with chemotherapy improves PFS and/or OS in metastatic colorectal cancer, non-squamous non-small cell lung cancer, HER2- metastatic breast cancer, metastatic renal cell cancer and ovarian cancer.

In the European Union (EU), bevacizumab in combination with the chemotherapeutic agents paclitaxel and carboplatin bevacizumab is approved for the first-line treatment of advanced ovarian cancer (FIGO IIIB – IV). For the treatment of VEGF(R)-inhibitor naïve platinum-sensitive ovarian cancer, bevacizumab is approved in combination with carboplatin and gemcitabine and for the treatment of VEGF(R)-inhibitor naïve platinum-resistant ovarian cancer, bevacizumab is approved by the EU in combination with paclitaxel, or pegylated liposomal doxorubicin (PLD), or topotecan. (Avastin Summary of Product Charactristics)
In Belgium, bevacizumab is reimbursed by the Health Authorities for the frontline treatment of metastatic (FIGO stage IV) ovarian cancer and for the treatment of platinum-sensitive VEGF(R)-inhibitor naïve ovarian cancer at first recurrence. (RIZIV/INAMI website, consulted 2014)

The benefit of bevacizumab in the frontline treatment of ovarian cancer has been demonstrated in 2 large phase III trials.(Burger et al. 2011; Perren et al.)

GOG-0218

The GOG-0218 study was a phase III multicenter, randomized, double-blind, placebo-controlled, three arm study evaluating the effect of adding bevacizumab to an approved standard chemotherapy regimen (carboplatin and paclitaxel) in patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer who had not received prior systemic treatment for ovarian cancer.

A total of 1873 patients were randomized in equal proportions to the following three arms:

- CPP arm: Five cycles of placebo (started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15 arm: Five cycles of bevacizumab 15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15+ arm: Five cycles of bevacizumab (15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles followed by continued use of bevacizumab (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

The trial significantly met its primary objective of PFS improvement: ($p<0.0001$)
- In the investigator determined analysis, PFS was significantly improved with 4,1 months when adding bevacizumab to chemotherapy and continuing bevacizumab until a maximum of 15 months (14.7 months versus 10.6 months, $p<0.0001$, HR 0.70)
- The Independent Review Committee analysis of PFS demonstrated a 6 months benefit in favor of adding bevacizumab when comparing CPP vs. CPB 15+ (PFS 19.1months versus 13.1 months, HR 0.62, $p<0.0001$)
- The regulatory requested analysis (censoring for CA-125 progressions and non-protocol treatment) showed a significantly improved PFS with a benefit of 6,7 months and patients who received bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone (CPB15+), had a relative reduction of 39% in the risk of tumor progression compared to CPP. (18,8 months versus 12,1 months, $p<0.0001$, HR 0.61) (Avastin Summary of Product Characteristic)

Overall Survival was a secondary endpoint of this study and despite over 30% cross-over to anti-angiogenic therapy (mostly bevacizumab) in further treatment lines, there still was a 3,2 month improvement with a 12% reduction in risk of dying for patients in arm CPB15+ versus patients in arm CPP. (40,6 months versus 43,8 months, $p<0.06$, HR 0.88)) (Avastin Summary of Product Characteristics)

Adding Bevacizumab only to the chemotherapy and not continuing until a maximum of 15 months (CPB15) did not result in the same benefit in PFS suggesting that bevacizumab needs to be continued beyond chemotherapy

ICON-7

ICON-7 was a Phase III, two arm, multicenter, randomized, controlled, open-label study comparing the effect of adding bevacizumab to carboplatin plus paclitaxel in patients with FIGO Stage I or IIA (Grade 3 or clear cell histology only; n = 142), or FIGO Stage IIB - IV (all grades and all histological types, n = 1386) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery. Patient who had received prior systemic treatment for ovarian cancer were not allowed.

A total of 1528 patients were randomized in equal proportions to the following two arms:
- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles of 3 weeks duration
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles of 3 weeks plus bevacizumab (7.5 mg/kg q3w) for up to 12 months (bevacizumab was started at cycle 2 of chemotherapy if treatment was initiated within 4 weeks of surgery or at cycle 1 if treatment was initiated more than 4 weeks after surgery)

The primary endpoint was PFS as assessed by the investigator using RECIST criteria.

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting, patients who received bevacizumab at a dose of 7.5 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab for up to 18 cycles had a statistically significant improvement in PFS of 2,4 months with a reduction in risk of tumor progression of 13% (p=0,0185) (Avastin Summary of Product Characteristics; Perren et al. 2011)
For both studies, toxic effects were as expected, with hypertension grade $\geqslant$2 being common but generally well controlled. Overall, the bevacizumab treatment was well tolerated. (Banerjee et al. 2012)

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The purpose of this study is to evaluate the safety and efficacy in the frontline treatment of ovarian cancer in a wider selection of patients $\geqslant$70 years old in a routine clinical practice in Belgium. Bevacizumab will be used as described in the summary of product characteristics, in combination with carboplatin/paclitaxel followed by bevacizumab as maintenance.

The primary endpoint of this study will be safety. The secondary endpoints will be PFS, ORR, treatment duration and as an adjunct to the general and cancer-specific clinical and diagnostic examinations, comprehensive geriatric assessment (CGA) will be used to evaluate Avastin treatment in elderly patients. The principal areas of focus of the CGA include the patient's functional status, comorbidity, cognition, mental health status, fatigue, social status and support, nutrition, and presence of geriatric syndromes.

7.2 OBJECTIVES

Objectives

The primary objectives for this study are as follows:

- To assess in routine clinical practice safety and tolerability of bevacizumab in the frontline treatment of elderly FIGO stage IV ovarian cancer patients

The secondary objectives for this study are as follows:

- To describe in a routine clinical practice:
    - The key demographic characteristics and medical history of the elderly population receiving bevacizumab as part of their frontline treatment of ovarian cancer
    - The clinical efficacy measured by progression free survival (PFS), defined as time from start of bevacizumab treatment until progression of death from any cause, whichever comes first and by the objective response rate
    - The evolution of the comprehensive geriatric assessment

- The dosage, schedule of bevacizumab and the chemotherapies used in combination with bevacizumab for the treatment of elderly ovarian cancer patients

8. RESEARCH METHODS

8.1 STUDY DESIGN

8.1.1 Overview of Study Design

This is a multi-center, non-interventional, post-authorization study to collect safety and efficacy data on the use of bevacizumab in ovarian cancer patients $\geqslant$ 70 years.

Dosing and treatment duration are at the discretion of the investigator in accordance with the local labeling and reimbursement.

Patients will be followed from start of bevacizumab treatment until progression or death from any cause, whichever comes first.

The study will be open for recruitment for about 3 years, then a follow-up period until the last patient has had disease progression or died, whichever comes first.

We estimate that we will recruit a total of 100 patients in approximately 20 centers in Belgium.

Start Date of Study: April 2015

The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database.

End of Study: July 2019

The end of the study will be the date from which the last information of the last subject is recorded in the study database.

A data collection overview is provided in Appendix 3.

8.1.2 Number of Patients Observed in the Study

The study aims to collect data of approximately 100 patients with ovarian cancer ≥ 70 years.

8.1.3 Rationale for Study Design

As described before, in Belgium, bevacizumab is registered and reimbursed for the frontline treatment of FIGO stage IV ovarian cancer patients, hence it is also available for patients of 70 years and older. This national, multicenter, non-interventional, post-authorization study will prospectively collect data in order to expand the knowledge on the safety profile and efficacy of Avastin in these elderly patients.

8.1.4 Rationale for Patient Population

This study will be performed in elderly patients, aged 70 or older, and diagnosed with epithelial ovarian, fallopian tube or primary peritoneal cancer. From a clinical point of view a cut-off point frequently used is the age of 70, since after this age, there is an increased incidence of age-related physiological changes, which increase the risk of

toxicity related to systemic therapy; hence age 70 is widely accepted as cut-off for "older"-specific analyses. (Pallis et al. 2010)

8.2 SETTING

8.2.1 Centers

This study will be conducted at approximately 20 centers in Belgium. Sites will be selected based on:

- Their experience in treating elderly OC patients
- Their experience with bevacizumab in this indication
- The availability of site personnel to perform CGA
- Their commitment to ensure good follow-up of each patient's treatment schedule until progression

8.2.2 Study Population

Elderly patients aged ≥ 70y, for whom it has been decided to administer frontline treatment for FIGO stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer with bevacizumab in combination with chemotherapy according to standard of care and in line with the current summary of product characteristics (SPC)/local labeling. Patients should not have any contraindication to bevacizumab therapy as per the local label and are eligible for observation in this cohort if the following applies: Written informed consent where local regulations allow or require it within up to 4 weeks after commencing treatment.

Each patient will undergo comprehensive geriatric assessment (CGA) at the start and a limited CGA during treatment, and the treatment pattern and safety profile of each patient will be followed-up until progressive disease.

Patients must meet the following criteria for study entry:

- Initially diagnosed with frontline stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer
- aged ⩾70 years
- have signed the written informed consent and received a copy.
- No treatment with any other investigational agent within 28 days or 2 investigational agent half-lives (whichever is longer) prior to enrolment in this study.

Patients who meet any of the following criteria will be excluded from study entry:

- Contraindications, warnings and precautions for use as specified in the bevacizumab SmPC.

8.2.3 Concomitant Medication and Treatment

Concomitant medication prescribed for concomitant diseases of special interest and treatment for ovarian cancer at the beginning of the observation period or introduced during the observation period will be documented on the eCRF (electronic Case Report Form) from start of therapy with bevacizumab until discontinuation of the treatment if applicable.

8.2.4 Dosage, Administration, and Compliance

Dosing and treatment duration of bevacizumab are at the discretion of the investigator in accordance with local clinical practice and local labeling.

8.3 VARIABLES

8.3.1 Primary Safety Variables

The primary variable for this study is as follows:

Safety and tolerability of bevacizumab as part of the frontline treatment of elderly patients with epithelial ovarian, fallopian tube or primary peritoneal cancer.

This means that we will collect all reports of serious adverse events (SAEs), adverse events of special interest (AESI) and non-serious AE. For adverse events of special interest, the time to first incidence or the AE will be analysed.

The following AESIs will be collected:

- Hypertension
- Proteinuria
- GI perforation
- Wound healing complications
- Thromboembolic events (ATE and VTE)
- Bleeding
- Congestive Heart Failure (CHF)
- Fistulae
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

8.3.2 Secondary Variables

The secondary variables for this study are as follows:

- The key demographic characteristics and medical history of the elderly population receiving bevacizumab
- Clinical efficacy measured by
    - Progression free survival, defined as time from start of bevacizumab treatment until progression or death from any cause, whichever comes first.
    - Objective Response Rate, defined as the rate of Complete Responses (CR) or Partial Responses (PR) as best overall response under treatment

  Tumor assessment will be based according to routine institutional clinical practice: radiographic assessment [through RECIST criteria (version 1.1) or through other interpretation criteria (non-standardized, non-quantitative criteria)] or other assessment (e.g. clinical criteria).

- Comprehensive Geriatric Assessment evolution
- The dosage, schedule of bevacizumab and the chemotherapy used in combination with bevacizumab for the treatment of elderly ovarian cancer patients

8.4 DATA SOURCES

8.4.1 Collection of Data on the CRF

Patients' medical records will be the source of all data that will be recorded on the CRFs. Therefore, only data available and already existing in patient's files will be recorded on CRFs. The degree of detail and completeness of data collected is dependent on what is recorded in the patient charts. Data from patient notes should be entered on the CRF as soon as they become available.

8.4.2 Data Collected during the Observation Period

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus, no study-specific visits or evaluations are required by this protocol.

The following data will be collected:

At baseline:

- Date of informed consent to the study (the informed consent can be signed up to a maximum of 4 weeks after the patient started bevacizumab treatment)
- Date of birth, height and weight, performance status
- Blood pressure, urine dipstick value
- Ca-125 level (if known)
- Tumour history; date of first diagnosis of ovarian cancer, any previous treatment for OC (incl. neo-adjuvant chemotherapy)
- Surgery for OC; staging, postoperative residual tumour, histology and Grade
- Gastrointestinal involvement with tumour (if known) and previous GI surgery
- Relevant medical history; hypertension and its previous/current treatment, cardiovascular history, bleeding disorders, recent major surgery, concomitant medications
- Comprehensive Geriatric Assessment evaluation

During the treatment phase:

- Patient weight and ECOG performance status
- Blood pressure, urine dipstick value recorded
- Any abnormal blood pressure or urine dipstick values recorded since last visit
- Ca-125 level (if measured)
- Type of chemotherapy, dosages and dates
- Dosage and dates of administration of bevacizumab
- Modification to chemotherapy and bevacizumab treatment (action taken, date when modified/stopped and reason)
- Interventions undertaken to address abnormal Blood pressure, urine protein, AEs
- Routine tumor assessment (CR/PR/CD/PD/Not Evaluable, date of response to therapy if any, date of disease progression if any)
- Concomitant medications
- All (S)AEs

- limited Comprehensive Geriatric Assessment (consisting of the following scores: G8, Pain, ADL, iADL, Mob-T and MNA) will be performed after chemotherapy (just before the first monotherapy cycle of Avastin) and after 10 months of bevacizumab treatment

During therapy with bevacizumab, assessments are routinely performed in accordance with current guidelines and local standard of care. When performed during the observational period, available results from the range of assessments described below will be documented on the CRF.

SPECIAL PROTOCOL ASSESSMENTS (e.g. QoL)

Patients included in the study will be asked to undergo comprehensive geriatric assessment. The geriatric assessment is a multidimensional, multidisciplinary diagnostic instrument designed to collect data on the medical, psychosocial and functional capabilities and limitations of elderly patients. The geriatric assessment differs from a standard medical evaluation in a way that it focuses on elderly individuals with complex problems and it emphasizes functional status and quality of life. The geriatric assessment consists of a questionnaire which effectively addresses many areas of geriatric care that are crucial to the successful treatment and prevention of disease and disability in older people. The completion of this questionnaire does not make the study interventional. The geriatric assessment scores will be integrated as part of the CRF.

Please see Appendix 4 for the Data Collection Overview (as per standard of care) during the treatment period.

8.4.3 Data Collected at Study Completion/ Early Termination Visit

For patients who complete treatment with bevacizumab the treatment completion visit should be documented.

Data collected on this document will be:

- Patient weight and performance status
- Blood pressure, urine dipstick value
- Any abnormal blood pressure or urine dipstick values recorded since last visit
- Ca-125 level (if measured)
- Date of and reason for final bevacizumab administration
- Interventions undertaken to address abnormal Blood pressure, urine protein, AEs

- Routine tumor assessment (CR/PR/SD/PD/Not Evaluable, date of response to therapy if any, date of progression if any)

- Date and cause of death, if death occurred before end of bevacizumab treatment

- Concomitant medications

- Persisting (S)AEs

- limited Comprehensive Geriatric Assessment (consisting of the following scores: G8, Pain, ADL, iADL, Mob-T and MNA)

Please see Appendix 4for the data collection overview at the treatment completion visit if available.

8.4.4 Data Collected during Follow-Up

Further progress of the patient will be recorded at 6 and 12 months after the end of bevacizumab treatment.

The following information will be collected:

- Patient status: progression-free, progressed, died, withdrawn consent or lost-to follow-up

- Basic information on further anti-tumour therapy; type of therapy and dates

- Date of disease progression and/or death

After the study completion/early termination visit, adverse events (AEs) should be followed as outlined in Section 10.1.4.2

Please see Appendix 4 for the data collection overview during follow-up.

8.4.5 Safety Data Collection

AEs, serious and non-serious, will be recorded on the CRF during the total observation period with investigator assessment of severity (mild, moderate, severe or in oncology studies using the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) and relationship to therapy (i.e., related or unrelated) as described in Section 10.

8.4.6 Retrospective Data Collection

Data collection may be prospective or retrospective from patient records with timings determined by routine standard of care at each center. When the patient informed

consent form has been signed after the start of bevacizumab treatment, the data from baseline will be collected retrospectively.**STUDY SIZE**

From all sites in Belgium, we expect 100 patients with age $\geqslant$ 70 will be enrolled in the study.

One hundred subjects are foreseen to be enrolled to assess the overall safety and tolerability of bevacizumab in this indication. This sample size was not based on a formal calculation but mainly driven by feasibility and a reasonable width of a 95% confidence interval for the rate of AEs and SAEs.

Assuming that a total of 100 patients included in the study, the following can be expected:

- for an observed proportion of 99% of patients presenting at least one AE (all grades) during the study (GOG-0218), the 95% confidence interval ('Agresti-Coull') around this proportion will extend between 94% and 100%

- for an expected proportion of 95% of patients presenting at least one severe AE (grade 3 to 5) during the study (GOG-0218), the 95% confidence interval ('Agresti-Coull') around this proportion will extend between 89% and 98%

- for an observed proportion of 97% of patients presenting at least one AE of Special Interest (all grades) during the study (GOG-0218), the 95% confidence interval ('Agresti-Coull') around this proportion will extend between 91% and 99%

- for an expected proportion of 90% of patients presenting at least one severe AE of Special Interest (grade 3 to 5) during the study (GOG-0218), the 95% confidence interval ('Agresti-Coull') around this proportion will extend between 82% and 95%

Following the small sample size of this study and no specified method used to compare with the overall population exposed to Avastin, the results of the study will be purely descriptive. (Cfr. 8.7 data analysis)

8.6 DATA MANAGEMENT

8.6.1 Data Quality Assurance

The marketing authorization holder will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data.

The marketing authorization holder will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the marketing authorization holder, and the marketing authorization holder's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

8.6.2 Electronic Case Report Forms

eCRFs are to be completed using a marketing authorization holder -designated electronic data capture (EDC) system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the marketing authorization holder and should be handled in accordance with instructions from the marketing authorization holder.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive the data related to patients from his or her site in an electronically readable format (e.g., on a compact disc [CD]). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

Accurate and reliable data collection will be assured by verification and cross-check of the CRFs against the investigator's records by the study monitor (source data verification [SDV]). A comprehensive validation check program utilizing back-end checks in the clinical database will verify the data, discrepancies will be generated accordingly, and data clarification from the sites will be requested. Queries will be transferred (e.g., by fax or electronic mail) to the site for resolution by the investigator.

8.6.3 Source Data Documentation

Study monitors will perform ongoing SDV as defined in the Trial Monitoring Plan to confirm that critical protocol data (i.e., source data) entered on the CRF by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records,

clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the CRF (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered on the CRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 8.6.5.

To facilitate SDV, the investigators and institutions must provide the marketing authorization holder direct access to applicable source documents and reports for trial-related monitoring, marketing authorization holder audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

8.6.4 Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

8.6.5 Retention of Records

Records and documents pertaining to the conduct of this study, including CRFs, PRO data (if applicable), and Informed Consent Forms, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the marketing authorization holder. Written notification should be provided to the marketing authorization holder prior to transferring any records to another party or moving them to another location.

8.7 DATA ANALYSIS

The following is an outline of the statistical methodology that will be used to analyze this study. A more detailed description will be provided in a separate statistical analysis plan (SAP) that may include additional exploratory analysis not explicitly mentioned in the following sections. The SAP will be finalized before closure of the database.

This non-interventional, exploratory, non-comparative study aims primarily to describe and estimate treatment data rather than to test pre-specified statistical hypotheses. Statistical analyses will be performed primarily for descriptive and estimation purposes. However, statistical models and tests may be used to explore interesting aspects of the data. Unless otherwise specified, all statistical hypotheses will be tested at the 5% significance level against two-sided alternative, and corresponding 95% confidence intervals according to 'Agresti-Coull' method (95% CI) will be reported as appropriate.

8.7.1 Safety Analyses

The safety analyses will include all patients who received at least one dose of bevacizumab, with patients grouped according to the treatment actually received.

Adverse events will be summarized according to the primary system-organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and CTCAE v. 4.0 toxicity grade. Summaries will include the incidence of AEs and SAEs, AEs leading to premature discontinuation of study treatment, and specific cardiac AEs and SAEs. For adverse events of special interest (hypertension, proteinuria, GI perforation, wound healing complications, thromboembolic events, bleeding, congestive heart failure, fistulae, RPLS), the time to first incidence of the AE will be analysed.

8.7.2 Effectiveness Analyses

Demographic and disease characteristics and other background information will be summarized by means of descriptive statistics.

Kaplan-Meier survival estimates and Kaplan-Meier Curve will be provided for time-to-event variables (e.g. treatment duration, PFS). If possible, the median survival time will be reported with its 95% confidence interval based on the nonparametric Brookmeyer and Crowley method.

Dose and duration of treatment will be described as well as the temporary discontinuations of the treatment and their reasons. The reason for definitive withdrawal of one or all of the components of treatment will be described as well as the period between discontinuation and progression/relapse.

Details will be describes in the statistical plan that will be finalized before data base lock.

8.7.3 Other Analyses

Not applicable.

8.7.4 Interim/Final Analysis and Timing of Analyses

An interim analysis that includes summaries of baseline characteristics for all 100 patients will be performed once recruitment has stopped.

8.8 QUALITY CONTOL

8.8.1 Study Documentation

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which include an audit trail containing a complete record of all changes to data.

8.8.2 Site Audits and Inspections

Site visits will be conducted by the marketing authorization holder or an authorized representative for inspection of study data, patients' medical records, and CRFs. The investigator will permit national and local health authorities, marketing authorization holder monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

8.8.3 Administrative Structure

Tata Consultancy Services (TCS) will be in charge of the data management process of the study for all the patients.

Keyrus Biopharma (KBP) will be in charge of statistical analysis, medical review and medical writing of the final clinical study report.

Quintiles will be responsible for the monitoring of the study.

All outsourced activities will be performed within the Roche requirements and Standard Operating Procedures.

8.9 LIMITATIONS OF THE RESEARCH METHOD

Selection bias is a frequent limitation of observational trials. Selection bias could occur:

- If the characteristics of the patients (or investigators) are systematically different from those in the target (observed) population;

- If the follow-up of patients included by the investigators in the study is not a mirror image of the real life frontline treatment of stage IV ovarian cancer.

Information bias could be related to the GCA questionnaire. Patients are affected by reporting bias. For example, they may not accurately remember or know the exact answer.

In order to reduce selection bias, the following controls should be done:

- The selection of investigators should be done using an exhaustive list and feasibility questionnaires.

- Patients should be enrolled consequently by the investigators since the setup of the study, after ensuring that inclusion and exclusion criteria are met.

- Raw data on the total number of patients ≥ 70 years, who are seen in the center, will be collected every 2 months during the recruitment period.

To limit potential bias by completing the GCA, it is preferable that the investigator point out one person to perform the assessment for all included patients. This person will receive training on how to perform the assessment properly.

8.10 OTHER ASPECTS

8.10.1 Scientific Committee

1.1.1 Role of scientific Committee

The role of the committee is to provide scientific leadership to the study team throughout the whole study period while maintaining ethical and scientific standards.

The committee can support the local study team by providing input on the clinical relevance of the proposed study design and protocol.

The members of the committee can be consulted by the study team during the study period whenever necessary and if necessary a meeting can be organized to discuss specific issues.

Members of the scientific committee will be involved in the analysis, interpretation and publication of the study results.

1.1.2 Composition of Scientific Committee

The Scientific Committee will consist of the members of the BGOG Steering Committee:

[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

9. PROTECTION OF HUMAN SUBJECTS

9.1 PATIENT DISCONTINUATION

The investigator has the right to withdraw a patient from the study at any time. In addition, patients have the right to voluntarily withdraw from the study at any time for any reason. Reasons for discontinuation of treatment with the drug under observation or withdrawal from the study may include, but are not limited to, the following*:*

- Patient withdrawal of consent at any time
- Investigator or marketing authorization holder judges discontinuation is in the patient's best interest.
- Patient is lost to follow-up.

9.1.1 Discontinuation from Treatment with Studied Medicinal Product

Patients must discontinue bevacizumab according to local labeling if they experience any of the following:

- gastrointestinal perforation
- tracheoesophageal (TE) fistula
- any Grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]
- necrotising fasciitis

- medically significant hypertension that cannot be adequately controlled with antihypertensive therapy
- hypertensive crisis
- hypertensive encephalopathy
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Grade 4 proteinuria (nephrotic syndrome) (NCI-CTCAE v.3)
- arterial thromboembolic reactions
- life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3)
- Grade 3 or 4 bleeding during Avastin therapy (NCI-CTCAE v.3)
- intracranial bleeding

The early termination visit should be completed by patients who discontinue treatment with bevacizumab earlier than planned according to labeling. The primary reason for early treatment discontinuation should be documented on the appropriate CRF page.

9.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate CRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

9.1.3 Study and Site Discontinuation

The marketing authorization holder has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Patient enrollment is unsatisfactory

The marketing authorization holder will notify the investigator if the study is placed on hold, or if the marketing authorization holder decides to discontinue the study or development program.

The marketing authorization holder has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiological Practices (GPP) or any other pertinent local law or guideline

9.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

9.3 INFORMED CONSENT

The marketing authorization holder ‘s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The marketing authorization holder or its designee must review and approve any proposed deviations from the marketing authorization holder ‘s sample Informed Consent Forms or any alternate Consent Forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final Consent Forms approved by the IRB/EC must be provided to the marketing authorization holder for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient’s legally authorized representative before her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

By signing the form, the patient confirms that he/she has been informed about the study and agrees to anonymous data collection, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities. It is the responsibility of the investigator to obtain written informed consent from each patient participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The investigator must also explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time, for any reason and without losing the benefit of any medical care to which the patient is entitled or is presently receiving.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the marketing authorization holder for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

9.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Site Operations Representative in consultation with the Scientific Responsible and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

In addition to the requirements for collecting and reporting all AEs, adverse events of special interest (AESI), and SAEs to the marketing authorization holder, physicians must comply with requirements for AE reporting to the local health authority and IRB/EC.

9.5 CONFIDENTIALITY

The marketing authorization holder maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any marketing authorization holder location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, marketing authorization holder monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

9.6 FINANCIAL DISCLOSURE

Physicians will provide the marketing authorization holder with sufficient, accurate financial information in accordance with local regulations to allow the marketing authorization holder to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Physicians are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV)

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

10.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

10.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to all studied medicinal products (observational products of interest, as specifically stated in the study Objectives). For safety reporting requirements for non-studied medicinal products, see section 10.2.

Safety assessments will consist of monitoring and recording SAEs and non-serious AEs (including AEs of special interest), performing safety laboratory assessments, measuring vital signs, and conducting other tests that are deemed critical to the safety evaluation of the study as per standard medical practice.

10.1.1.1 Adverse Events

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Appendix 3.3.10.

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorization Holder), Non-serious Adverse Events of Special Interest (AESI) and Other Non-serious Adverse Events

10.1.1.2.1 Serious Adverse Events

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization (see Appendix 3.3.11)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are <u>not</u> synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Appendix 3.1); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF. (for detailed instructions, see Appendix 3.1).

10.1.1.2.2 Non-Serious Adverse Events of Special Interest

AEs of special interest for this study include the following:

- Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Appendix 3.3.7).
- Suspected transmission of an infectious agent by the study medicine, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected.

- Hypertension
- Proteinuria
- GI perforation
- Wound healing complications
- Thromboembolic events (ATE and VTE)
- Bleeding
- Congestive Heart Failure (CHF)
- Fistulae
- Reversible Posterior Leukoencephalopath Syndrome (RPLS)

10.1.1.2.3 Non-Serious Adverse Events other than Adverse Events of Special Interest

All non-serious AEs (in addition to AEs of special interest) must be collected for this study.

10.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is responsible for ensuring that all AEs collected as per protocol (see Section 10.1.1.1 for definition) are recorded in the AE section of the eCRF and reported to the marketing authorization holder in accordance with instructions provided in this section and in Section 10.1.3.

For each AE recorded in the AE section of the eCRF, the physician will make an assessment of seriousness (see Section 10.1.1.2.1), severity (see Appendix 3.1), and causality (see Appendix 3.2).

10.1.2.1 Adverse Event Reporting Period

Physicians will seek information on AEs at each patient contact. All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and in the AE section of the CRF.

Once the patient is enrolled in the study, Adverse events will be collected until at least 28 days after the last administration of bevacizumab. Related SAEs need to be collected until 6 months after last dose. AESIs should be reported if they start up to 6 months after last dose. SAEs & AESIs should be followed up to final resolution. After this period, the physician is not required to actively monitor patients for AEs but if the treating physician becomes aware of any related AEs to any medicinal product they should be notified to the marketing authorization holder.

10.1.2.2 Procedures for Recording Adverse Events

Physicians should use correct medical terminology/concepts when recording AEs in the AE section of the CRF. Colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field of the CRF.

See Appendix 3for further specific instruction regarding:

- Infusion-Related Reactions
- Diagnosis versus signs and symptoms
- Adverse Events occurring secondary to other Adverse Events
- Persistent or recurrent Adverse Events
- Abnormal Laboratory Values
- Abnormal Vital Sign Values
- Abnormal Liver Function Tests
- Deaths
    - All events with an outcome or consequence of death should be classified as serious adverse events (SAEs) and reported to the marketing authorization holder immediately. In certain circumstances, however, suspected adverse reactions with fatal outcome may not be subject to expedited reporting (see Section 10.6). All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study medicine, must be recorded in the AE section of the CRF and immediately reported to the marketing authorization holder
- Pre-existing Medical Conditions
- Lack of Therapeutic Efficacy or worsening of Ovarian Cancer
- Hospitalization or Prolonged Hospitalization
- Overdoses**,** Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error
- Drug Interactions
- Quality Defects and Falsified Medicinal Products

10.1.3 Reporting Requirements from Physician to Marketing Authorisation Holder

10.1.3.1 Immediate Reporting Requirements from Physician to Marketing Authorization Holder

Certain events require immediate reporting to allow the Marketing Authorization Holder and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The physician must report such events to the marketing authorization holder immediately; under no circumstances should reporting take place more than 24 hours after the physician learns of the event. The following is a list of events that the physician must report to the marketing authorization holder within 24 hours after learning of the event, regardless of relationship to study medicine:

- SAEs
- Non-serious AEs of special interest

The physician must report new significant follow-up information for these events to the marketing authorization holder immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

For reports of SAEs and non-serious AEs of special interest, including follow-up, physicians should record all case details that can be gathered immediately (i.e., within 24 hours) in the AE page of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety by the EDC system.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.1.3.3.

Physicians must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

10.1.3.2 Reporting Requirements for Non-Serious Adverse Events

For all non-serious AEs, including follow-up reports, physicians must record all case details that can be gathered within 30 calendar days of learning of the event on the AE section of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety or the relevant marketing authorization holder (for non-Roche studied products) to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.1.3.3.

10.1.3.3 If EDC System is Temporarily Unavailable

In the event that the EDC system is temporarily unavailable or not used, a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the event) or within 30 days for non-serious AEs if not AEs of special interest, using the fax number or email address provided to physicians.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

10.1.3.4 Reporting Requirements for Pregnancies/Breastfeeding

Pregnancies/Breastfeeding in Female Patients

Not applicable in a population of women ≥70 years.

Pregnancies in Female Partners of Male Patients

Not applicable in a population of women ≥70 years.

Abortions

Not applicable in a population of women ≥70 years.

Congenital Anomalies/Birth Defects

Not applicable in a population of women ≥70 years.

10.1.4 Follow-Up of Patients after Adverse Events

10.1.4.1 Physician Follow-Up

The physician should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the physician, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to studied medicinal product until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented in the AE section of the eCRF and in the patient's medical record to facilitate SDV.

10.1.4.2 Marketing Authorization Holder Follow-Up

For all AEs, the Marketing authorization holder or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

10.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED MEDICINAL PRODUCTS

Although adverse event information is not being actively solicited for non-studied medicinal products, the physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a medicinal product) that come to their attention to the marketing authorization holder of the suspected medicinal product, or to the concerned competent authorities via the national spontaneous reporting system.

In addition, the following should also be reported if occurring during exposure to a marketed medicinal product, even in the absence of adverse events:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products
- Data related to a suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

When a patient is not exposed to a marketed medicinal product, but the physician/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

10.3 EXPEDITED REPORTING TO HEALTH AUTHORITIES, PHYSICIANS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The marketing authorization holder will promptly evaluate all SAEs and non-serious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to physicians, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the marketing authorization holder will assess the expectedness of these events using the following reference document:

- Local prescribing information for bevacizumab
- Bevacizumab Core Data Sheet

The marketing authorization holder will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the physician's assessment of causality and seriousness, with allowance for upgrading by the marketing authorization holder as needed.

11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the marketing authorization holder is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The marketing authorization holder will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the marketing authorization holder prior to submission for publication or presentation. This allows the marketing authorization holder to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, the marketing authorization holder will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of marketing authorization holder personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate marketing authorization holder personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the marketing authorization holder, except where agreed otherwise.

12. REFERENCES

Armstrong DK, Bundy B, Wenzel L, *et al*. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;354:34-43.

Banerjee S, Kaye S. 2012. Gynecological cancer: First-line bevacizumab for ovarian cancer—new standard of care? *Nat. Rev. Clin. Oncol. 2012;9:194-196*.

Belgian Cancer Registry. http://www.kankerregister.org/ Accessed April, 2014

Bevacizumab Summary of Product Characteristics

Bookman MA. Developmental chemotherapy and management of recurrent ovarian cancer. *J Clin Oncol* 2003;21:149s–167s.

Bookmann MA. The addition of new drugs to standard therapy in the first-line treatment of ovarian cancer. *Ann Oncol 2010*;21:vi211-17.

Burger R, Brady M, Bookman M *et al.* 2011. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer *N Engl J Med; 365;26:2473-83.*

Chan JK, Cheung MK, Husain A, *et al*. Patterns and progress in ovarian cancer over 14 years. *Obstet Gynecol* 2006; 108: 521-28.

du Bois A, Lück H-J, Meier W, *et al*. A randomized clinical trial of cisplatin/paclitaxel ver- sus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003;95:1320-29.

Engel J, Eckel R, Schubert-Fritschle G, *et al*. Moderate progress for ovarian cancer in the last 20 years: prolongation of survival, but no improvement in the cure rate. *Eur J Cancer* 2002;38:2327-45.

Harries M, Gore M. Part I: chemotherapy for epithelial ovarian cancer treatment at first diagnosis. *Lancet Oncol* 2002;3:529-36.

International Agency for Research on Cancer. Globocan 2008. http://globocan.iarc.fr/. Accessed September 07, 2012.

International Collaborative Ovarian Neoplasm Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxo- rubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet* 2002; 360:505-15.

Ledermann, Raja, Fotopoulou *et al.* 2013 Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol 2013;24: suppl 6: vi24-vi32*

McGuire WP, Hoskins WJ, Brady MF, *et al*. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1-6.

Muggia FM, Braly PS, Brady MF, *et al*. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 2000;18:106-15.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Senior Adult Oncology. Version 2.2014, 2013 Oct 24 at http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf

Ozols RF, Bundy BN, Greer BE, *et al*. Phase III trial of carboplatin and paclitaxel com- pared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003;21:3194-200.

Pallis AG, Fortpied C, Wedding U *et al.* 2010. EORTC elderly task force position paper: approach to the older cancer patient. *Eur J Cancer. 2010 Jun;46(9):1502-13.*

Perren T, Swart AM, Pfisterer J *et al.* 2011. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. *N Engl J Med 365;26:2484-96.*

Piccart MJ, Bertelsen K, James K, *et al*. Randomized intergroup trial of cisplatin- paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000; 92:699-708.

Pfisterer J, Plante M, Vergote I, *et al*. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, The NCI CTG, and the EORTC GCG. *J Clin Oncol* 2006;24:4699-707.

RIZIV/INAMI at http://www.riziv.fgov.be/drug/nl/ consulted Apr 2014

Siegel R, Ward E, Browly O, et al. Cancer statistics, 2011: the impact of eliminating socio economic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011;61:212-36.

Spannuth WA, Sood AK, Coleman RL. Angiogenesis as a strategic target for ovarian cancer therapy*. Nat Clin Pract Oncol* 2008;5:194-204.

Stuart, Kitchener, Bacon *et al.* 2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer. Report From the Fourth Ovarian Cancer Consensus Conference. *Int J Gynecol Cancer 2011; 21: 750Y755*

Tate S. Ovarian Cancer: be alert to the symptoms and give women a fighting chance. *J Fam Health Care* 2009; 19:169-72.

Tew WP 2013. Considerations regarding the administration of systemic therapy for elderly patients with ovarian cancer. *Curr Treat Options Oncol. 2013 Mar;14(1):1-11*.

Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

- List of contact details of responsible parties and all investigators
- Bevacizumab Summary of Product Characteristics

Appendix 2 European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols

ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 1)
ADOPTED BY THE ENCEPP STEERING GROUP ON 19 AUGUST 2011

The purpose of the Checklist developed by ENCePP (European Network of Centers for Pharmacoepidemiology and Pharmacovigilance) is to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and writing a study protocol. The checklist is intended to promote the quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each of the questions of the checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer "NA" (not applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

Appendix 2 European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols (cont.)

Section 1: Research question	**Yes**	**No**	**NA**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:	☒	☐	☐	26-27
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	28
1.1.2 The objectives of the study?				
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	29-30
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Due to the limited sample size, no formal hypothesis can be tested and statistics will be solely descriptive

Section 2: Source and study populations	**Yes**	**No**	**NA**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	29-30
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	28-29-30
2.2.2 Age and sex?	☒	☐	☐	
2.2.3 Country of origin?	☒	☐	☐	
2.2.4 Disease/indication?	☒	☐	☐	
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	29-30

Comments:

Appendix 2 European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols (cont.)

Section 3: Study design	**Yes**	**No**	**NA**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	28
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	28-29
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	28
3.4 Is sample size considered?	☒	☐	☐	36
3.5 Is statistical power calculated?	☒	☐	☐	36-37

Comments:

Section 4: Data sources	**Yes**	**No**	**NA**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	39
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	
4.1.3 Covariates?	☒	☐	☐	
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	32-33-34-35-36
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	29
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	37
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	1
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	43

Comments:

Appendix 2 European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols (cont.)

Section 5: Exposure definition and measurement	**Yes**	**No**	**NA**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	☒	☐	☐	32
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	39
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**NA**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	30-36
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Appendix 2 European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols (cont.)

Section 7: Biases and Effect modifiers	**Yes**	**No**	**NA**	**Page Number(s)**
7.1 Does the protocol address: 7.1.1 Selection biases? 7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒ ☒	☐ ☐	☐ ☐	40-41
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	
7.4 Does the protocol address other limitations?	☐	☐	☒	

Comments:

Section 8: Analysis plan	**Yes**	**No**	**NA**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	37
8.2 Is the choice of statistical techniques described?	☒	☐	☐	37
8.3 Are descriptive analyses included?	☒	☐	☐	37
8.4 Are stratified analyses included?	☐	☒	☐	37
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders? 8.5.2 Effect modifiers?	 ☐ ☐	 ☐ ☐	 ☒ ☒	
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding? 8.6.2 Effect modification?	 ☐ ☐	 ☐ ☐	 ☒ ☒	

Comments:

Appendix 2 European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols (cont.)

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**NA**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	40
9.2 Are methods of quality assurance described?	☒	☐	☐	39
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	39
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	36
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	22
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	
9.5.3 Study completion?	☒	☐	☐	
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	22
9.7 Are communication methods to disseminate results described?	☒	☐	☐	56
9.8 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Appendix 2 European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols (cont.)

Section 10: Ethical issues	**Yes**	**No**	**NA**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	42
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☐	
10.3 Have data protection requirements been described?	☒	☐	☐	41-43

Comments:

Name of the coordinating study entity[1]: _____

Name of (primary) lead investigator[2]: _____

Date: / /

Signature: _____

[1] A legal person, institution or organization which takes respons bility for the design and/or the management of a study. The (primary) lead investigator is the person authorized to represent the coordinating study entity.

[2] A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site. If a study is conducted at several study sites by a team of investigators, the (primary) lead.

Appendix 3

3.1 Assessment of Severity of Adverse Events
3.2 Assessment of Causality of Adverse Events
3.3 Procedures for recording Adverse Events

Appendix 3.1 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity. The table below will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to AE [d]

Note: Based on the NCI CTCAE (v4.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE (see Section 10.1.3 for reporting instructions), per the definition of SAE in Section 10.1.1.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 10.1.3 for reporting instructions), per the definition of SAE in Section 10.1.1.2.

Appendix 3.2 Assessment of Causality of Adverse Events

Physicians should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study medicine, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study medicine

- Course of the event, considering especially the effects of dose reduction, discontinuation of study medicine, or reintroduction of study medicine (when applicable)
- Known association of the event with the study medicine or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each of the medicinal product.

Appendix 3.3 Procedures for recording Adverse Events

Appendix 3.3.1 Infusion-Related Reactions

AEs that occur during or within 24 hours after study medicine administration and are judged to be related to studied medicinal product infusion should be captured as a diagnosis (e.g., infusion-related reaction) in the AE section of the eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of studied medicinal product, each reaction should be recorded separately in the AE section of the eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

Appendix 3.3.2 Diagnosis versus Signs and Symptoms

For AEs, other than infusion-related reactions (see Section 3.3.1) a diagnosis (if known) should be recorded in the AE section of the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the AE section of the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Appendix 3.3.3 Adverse Events Occurring Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event in the AE section of the eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately in the AE section of the eCRF if it is unclear as to whether the events are associated.

Appendix 3.3.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once in the AE section of the eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded in the AE section of the eCRF. If the event becomes serious, it should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 10.1.3.1 for reporting instructions). The AE section of the eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately in the AE section of the eCRF.

Appendix 3.3.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the physician's judgment

Note: For oncology studies, certain abnormal values may not qualify as AEs.

It is the physician's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded in the AE section of the eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the AE section of the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be

characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 3.3.4 for details on recording persistent AEs).

Appendix 3.3.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the physician's judgment

It is the physician's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the AE section of the eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 3.3.4 for details on recording persistent AEs).

Appendix 3.3.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ the ULN) in combination with either an elevated total bilirubin ($> 2 \times$ the ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, physicians must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ the ULN
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the AE section of the eCRF (see Appendix 3.3.5) and reported to the marketing authorization holder immediately (i.e., no more than

24 hours after learning of the event) either as an SAE or a non-serious AE of special interest (see Section 10.1.3.1 and 10.1.3.2).

Appendix 3.3.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.1.2.1), regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to the marketing authorization holder (see Section 10.1.3.1 and 10.1.3.2)

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE section of the eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the AE section of the eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Appendix 3.3.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions in the eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events in the AE section of the CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Appendix 3.3.10 Lack of Therapeutic Efficacy or Worsening of Ovarian Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on RECIST criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

Appendix 3.3.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 10.1.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not suffered an AE.
- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenarios are not considered to be SAEs but should be reported as AEs instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

Appendix 3.3.12 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the CRF. Any overdose, misuse, abuse, off-label use, occupational exposure or medication error (including intercepted or potential) reports must be forwarded to the marketing authorization holder with or without an AE.

Reports with or without an AE should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a medicine means an exposure to a medicine as a result of one's professional or non-professional occupation.

Appendix 3.3.13 Quality Defects and Falsified Medicinal Products

Reports of suspected or confirmed falsified medicinal product or quality defect of a medicinal product, with or without an associated AE, should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills

the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1).

Appendix 3.3.14 Drug Interations

Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol interactions should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1)

Appendix 3.3.15 Safety data other than Adverse Events

Safety data other than AEs (see section 8.3 Variables) should be recorded in an appropriate section of the eCRF and reviewed on an ongoing basis.

APPENDIX 4
DATA COLLECTION OVERVIEW (AS PER STANDARD OF CARE)

	Study entry[1]	Baseline, before start of bevacizumab therapy	During bevacizumab therapy[2]	End of bevacizumab therapy	Follow-up, 6 & 12 months after end of bevacizumab
Informed Consent	X				
Date of birth		X			
Height		X			
Weight		X	X	X	
ECOG Performance Status		X	X	X	
Blood pressure		X	X	X	
Dipstick Urinalysis		X	X	X	
Ca-125 (if measured)[3]		X	X	X	
Ovarian cancer history		X			
Ovarian cancer surgery		X			
GI involvement		X			
Medical History		X			
Concomitant Medication		X	X		
Disease assessment[4]		X	X	X	X
Comprehensive Geriatric Assessment[5]		X	X	X	X
Chemotherapy administration		X (if chemotherapy started before bevacizumab)	X (up to a max. of 6 cycles of chemotherapy)	X (if applicable)	
Avastin administration			X		
Adverse Events			X	X	
Interventions for AEs			X	X	
Survival status			X	X	X
Reason for stopping Avastin				X	

[1]Study entry is at time of informed consent, this may occur before or after first bevacizumab administration, but must be after the decision to initiate bevacizumab therapy. [2]Timing of visits determined by routine clinical practice at each center [3]Ca-125 measurement not mandatory, record only if measured in routine clinical care. [4] Assessment according to local standard of care (e.g. clinical examination or ultrasound or CT-scan). [5] CGA will be performed at baseline, limited CGA will be performed after chemotherapy has ended just before the first cycle of bevacizumab monotherapy, 10 months after start of bevacizumab treatment and 15 months after start of bevacizumab treatment or at progression of disease whichever comes first.