PROTOCOL	
TITLE:	**AN INDIAN MULTICENTRIC, OPEN LABEL, PROSPECTIVE *PHASE IV* STUDY OF BEVACIZUMAB IN THE FRONT LINE MANAGEMENT OF ADVANCED/METASTATIC EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER OR PRIMARY PERITONEAL CANCER IN REAL-LIFE CLINICAL PRACTICE**
PROTOCOL NUMBER:	ML28446
VERSION NUMBER:	3.0
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not Applicable
NCT NUMBER:	NCT01932125
TEST PRODUCT:	Bevacizumab (RO4876646)
MEDICAL MONITOR:	[redacted], *MD, DNB, MNAMS*
SPONSOR:	Roche Products (India) Pvt. Ltd.
DATE FINAL:	See electronic date stamp below

Name: Dr. [redacted] **Designation: Medical Director** **Roche Products (India) Pvt. Ltd.**	**Signature:** DocuSigned by: [redacted] **Date:** 22-Jun-2020
Name: Dr. [redacted] **Designation: Medical Value Lead, Oncology** **Roche Products (India) Pvt. Ltd.**	**Signature with Date:** DocuSigned by: [redacted] **Date:** 25-Jun-2020
Name: [redacted] **Designation: General Manager-SAS & Biostats** **JSS Medical Research India Pvt. Ltd.**	**Signature with Date:** DocuSigned by: [redacted] **Date:** 23-Jun-2020

PROTOCOL HISTORY

Version	Date Final
3	12 Jun 2020
2	13 Jul 2015
1	26 Nov 2012

PROTOCOL AMENDMENT, VERSION 3.0: RATIONALE

The design of the protocol has been changed from non-interventional study to an interventional study based on the recommendation of the Health Authorities (Drugs Controller General of India).

Under the interventional design of the study, the investigational medicinal product, bevacizumab and the cost of treatment will be provided to the participants of the study. Safety reporting will also be done as per the requirements of an interventional study. Remaining all other aspects of the study remain unaltered.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN INDIAN MULTICENTRIC, OPEN LABEL, PROSPECTIVE PHASE IV STUDY OF BEVACIZUMAB IN THE FRONT LINE MANAGEMENT OF ADVANCED/METASTATIC EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER OR PRIMARY PERITONEAL CANCER IN REAL-LIFE CLINICAL PRACTICE**
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SPONSOR:	Roche Products (India) Pvt. Ltd.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to your local study monitor.

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_____ _____

Principal Investigator's Signature Date

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PROTOCOL SYNOPSIS

TITLE:	**AN INDIAN MULTICENTRIC, OPEN LABEL, PROSPECTIVE, *PHASE IV* STUDY OF BEVACIZUMAB IN THE FRONT LINE MANAGEMENT OF ADVANCED/METASTATIC EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER OR PRIMARY PERITONEAL CANCER IN REAL-LIFE CLINICAL PRACTICE**
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IND NUMBER:	Not applicable
NCT NUMBER:	NCT01932125
TEST PRODUCT:	Bevacizumab (RO4876646)
PHASE:	*Phase IV, interventional study*
INDICATION:	Advanced/metastatic epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer
SPONSOR:	Roche Products (India) Pvt. Ltd.

Objectives and Endpoints

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The primary objective of this study is to determine the safety profile (adverse events [AEs] all grade 3 and above) of bevacizumab when added to standard chemotherapy (carboplatin and paclitaxel) in front line advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV) in Indian population.

The corresponding primary endpoint will be as follows:

- Incidence of AEs of Grade 3 and above as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03

The secondary endpoints of safety will be as follows:

- Incidence of serious adverse events (SAEs) as per NCI-CTCAE, version 4.03
- Incidence of adverse events of special interest (AESI)
- Laboratory results abnormalities

The secondary objective of this study is to evaluate the efficacy of bevacizumab when added to standard chemotherapy (carboplatin and paclitaxel) in the front-line management of the study population based on the following endpoints:

- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rates (ORR; Complete response [CR] + Partial response [PR])
- Clinical benefit rate (CR + PR + stable disease [SD])

Study Design

Description of Study

This is a Phase IV, single-arm, open-label, prospective, *interventional*, multicenter study designed to evaluate the safety and efficacy of bevacizumab when added to standard chemotherapy (carboplatin and paclitaxel) in the front-line management of advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV) in Indian population. The estimated duration of patient enrollment is 12 months.

All patients fulfilling the eligibility criteria and willing to provide informed consent will receive five cycles of bevacizumab 15 mg/kg concurrently with six cycles of the standard chemotherapy (paclitaxel and carboplatin) every three weeks (q3w), followed by extended cycles of bevacizumab 15 mg/kg q3w as a single agent for additional 16 cycles. A total of 21 cycles of bevacizumab will be administered in this study, with the first cycle of bevacizumab administered concurrently on Cycle 2 of the standard chemotherapy. Paclitaxel and carboplatin will be administered as per the local prescribing information. The sequence of drug administration in the concurrent cycles will be paclitaxel, followed by carboplatin and bevacizumab. *Patients will receive bevacizumab as per the protocol-specified schedule until the completion of extended bevacizumab cycles, disease progression, treatment discontinuation due to an AE, or death, whichever occurs earlier.*

Concurrent cycles: • Six cycles of paclitaxel and carboplatin: on Day 1 of Cycle 1 to Cycle 6, as per local prescribing information, q3w • Five cycles of Bevacizumab: on Day 1 of Cycle 2 to Cycle 6, as 15 mg/kg q3w
Extended cycles: • Sixteen cycles of Bevacizumab: on Day 1 of Cycle 7 to Cycle 22, as 15 mg/kg q3w

Duration of each cycle is 21 days (every three weeks).

The study will include a screening phase, treatment phase and post-treatment safety follow-up phase for each patient.

Patients who complete or prematurely discontinue the study treatment will be followed up for survival till the end of study. Post-treatment safety follow-up will be performed 30 days after the last bevacizumab cycle, followed by every 3 months until the end of study, consent withdrawal, lost to follow-up, or death, or study termination by the Sponsor, whichever occurs earlier.

Follow-up information will be collected via telephone calls and/or clinic visits (only if they happen during the normal course of treatment) until death, lost to follow-up, or study termination by the Sponsor, whichever occurs earlier.

Number of Patients

Approximately 100 patients will be enrolled across multiple study centers in India.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Female subjects ≥18 years of age
- Subjects willing and able to give informed consent

- Subjects who are prescribed to receive bevacizumab for advanced/metastatic epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer (FIGO Stage lllb, lllc and IV) according to the routine clinical practice.
- Women of childbearing potential must agree to use adequate contraception (per institutional standard of care) during treatment and until 6 months after the last administration of bevacizumab.

Exclusion Criteria

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

- There is no specific exclusion criteria for this study and subjects who are considered not eligible to receive bevacizumab for advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc and IV) according to the local prescribing information will not be enrolled in the study.

End of Study

The last patient last visit (LPLV) is to occur 6 months after the last patient enrolled has completed treatment; unless they have been lost to follow-up, withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs earlier. In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3 to 4 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product (IMP) for this study is bevacizumab (Avastin®) manufactured by Hoffman La-Roche. *Bevacizumab will be administered in combination with carboplatin and paclitaxel initially and later as a single agent. Study treatment administration, dose, and schedule will be per the Schedule of assessments.*

The initial five cycles of bevacizumab will be administered concurrently with six cycles of paclitaxel and carboplatin, followed by extended cycles of bevacizumab as single agent for a total up to 16 cycles.

The recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Non-Investigational Medicinal Products

Carboplatin and paclitaxel will be considered as non-investigational medicine in this study and will be administered in line with the approved local prescribing information. 6 cycles of paclitaxel and carboplatin: on Day 1 of Cycle 1 to Cycle 6, as per local PI, q3w (every 3 weeks)

Statistical Methods

Primary Analysis

The primary analyses will be conducted on the safety population that will include all enrolled patients who receive at least one dose of study medication. The data from the patients in the safety population, enrolled under the non-interventional and interventional design, will be pooled for analysis.

The incidence of AEs and SAEs will be summarized according to the primary system organ class (SOC) and preferred term within each SOC, by using the Medical Dictionary for Regulatory Activities (MedDRA). A summary of AESI will also be provided.

A descriptive statistics will also be presented for physical examinations, vital signs, ECG, and laboratory evaluations.

Secondary Analysis

Kaplan-Meier method will be used to estimate the median PFS and OS for total as well as for patient subgroup with ECOG PS 0 and ECOG PS 1-2 at baseline. The log-rank test will be used to compare the median survival time between patients with ECOG PS 0 and ECOG PS 1-2 at baseline. For OS analyses, patients who were alive at the time of the analysis will be censored at the date of the last follow-up assessment (two years from last patient enrolled in the study).

The ORR (CR + PR) will be summarized using number and percentage along with two sided 95% Pearson-Clopper CI. Similarly, the Clinical Benefit Response rate (CR + PR + SD) will be summarized using number and percentage along with the two-sided 95% Pearson-Clopper CI.

Determination of Sample Size

This study will enroll approximately 100 patients at 20 sites across India.

The sample size was calculated using the formula:

$$n = \frac{Z^2 \times p \times (1 - p)}{d^2}$$

Where,

p :Incidence of any adverse events (All grade 3 and above) related to bevacizumab in Ovarian cancer

d : Precision

Z: Z value (1.96 for 95% confidence level)

In order to estimate the incidence of any AEs (All grade 3 and above) related to bevacizumab in ovarian cancer by assuming level of significance 5%, incidence of any AEs (All grade 3 and above) 66% [Perren TJ, 2011], precision 10% and dropout rate 10%, a total of 97 patients are required. Hence, it is proposed to enroll 100 patients for the present study.

Interim Analyses

In addition to the final analysis, there will an interim analysis for safety reporting that will be conducted when approximately 50% of the planned population has had any of the following: disease progression, death, treatment discontinuation, consent withdrawal, or is lost to follow up.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event Of Special Interest
ALT	Alanine Aminotransferase
ASR	Annual Status Report
AST	Aspartate Aminotransferase
ATE	Arterial Thromboembolic Event
CI	Confidence Interval
CR	Complete Response
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DCGI	Drugs Controller General of India
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
FIGO	International Federation of Gynecology and Obstetrics
GCP	Good Clinical Practice
GI	Gastrointestinal
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
LPLV	Last Subject, Last Visit
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PI	Prescribing Information
PFS	Progression Free Survival
PRES	Posterior Reversible Encephalopathy Syndrome
PR	Partial Response
PS	Performance Status
RBC	Red Blood Cell

RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SDV	Source Data Verification
SPC	Summary of Product Characteristics
ULN	Upper Limit Of Normal
VEGF	Vascular Endothelial Growth Factor
VTE	Venous Thromboembolic Event
WBC	White Blood Cell

1. BACKGROUND

1.1 BACKGROUND ON OVARIAN CANCER

Ovarian cancer is the fourth most common cause of cancer-related deaths in women, with an estimated 200,000 cases and 125,000 deaths occurring annually worldwide. In India, ovarian cancer is the fourth most common cancer with 26,834 new cases and 19,549 deaths per year [Globocan 2012]. For the past decade, the standard treatment for women with advanced ovarian cancer has been surgery and platinum-based chemotherapy [Perren TJ et al, 2011]. Surgery to remove as much of the tumor as possible is a mainstay of treatment but unfortunately, the majority of patients are diagnosed with late stage disease (when the cancer has grown or spread) and they require further treatment [Hennessy B et al, 2009]. Attempts to improve the standard two-drug chemotherapy by adding a third cytotoxic drug failed to affect either progression free survival (PFS) or Overall Survival (OS) and resulted in an increase in toxic effects. Although intraperitoneal chemotherapy has extended OS by 12 to 17 months, it is an option only for women with advanced ovarian cancer who have a small amount of residual disease after surgery and is not widely used [Perren TJ et al, 2011]. Intraperitoneal chemotherapy has its own drawbacks in terms of increased toxicity and infections.

1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab (Avastin®, Roche) is a recombinant humanized monoclonal Immunoglobulin G1 (IgG1) antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems.

Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression [Avastin® Local prescribing information; Burger RA et al. 2010].

The efficacy and safety of bevacizumab in the front-line treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707). These trials have demonstrated the efficacy and safety of the addition of bevacizumab to carboplatin and paclitaxel when compared to the chemotherapy regimen alone [Avastin® Local prescribing information; Burger RA et al. 2010].

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 chemotherapy regimen (carboplatin and paclitaxel) in patients with advanced (FIGO [International Federation of Gynecology and Obstetrics] stages III(Incompletely resectable) and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer [Burger RA et al 2010].

The trial met its primary objective of improvement in PFS. In comparison to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting (median PFS of 10.6 months), patients who received bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone for up to 22

cycles (CPB15+), had a clinically meaningful and statistically significant improvement in PFS (median PFS of 14.7 months) [Burger RA et al 2010].

BO17707 (ICON 7) was a Phase III, two arm, multicenter, randomized, controlled, open-label study comparing the effects 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 [Yamamoto S et al. 1997].

The trial met its primary objective of PFS improvement. In comparison to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting (median PFS of 16.9 months), 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 (median PFS of 19.3 months) [Avastin® Local prescribing information; Yamamoto S et al. 1997].

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Ovarian cancer is associated with high concentrations of VEGF, a protein associated with tumor growth and spread. Studies have shown a correlation between a high concentration of VEGF and ascites development (excess fluid in the body cavity), disease worsening, and a poorer prognosis in women with ovarian cancer [Yamamoto S et al. 1997; Trinh XB et al. 2009].

Bevacizumab is designed to specifically target VEGF. Bevacizumab is a monoclonal antibody that binds to all isoforms of the VEGF-receptor ligand VEGF-A, with evidence of efficacy in metastatic colorectal and lung cancers, as well as activity in renal, and brain cancers [Avastin® Local prescribing information].The safety and efficacy of bevacizumab in the front-line treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707) that evaluated the effect of the addition of bevacizumab to carboplatin and paclitaxel compared to the chemotherapy regimen alone [Local prescribing information; Burger RA et al 2010; Yamamoto S et al. 1997]. Based on these pivotal trials, bevacizumab in combination with carboplatin and paclitaxel has been approved for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer in the European Union as well as in India.

The aim of this study is to fulfill regulatory requirements by characterizing the safety profile of bevacizumab in Indian patients in real life practice.

2. OBJECTIVES AND ENDPOINTS

Safety Objectives

Effectiveness Objectives

The effectiveness secondary objectives of this study are as follows:

- Progression free survival (PFS)
- Overall survival (OS)

- Overall Response rates (Complete response (CR)+ Partial response (PR))
- Clinical Benefit Response rates (CR+PR+ Stable disease(SD))

2.1 SAFETY OBJECTIVES

The primary objective of this study is as follows:

- To determine the safety profile (all grade 3 and above) of bevacizumab when added to standard chemotherapy (carboplatin and paclitaxel) in front line advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV) in Indian population.

The corresponding endpoints will be as follows:

- Incidence of adverse events (AEs) of Grade 3 and above as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03
- Incidence of serious adverse events (SAEs) as per NCI-CTCAE, version 4.03
- Incidence of adverse events of special interest (AESI)
- Laboratory results abnormalities

2.2 EFFICACY OBJECTIVES

The secondary objective of this study is to evaluate the efficacy of bevacizumab when added to standard chemotherapy (carboplatin and paclitaxel) in the front-line management of the study population based on the following parameters:

- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rates (ORR; complete response [CR] + partial response [PR])
- Clinical benefit response rates (CR + PR + stable disease [SD])

The corresponding endpoints will be as follows:

- Progression-free survival, defined as the time from enrollment to the first radiographically documented disease progression as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1, or death from any cause, whichever occurs first.
- Overall Survival, defined as the time from the date of enrollment to the date of death, regardless of the cause of death.
- Overall response rate (CR + PR), determined by the investigator using RECIST criteria v1.1. Overall response rate is defined as the best response recorded from the start of study treatment until disease progression/recurrence or death and confirmed ≥4 weeks later.
- Clinical benefit response rates (CR + PR + SD)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase IV, single-arm, open-label, prospective, *interventional*, multicenter study designed to evaluate the safety and efficacy of bevacizumab when added to standard chemotherapy (carboplatin and paclitaxel) in the front-line management of advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIB, IIIC, and IV) in Indian population.

3.1.1 Overview of Study Design

Approximately 100 patients will be enrolled in the study. The estimated duration of patient enrollment is 12 months.

All patients fulfilling the eligibility criteria and willing to provide informed consent will receive five cycles of bevacizumab 15 mg/kg concurrently with six cycles of the standard chemotherapy (paclitaxel and carboplatin) every three weeks (q3w), followed by extended cycles of bevacizumab 15 mg/kg q3w as a single agent for additional 16 cycles. A total of 21 cycles of bevacizumab will be administered in this study, with the first cycle of bevacizumab administered concurrently on Cycle 2 of the standard chemotherapy. Paclitaxel and carboplatin will be administered as per the local prescribing information. The sequence of drug administration in the concurrent cycles will be paclitaxel, followed by carboplatin and bevacizumab. Patients will receive bevacizumab as per the protocol-specified schedule until the completion of extended bevacizumab cycles, disease progression, treatment discontinuation due to an AE, or death, whichever occurs earlier.

Concurrent cycles: • Six cycles of paclitaxel and carboplatin: on Day 1 of Cycle 1 to Cycle 6, as per local prescribing information, q3w • Five cycles of Bevacizumab: on Day 1 of Cycle 2 to Cycle 6, as 15 mg/kg q3w
Extended cycles: • Sixteen cycles of Bevacizumab: on Day 1 of Cycle 7 to Cycle 22, as 15 mg/kg q3w

Duration of each cycle is 21 days (every three weeks).

The study will include a screening phase, treatment phase and post-treatment safety follow-up phase for each patient.

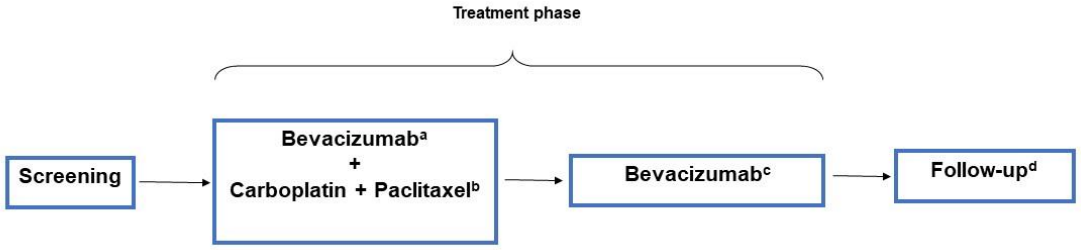
Patients who complete or prematurely discontinue the study treatment will be followed up for survival till the end of study. Post-treatment safety follow-up will be performed 30 days after the last bevacizumab cycle, followed by every 3 months until the end of study,

consent withdrawal, lost to follow-up, or death, or study termination by the Sponsor, whichever occurs earlier.

Follow-up information will be collected via telephone calls and/or clinic visits (only if they happen during the normal course of treatment) until death, lost to follow-up, or study termination by the Sponsor, whichever occurs earlier.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



[a] Concurrent 5 cycles of bevacizumab starting from Cycle 2 of chemotherapy.
[b] Chemotherapy up to 6 cycles.
[c] Up to 16 Extended cycles of bevacizumab through Cycle 7 to Cycle 22.
[d] Thirty days after the last cycle of bevacizumab, then every 3 months until the end of study, withdrawal of consent, lost to follow-up, or death, whichever occurs earlier.

3.2 END OF STUDY AND LENGTH OF STUDY

The last patient last visit (LPLV) is to occur 6 months after the last patient enrolled has completed treatment; unless they have been lost to follow-up, withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs earlier.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3 to 4 years.

3.3 RATIONALE FOR STUDY DESIGN

This Phase IV study has been designed to evaluate the safety of bevacizumab in Indian population. Therefore, the primary objective is safety and secondary objective includes efficacy evaluation routinely used in oncology studies.

The study design employs standard methods for safety studies in patients with cancer. *All patients will receive the active treatment.* Safety will be carefully evaluated, and the type of data collected and the frequency with which patients are monitored will ensure safety of the patients.

3.3.1 Rationale for Bevacizumab Dose and Schedule

Bevacizumab in combination with carboplatin and paclitaxel has been approved in India for the front-line treatment of advanced (FIGO stages IIIB, IIIC, and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. The approved dose of bevacizumab is 15 mg/kg q3w in India.

3.3.2 Rationale for Patient Population

Bevacizumab has demonstrated clinical benefit in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer in two Phase III trials (GOG-0218 and BO17707) that evaluated the effect of the addition of bevacizumab to carboplatin and paclitaxel compared to the chemotherapy regimen alone (local Prescribing Information; Burger et al. 2010; Yamamoto et al. 1997). Based on these pivotal trials, bevacizumab in combination with carboplatin and paclitaxel has been approved for the front-line treatment of advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer in the European Union as well as in India. Hence, to fulfill regulatory requirements, patients with advanced/metastatic epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer will be enrolled in this study to characterize the safety profile of bevacizumab in Indian patients.

4. MATERIALS AND METHODS

4.1 PATIENTS

A total of 100 patients will be enrolled in the study across India.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Female subjects ≥18 years of age
- Subjects willing and able to give informed consent
- Subjects who are prescribed to receive bevacizumab for advanced/metastatic epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer (FIGO Stage lllb, lllc and lV) according to the routine clinical practice.
- *Women of childbearing potential must agree to use adequate contraception (per institutional standard of care) during treatment and until 6 months after the last administration of bevacizumab.*

4.1.2 Exclusion Criteria

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

- Subjects who are considered not eligible to receive bevacizumab for advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc and IV) according to the local prescribing information and investigator's discretion will not be enrolled in the study

4.1.3 Treatment Assignment

This is a non-randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and

eligibility has been established for a patient, the patient will be allocated a patient's identification number and the treatment administration will be performed at the study site.

4.2 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is bevacizumab manufactured by F Hoffman La-Roche. Bevacizumab will be administered in combination with carboplatin and paclitaxel.

4.2.1 Study Treatment Formulation and Packaging

4.2.1.1 Bevacizumab

Bevacizumab will be supplied by the Sponsor as injection in single-dose vial. For information on the formulation and handling of bevacizumab, see the local prescribing information for Avastin® (bevacizumab).

4.2.1.2 Carboplatin

Carboplatin will be used as per local clinical practice and re-imbursed by the Sponsor. Refer to see the local prescribing information of carboplatin for information on the formulation and handling of carboplatin.

4.2.1.3 Paclitaxel

Paclitaxel will be used as per local clinical practice and will be re-imbursed by the Sponsor. Refer to see the local prescribing information of paclitaxel for information on the formulation and handling of paclitaxel.

4.2.2 Study Treatment Dosage, Administration, and Compliance

Bevacizumab will be administered as intravenous infusion of 15 mg/kg q3w for five cycles concurrently with six cycles of standard chemotherapy (paclitaxel and carboplatin), followed by extended cycles of bevacizumab 15 mg/kg q3w as a single agent for additional 16 cycles or until disease progression, or death, whichever occurs earlier. A total of 21 cycles of bevacizumab will be administered in this study.

Carboplatin and paclitaxel will be considered as non-investigational medicine in this study and will be administered in line with the approved local prescribing information.

Refer to the local prescribing information for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience AEs are provided in local prescribing information.

Study treatment administration will be per the instructions outlined in local prescribing information.

4.2.3 Investigational Medicinal Product Handling and Accountability

Bevacizumab, the IMP for this study, required for completion of this study will be provided by the Sponsor. Paclitaxel and carboplatin will be re-imbursed by the Sponsor.

The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the local prescribing information for information on IMP handling, including preparation and storage, and accountability.

4.2.4 Continued Access to Bevacizumab

The Roche IMP bevacizumab or other study treatments will not be provided to patients who have completed the study since these are marketed products available in India. The Sponsor may evaluate whether to continue providing bevacizumab in accordance with the Roche Global Policy on Continued Access to IMP, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.3 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.3.1 Permitted Therapy

Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.3.2 Prohibited Therapy

Concomitant treatment with anti-tumor agents other than chemotherapy specified in this protocol or other concurrent investigational agents are not allowed during the study.

4.4 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.4.1 Informed Consent Forms and Screening Log

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample

Informed Consent Forms or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before Institutional Review Board (IRB) / Ethics Committee (EC) submission. The final Consent Forms approved by the IRB/EC must be provided to the Sponsor 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 she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities. It is the responsibility of the physician 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 physician 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 Sponsor 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.

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.4.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit will be recorded (Appendix 1).

Demographic data will include age, sex, and self-reported race/ethnicity.

4.4.3 Physical Examinations

As per routine clinical practice, physical examination data of relevant body systems will be recorded on the eCRF.

The medical history of the subject and the AEs will be captured in the eCRF. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event Form.

4.4.4 Vital Signs

As per routine clinical practice, vital signs including measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature will be recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event Form.

4.4.5 Tumor and Response Evaluations

Available data on tumor and treatment outcome from the medical records and a patient interview on medical history and disease characteristics (which are routinely performed in accordance with current guidelines and local clinical practice) will be documented in the eCRF. The data available according to the response assessment will be captured in the eCRF.

4.4.6 Laboratory Samples

Laboratory assessment data routinely performed in accordance with current guidelines and local standard of care during therapy with bevacizumab, will be recorded in the eCRF.

- Hematology (WBC count, red blood cell (RBC count, hemoglobin, hematocrit, platelet count, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes]).

Serum chemistry (sodium, potassium, chloride, bicarbonate, fasting glucose, blood, urea nitrogen creatinine, total protein, albumin, phosphorus, calcium, magnesium, total and direct bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), Asparate aminotransferase (AST), uric acid, LDH, creatine phosphokinase).

New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event Form.

4.5 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.5.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- *Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if she continues to receive study treatment*
- *Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient*
- *Pregnancy*
- *Use of an anti-cancer therapy not required per protocol*
- *Symptomatic deterioration attributed to disease progression*
- *Confirmed disease progression per investigator assessment according to RECIST v1.1*
- In accordance with the local PI, the following situations might require treatment discontinuation:
    - GI perforation
    - Tracheoesophageal fistula or any Grade 4 fistula
    - Medically significant hypertension which cannot be adequately controlled with antihypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy
    - Arterial thromboembolic events
    - Grade 4 proteinuria

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment completion or treatment discontinuation visit 30 days after the final dose of study drug.

4.5.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

4.5.3 Study Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the physician if the study is placed on hold, or if the Sponsor decides to discontinue the study.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF page. The Sponsor will notify the investigator if the Sponsor decides to discontinue the study. Patients who withdraw from the study will not be replaced.

4.5.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing 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 International Council for Harmonisation (ICH) guideline for Good Clinical Practice and applicable local regulations

- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Bevacizumab was approved by Drug Controller General of India (DCGI) in Jan 2012 for the treatment of patients with advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIB, IIIC, and IV).

The safety plan for patients in this study is based on clinical experience with bevacizumab in completed studies. The anticipated important safety risks for bevacizumab are outlined below. Please refer to the bevacizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 *Risks Associated with Bevacizumab*

A complete list of risk associated with use of bevacizumab is available in local prescribing information for bevacizumab (Avastin® local prescribing information).

5.1.1.1 Gastrointestinal Perforations and Fistulae

Bevacizumab should be avoided in patients with ovarian cancer who have evidence of recto-sigmoid involvement (by pelvic examination) or bowel involvement (on CT scan or having clinical symptoms). Bevacizumab should be discontinued in patients who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula, and with fistula in internal organs.

5.1.1.2 Surgery and Wound Healing Complications

Serious and fatal wound healing complications has been reported in patients who underwent surgery and received bevacizumab during and after surgery.

Necrotizing fasciitis including fatal cases, has been reported in patients receiving bevacizumab, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.

Bevacizumab should be discontinued in patients with wound healing complications requiring intervention and in those who develop necrotizing fasciitis.

5.1.1.3 Hemorrhage

Bevacizumab can result in minor hemorrhage (most commonly Grade 1 epistaxis) and serious hemorrhage (some cases had been fatal). Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, vaginal bleeding, and pulmonary hemorrhage have been reported with use of bevacizumab. Bevacizumab should not be administered in patients with recent history of hemoptysis.

5.1.1.4 Arterial Thromboembolic Events

Arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina are associated with use of bevacizumab. The risk of developing ATE is more in patients with a history of arterial thromboembolism, diabetes, or >65 years. Bevacizumab should be discontinued in patients who develop a severe ATE.

5.1.1.5 Venous Thromboembolic Events

An increased risk of venous thromboembolic events (VTE) have been observed across clinical studies with bevacizumab. Bevacizumab should be discontinued in patients with Grade 4 VTE.

5.1.1.6 Hypertension

Incidence of severe hypertension have been reported in patients receiving bevacizumab. Blood pressure should be monitored during the treatment with bevacizumab. Bevacizumab should be withheld in patients with severe hypertension that is not controlled with medical management; treatment may be resumed once controlled with medical management. Bevacizumab should be discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

5.1.1.7 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) are reported in clinical studies with bevacizumab. PRES may be present with headache, seizure, lethargy, confusion, blindness, other visual and neurologic disturbances, and hypertension. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Bevacizumab should be dscontinued in patients who develop PRES.

5.1.1.8 Renal Injury and Proteinuria

Bevacizumab is associated with elevated serum creatinine levels (between 1.5 to 1.9 times baseline levels) and proteinuria. In clinical studies, incidence of nephrotic syndrome has been reported, in some instances with fatal outcome. Proteinuria should be monitored for the development or worsening of proteinuria with serial urinalyses during bevacizumab therapy. Bevacizumab should be discontinued in patients who develop nephrotic syndrome.

5.1.1.9 Infusion Related Reactions

Infusion-related reactions reported across clinical studies and postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis.

The rate of infusion may be decreased for mild, clinically insignificant infusion-related reactions and interrupted in patients with clinically significant infusion-related reactions and resuming at a slower rate may be considered following resolution. Treatment should be discontinued in patients who develop a severe infusion-related reaction.

5.1.1.10 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, bevacizumab may cause fetal harm when administered to pregnant women.

5.1.1.11 Ovarian Failure

The incidences of ovarian failure in pre-menopausal women are reported in patient receiving bevacizumab. Long-term effects of bevacizumab on fertility are unknown. Women of reproductive potential should be informed of the risk of ovarian failure prior to initiating bevacizumab therapy.

5.1.1.12 Congenital Heart Failure

Left ventricular dysfunction has been reported in patients receiving bevacizumab; CHF has been reported for patients receiving bevacizumab with chemotherapy. Bevacizumab is not indicated for use with anthracycline-based chemotherapy. Bevacizumab should be discontinued in patients who develop CHF.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

Below table describes the dose modification for specific adverse reactions associated with use of bevacizumab:

Adverse Reaction	***Severity***	***Dosage Modification***
Gastrointestinal Perforations and Fistulae	*Gastrointestinal perforation, any grade* *Tracheoesophageal fistula, any grade* *Fistula, Grade 4* *Fistula formation involving any internal organ*	*Discontinue bevacizumab*

Wound Healing Complications	*Wound healing complications requiring medical intervention* *Necrotizing fasciitis*	*Discontinue bevacizumab*
Hemorrhage	*Grade 3 or 4*	*Discontinue bevacizumab*
	Recent history of hemoptysis of half teaspoon (2.5 mL) or more	*Withhold bevacizumab*
Thromboembolic Events	*Arterial thromboembolism, severe*	*Discontinue bevacizumab*
	Venous thromboembolism, Grade 4	*Discontinue bevacizumab*
Hypertension	*Hypertensive crisis* *Hypertensive encephalopathy*	*Discontinue bevacizumab*
	Hypertension, severe	*Withhold bevacizumab if not controlled with medical management; resume once controlled*
Posterior Reversible Encephalopathy Syndrome (PRES)	*Any*	*Discontinue bevacizumab*
Renal Injury and Proteinuria	*Nephrotic syndrome*	*Discontinue bevacizumab*
	Proteinuria greater than or equal to *2 grams per 24 hours in absence of nephrotic syndrome*	*Withhold bevacizumab until proteinuria less than 2 grams per 24 hours*
Infusion-Related Reactions	*Severe*	*Discontinue bevacizumab*
	Clinically significant	*Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve*

	Mild, clinically insignificant	*Decrease infusion rate*
Congestive Heart Failure	*Any*	*Discontinue bevacizumab*

5.1.2.2 Treatment Interruption

Treatment interruption of bevacizumab during the study will be per the instructions outlined in local prescribing information. Bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and Medical Monitor will determine the acceptable length of treatment interruption.

5.1.2.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in the local PI.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including SAEs and AEs of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event 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) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- 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., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event 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 not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); 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 adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., *within 24 hours of knowledge of occurrence of the event* ; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., *within 24 hours of knowledge of occurrence of the event* ; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Gastrointestinal (GI) perforation, abscesses and fistulae (any grade)

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- Wound healing complication ≥ grade 3
- Hemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Venous thromboembolic events ≥ grade 3
- Arterial thromboembolic events (any grade)
- Congestive heart failure ≥ grade 3
- Posterior Reversible Encephalopathy Syndrome (any grade)
- Non-GI fistula or abscess ≥ grade 2

5.2.4 Selected Adverse Events

In addition to the primary safety variable, guided questionnaires will be completed for the following:

Bevacizumab specific

- Arterial Thromboembolic Events
- Congestive Heart Failure
- Interstitial Lung Disease
- Osteonecrosis of Jaw

Non-product specific

- Drug Induced Liver Injury
- Progressive Multifocal Leukoencephalitis
- Suspected Transmission of Infectious Agent by Medicinal Product

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4□5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of bevacizumab, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of bevacizumab, all AEs will be reported until 30 days after the final dose of bevacizumab.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v 4.03) 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 (v 4.03).

Table 1 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 (v 4.03), which can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

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 10.3.2 for reporting instructions), per the definition of SAE in Section 10.1.2.

d Grade 4 and 5 events must be reported as SAEs (see Section 10.3.2 for reporting instructions), per the definition of SAE in Section 10.1.2.

5.3.4 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.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study medicine administration should be captured as individual signs and symptoms in the AE section of the eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction.

5.3.5.2 Diagnosis versus Signs and Symptoms

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.

5.3.5.3 Adverse Events That Are 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.

5.3.5.4 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 on the Adverse Event 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 on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours of *knowledge of* occurrence that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event 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 serious adverse events.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 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

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 CRF.

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 CRF, 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 on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 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 Section 5.3.5.4 for details on recording persistent AEs).

5.3.5.7 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 on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., within 24 hours of knowledge of occurence of the event), either as a serious adverse event or an AESI (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, should be classified as serious adverse event and must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor and EC (see Section 5.4.2). This includes death attributed to progression of advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV).

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 Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of disease, “advanced/metastatic epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (FIGO Stage IIIb, IIIc, and IV) progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 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 section of 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 eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.10 Lack of Therapeutic Efficacy

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 v1.1. 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.

5.3.5.11 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 5.2.2), 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 solely due to the progression of underlying malignancy should NOT be reported as an SAE.

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

5.3.5.12 Cases of Accidental Overdose or Medication Error, Drug Abuse, or Drug Misuse}

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 eCRF. Any overdose, abuse, misuse, inadvertent/erroneous administration, medication error (including intercepted or potential), or occupational exposure reports must be forwarded to the Sponsor with or without an AE.

Reports with or without an AE should be forwarded to the Sponsor as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours of *knowledge of* occurrence of the event, see Section 5.4.2).

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.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)

Pregnancies (see Section 5.4.3 for details on reporting requirements)

For SAEs and AEs of special interest, the investigator must report new significant follow-up information to the Sponsor 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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for all sites

Medical Monitor: [redacted]

Telephone No.:

Mobile Telephone No.:

Emergency Medical Contact: [redacted]

Telephone No.:

Mobile Telephone No.:

Drug Safety Team: [redacted]

Telephone No.:

Mobile Telephone No.

E-mail:

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events (SAES) caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., within 24 hours of knowledge of occurrence of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, SAEs and AESIs will be reported until 30 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours of knowledge of occurrence of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., within 24 hours of knowledge of occurrence of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Telephone No.: [redacted]

Direct: [redacted]

Fax: [redacted]

E-mail: [redacted]

Instructions for reporting SAEs that occur >30 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the study or within 3 months after the last dose of medicine. A Pregnancy Report eCRF (if available) should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the AE eCRF. The physician should discontinue the medicine andcounsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE section of the eCRF.

In the event that the EDC system is temporarily unavailable, please refer to Section 5.6.

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should be reported to Roche Safety Risk Management.

5.4.3.2 Abortions

A spontaneous abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., within 24 hours of knowledge of occurrence of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as an SAE, recorded on the

Adverse Event eCRF, and reported to the Sponsor immediately (i.e., within 24 hours of knowledge of occurrence of the event ; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an AE.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., within 24 hours of knowledge of occurrence of the event ; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, 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 study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For SAEs, AESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, 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.

5.6 *ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

The Sponsor should be notified if the investigator becomes aware of any SAE that occurs after the end of the AE reporting period (defined as 30 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs AESIs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Bevacizumab (Avastin®)	Avastin® Local Prescribing Information
Paclitaxel	Paclitaxel Local Prescribing Information
Carboplatin	Carboplatin Local Prescribing Information

The Sponsor 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 investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The sample size was calculated using the formula:

$$n = \frac{Z^2 \times p \times (1-p)}{d^2}$$

Where,

p :Incidence of any AE (All grade 3 and above) related to bevacizumab in ovarian cancer

d : Precision

Z: Z value (1.96 for 95% confidence level)

In order to estimate the incidence of any AEs (All grade 3 and above) related to bevacizumab in ovarian cancer by assuming level of significance 5%, incidence of any AEs (All grade 3 and above) 66% [Perren TJ et al, 2011], precision 10% and dropout rate 10%, a total of 97 patients are required. Hence, it is proposed to recruit 100 patients for the present study.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF ANALYSIS POPULATION AND DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Safety analyses will include all patients who received at least one dose of bevacizumab. Efficacy analyses will be based on all enrolled patients.

Demographic and baseline characteristics (including age, weight etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 SAFETY ANALYSES

All AE and SAE data will be summarized by using number and percentage (Incidence of AEs and SAEs). Adverse events and SAEs will be coded using the applicable version of the Medical Dictionary for Regulatory Activities (MedDRA) classification of the ICH, AEs and SAEs also will be summarized using number and percentage by System Organ Class and Preferred Term. Summaries will be presented for all AEs and AEs related to bevacizumab.

Descriptive statistics for all the physical examination parameters will be computed for baseline and at end of the treatment period. A listing will also be prepared for all the patients.

Descriptive statistics for all the vital sign parameters will be computed for baseline and at end of the treatment period. A listing will also be provided as per the parameters available for all patients.

For hematology and biochemistry parameters, descriptive statistics will be reported at screening, all cycles and end of treatment period. Change from baseline will also be reported from all the available clinic visits. Individual patient laboratory results will be provided in listing with abnormalities

6.5 EFFICACY ANALYSES

Based on the observation during real-life clinical practice, all efforts will be made to regularly follow up patients to ensure that Progression Free survival (PFS) (using Response Evaluation Criteria In Solid Tumors [RECIST] v 1.1) and Overall Survival (OS) data are reported. The log rank test will be used to compare the median survival time between subjects with ECOG PS 0 and ECOG PS 1-2 at baseline. The overall response rate (CR + PR) will be summarized using number and percentage along with two-sided

95% Pearson-Clopper confidence interval (CI). Similarly, the Clinical Benefit Response rate (CR + PR + SD) will be summarized using number and percentage along with the two-sided 95% Pearson-Clopper CI.

All statistical tests will be done at 5% level of significance. All patients enrolled would be evaluated for efficacy.

6.5.1 Analyses of Exposure, Adverse Event, Laboratory and Vital Sign

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim tAE terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v 4.03. All AEs, SAEs, AEs leading to death, AESIs, and AEs leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data, if available, will be displayed by time, with grades identified where appropriate. Changes in vital signs and ECGs will be summarized.

6.6 INTERIM ANALYSIS

6.6.1 Planned Interim Analysis

In addition to the final analysis, there will an interim analysis for safety reporting that will be conducted when approximately 50% of the planned population has had any of the following: disease progression, death, treatment discontinuation, consent withdrawal, or is lost to follow up.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor 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 through use of 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 Sponsor 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 Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

CRFs and correction documentation will be maintained in the EDC system's 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.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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 patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs 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, patient-reported outcomes, 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 eCRFs (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 into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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 Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of India where the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing 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 Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or 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.

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 Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. 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.

8.3 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 Principal Investigator 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.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor 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 data sets that are transmitted to any Sponsor 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 national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the studyI.e..

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 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, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. the *Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.*

9.4 *SITE INSPECTIONS*

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

9.5 *ADMINISTRATIVE STRUCTURE*

Sponsor *Roche Products (India) Pvt. Ltd.*

Clinical Supplies	[redacted]
Clinical Laboratory	*Institutional laboratories and/or external laboratories*
Study Monitoring	[redacted]
Project Management	*Roche Products (India) Pvt. Ltd.*
Data Management	[redacted]
List of Investigators	*List is included in the clinical trial application dossier to local health authorities*

9.6 *DISSEMINATION* OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator 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 Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor 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 Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/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 necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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5. Burger RA, et al. Phase III trial of Bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal (PPC) or Fallopian tube cancer (FTC): A Gynaecologic Oncology Group study. J Clin Oncol 2010; 28 (June 20 Suppl.): 946s (Abstract LBA1).

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7. X B Trinh, W A A Tjalma, P B Vermeulen et al. The VEGF pathway and the AKT/mTOR/p70S6K1 signalling pathway in human epithelial ovarian cancer. Br J Cancer. 2009 March 24; 100(6): 971–978.

Appendix 1

List of Stand-Alone Documents Not Included in the Protocol

- List of contact details of responsible parties and all physicians
- FIGO Staging
- RECIST (v 1.1) Criteria
- NCI-CTCAE (V 4.03)
    - ECOG PS

Appendix 2
Schedule of Activities

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 either before or after start of medicinal product

[a] Written informed consent must be obtained before any data collection.

	Screening	**Treatment cycles (each cycle = 3 weeks)**									**Completion/Early Termination Visit** [b]	**Follow-Up** [c]
	At any time after bevacizumab is prescribed and Informed consent is taken/treatment is ongoing and Informed Consent is taken but before recording data/entering data	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9***		
Informed consent	x											
Demographic data	x											
General medical history and baseline conditions	x											
Vital signs [d]	x										x	
Weight	x	x	x	x	x	x	x	x	x	x	x	x
Height	x											
Physical examination [e]	x										x	
Hematology [f]	x	x	x	x	x	x	x	x	x	x	x	
Biochemistry [g]	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities

Treatment administration	x	x	x	x	x	x	x	x	x	x		
Response assessment	x			x			x			x		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	
Adverse events (After ICF is signed)	x	x	x	x	x	x	x	x	x	x	x	x

Notes:

[a] *Visits are not specified by the protocol and will be conducted as per clinical practice of the Investigators*.

[b] Patients who complete the study or discontinue from the study early will be followed up for AEs and survival. Adverse events will be collected for up to 30 days after last dose of bevacizumab treatment.

[c] Follow-up information will be collected via telephone calls and/or clinic visits (only if they happen during the normal course of treatment) until death, loss to follow-up, or study termination by the Sponsor.

[d] Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position

[e] An abnormalities present in medical records at baseline on the General Medical History and Baseline Conditions would be recorded. New or worsening abnormalities should be recorded on the Adverse Event section.

[f] Includes the following data as available in medical records [hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells)].

[g] Includes the following data as and *whatever is evaluated as per clinical; practice* (sodium, potassium, chloride, bicarbonate, fasting glucose, Blood urea nitrogen or urea, creatinine, calcium, total and direct bilirubin, total protein, albumin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, phosphorus, magnesium, lactate dehydrogenase, creatinine phosphokinase, uric acid).

* Treatment may continue post 9 cycles.

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Dr. [redacted] [redacted] Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted] Signed using mobile	Sent: 6/22/2020 6:52:53 PM Viewed: 6/22/2020 9:41:51 PM Signed: 6/22/2020 9:45:36 PM
Electronic Record and Signature Disclosure: Accepted: 6/22/2020 9:41:51 PM ID: [redacted] Company Name: Roche Trial on Production Account		
Dr. [redacted] [redacted] Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 6/22/2020 6:52:53 PM Resent: 6/25/2020 6:03:32 AM Viewed: 6/25/2020 6:13:06 AM Signed: 6/25/2020 9:11:46 AM
Electronic Record and Signature Disclosure: Accepted: 6/25/2020 6:13:06 AM ID: [redacted] Company Name: Roche Trial on Production Account		
[redacted] [redacted] Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 6/22/2020 6:52:54 PM Viewed: 6/23/2020 10:18:54 AM Signed: 6/23/2020 10:19:16 AM
Electronic Record and Signature Disclosure: Accepted: 6/23/2020 10:18:54 AM ID: [redacted] Company Name: Roche Trial on Production Account		

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Envelope Sent	Hashed/Encrypted	6/25/2020 6:03:32 AM
Certified Delivered	Security Checked	6/25/2020 6:13:06 AM
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