Official Title: A Single Arm, Open Label Multicentre Extension Study of Bevacizumab in Patients With Solid Tumours on Study Treatment With Bevacizumab, at the End of A F. Hoffmann-La Roche and/or Genentech Sponsored Study

NCT Number: NCT01588184

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PROTOCOL

TITLE:	**A SINGLE ARM, OPEN LABEL MULTICENTRE EXTENSION STUDY OF BEVACIZUMAB IN PATIENTS WITH SOLID TUMOURS ON STUDY TREATMENT WITH BEVACIZUMAB, AT THE END OF A F. HOFFMANN-LA ROCHE AND/OR GENENTECH SPONSORED STUDY**
PROTOCOL NUMBER:	MO25757
VERSION NUMBER:	3
EUDRACT NUMBER:	2011-002009-31
IND NUMBER:	Not applicable
TEST PRODUCT:	Bevacizumab (RO4876646)
MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

Approver's Name	**Title**	**Date and Time (UTC)**
[redacted]	Company Signatory	08-Nov-2018 14:47:13

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GLOSSARY OF ABBREVIATIONS

18-FDG	[18]-fluorodeoxyglucose
AE	Adverse event
AESI	Adverse Events of Special Interest
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase
BP	Blood pressure
CHF	Congestive heart failure
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central nervous system
CrCl	Creatinine clearance
CT	Computed tomography
CVA	Cerebrovascular accident
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ESF	Eligibility screening form
EU	European Union
E-Trial	Extension trial (i.e. this protocol MO25757)
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IgG	Immunoglobulin G
IND	Investigational new drug
INR	International normalized ratio
IMP	Investigational medicinal product

GLOSSARY OF ABBREVIATIONS

IRB/IEC	Institutional Review Board / Independent Ethics Committee
i.v.	Intravenous
mBC	Metastatic breast cancer
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mRCC	Metastatic renal cell carcinoma
MRI	Magnetic resonance imaging
MRI	Magnetic resonance image
NCI CTC-AE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
OS	Overall survival
P-Trial	Parent trial (i.e original study from which eligible patients enrol into this extension study (E-Trial))
PD	Progression of disease / progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PTAP	Post-Trial Access Program
q3w	Every 3 weeks
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumours
RPLS	Reversible posterior leucoencephalopathy syndrome
SAE	Serious adverse event
SAP	Statistical Analyses Plan
SBP	Systolic blood pressure
SOC	Standard of care
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
SWFI	Sterile water for injection
ULN	Upper limit of normal
USP	United States Pharmacopeia
VEGF	Vascular endothelial growth factor
WOCP	Women of child-bearing potential

SYNOPSIS OF PROTOCOL

TITLE	A single arm open label multicentre extension study of bevacizumab in patients with solid tumours on study treatment with bevacizumab at the end of a F. Hoffmann-La Roche and/or Genentech sponsored study.
SPONSOR	F. Hoffmann-La Roche Ltd. CLINICAL PHASE Phase IIIb/IV
INDICATION	Patients with solid tumours
OBJECTIVES	Primary: • To provide continued bevacizumab therapy as single agent or in combination with an anti-cancer drug to patients with cancer, who were previously enrolled in a F. Hoffmann-La Roche (Roche)/ Genentech sponsored bevacizumab study (i.e. the Parent, P-trial) and who derived benefit from the therapy administered in the P-trial. • To collect safety data with regard to long-term administration of bevacizumab.
TRIAL DESIGN	Multicenter, open-label, single-arm phase IIIb/IV trial. Patients on bevacizumab at P-trial end should be enrolled immediately thereafter. Patients will receive treatment with bevacizumab as during their P-trial until progression of disease, unacceptable toxicity, withdrawal of consent, death or transition to another option for treatment with bevacizumab (e.g. licensed product or Post-Trial Access Program [PTAP]) (whichever occurs first).
NUMBER OF PATIENTS	Open
NUMBER OF CENTRES	International, multi-centre trial
TARGET POPULATION	Patients with solid tumours who derived benefit from bevacizumab therapy as single agent or in combination with an anti-cancer drug enrolled in a Roche/ Genentech sponsored bevacizumab P-trial.
LENGTH OF STUDY	Enrolment period: Approximately 5 years Follow-up period: until the last patient permanently discontinues bevacizumab treatment in this extension trial (E-trial)
END OF STUDY	The last patient safety FU visit (latest 30 days after last patient permanently discontinues bevacizumab treatment in this E-trial)
INVESTIGATIONAL MEDICAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	Bevacizumab Dose: 7.5 or 15 mg/kg IV every 21 days or 5 or 10 mg/kg IV every 14 days The same dose and regimen as used in the P-trial must be continued throughout this E-trial. Treatment with bevacizumab can continue until progression of disease, unacceptable toxicity (see also Section 6.1.1), withdrawal of consent, death, or transition to another option for treatment with bevacizumab (e.g. licensed product or PTAP), (whichever occurs first). Bevacizumab cannot be restarted after an interruption of > 42 days unless because of planned surgery requiring bevacizumab interruption during P-trial. Bevacizumab can be restarted only after Sponsor's medical monitor approval.

NON-INVESTIGATIONAL MEDICAL PRODUCT(S)	If applicable: Anti-cancer therapy given as investigational medicinal product (IMP) together with bevacizumab in the P-trial will be continued in the E-trial as per instructions in the P-trial, but classified as **Non-IMP in the E-trial**. The Sponsor will continue to provide those anti-cancer therapies until bevacizumab is permanently discontinued. Investigators may prescribe other non-IMP in accordance with their local label and standard of care. They will not be provided by the Sponsor.
COMPARATOR "DRUG" (or STANDARD OF CARE) DOSE/ ROUTE/ REGIMEN	Not applicable
INCLUSION CRITERIA AT ENROLMENT	1. Written informed consent must be obtained prior to any study-specific procedure. 2. Patient is treated with bevacizumab at the end of the Roche/Genentech sponsored P-trial and continues to have benefit as judged by the investigator 3. Eligible for continuation of bevacizumab treatment at the end of the P-trial, according to P-trial protocol 4. Able to comply with the E-trial protocol (MO25757) 5. Female patients should not be pregnant or breast-feeding. Female patients of childbearing potential (defined as <2 years after last menstruation or not surgically sterile) must use a highly effective contraceptive method (allowed methods of birth control, i.e. with a failure rate of less than 1 % per year, are implants, injectables, combined oral contraceptives, IUDs [only hormonspirals], sexual abstinence or vasectomised partner) during the E-trial and for a period of at least 6 months following the last administration of E-trial drug(s). Female patients with an intact uterus (unless amenorrhoeic for the last 24 months) must have a negative serum pregnancy test prior to first study treatment (see Section 5.4.1). 6. Fertile male patients must agree to use a highly effective contraceptive method (allowed methods of birth control, i.e. with a failure rate of less than 1 % per year, female partner using implants, injectables, combined oral contraceptives, IUDs [only hormonspirals], sexual abstinence or prior vasectomy) during the E-trial and for a period of at least 6 months following the last administration of E-trial drug(s).
EXCLUSION CRITERIA	1. Evidence of disease progression assessed according to P-trial protocol during the screening phase for this E-trial 2. Evidence of any adverse event potentially attributable to bevacizumab, for which the local label recommends permanent discontinuation. 3. A treatment interruption with bevacizumab of more than 42 days since the last administration of bevacizumab in the P-trial. 4. Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or

	laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of the investigational drug(s) or puts the patient at high risk for treatment-related complications.
ASSESSMENTS OF: - EFFICACY	Assessments for progression of disease will be done as per local standard, although it is recommended to continue using the same methods as in the P-trial. Results of tumour assessments will be recorded in the eCRF (i.e. the date of progression).
- SAFETY	All SAEs and AEs will be recorded. All patients will have safety assessments as per local standard. Adverse events (AEs) will be assessed using the National Cancer Institute Common Terminology Criteria for AEs (NCI CTC-AE) criteria. Version 4.0 should preferably be used. The incidence of serious AEs (SAEs) and AEs will be determined. Date of and reason for death will be captured
- PHARMACOKINETICS/ PHARMACODYNAMICS	NA
- EXPLORATORY - BIOMARKERS (non-DNA)	NA
- EXPLORATORY BIOMARKERS (DNA)	NA
- CLINICAL GENOTYPING (CG) SAMPLES	NA
MANDATORY BIOMARKER SAMPLES	NA
PROCEDURES (summary):	Tumour assessments will be done as per local standard
RANDOMIZATION PROCEDURES	NA
STATISTICAL ANALYSES	The primary variable will be based on the following safety endpoints: AE grade ≥3 related to bevacizumab, SAEs, cause of deaths. No formal statistical hypothesis testing is planned. Data may be linked with each P-trial's database. More details will be written in the Statistical Analysis Plan (SAP). There will be a safety interim analysis approximately 3 years after the enrolment of the first patient in this E-trial. No formal interim analyses for efficacy are planned for this E-trial. Information on study drug will be summarized by duration, starting dose and cumulative dose using descriptive statistics.

All summaries will be presented for the safety population that will include all enrolled patients in the E-trial who received at least one dose of bevacizumab.

Progression free survival and overall survival will be summarised using Kaplan-Meier approach. The efficacy data also might be pooled with corresponding P-trial database. More details will be written in the SAP.

Sample Size Estimation

This is an E-trial. Patients will be enrolled from qualifying P-trials. The formal estimation of sample size is not possible.

The table below presents a few possible scenarios for Percentage and Number of Patients with AEs grade ≥3 related to bevacizumab and corresponding 95% Clopper-Pearson exact confidence intervals (CI).

Table: Scenarios for Percentage and Number of Patients with AEs grade ≥3 related to bevacizumab and corresponding Confidence Intervals

Sample Size	Percentage and Number of Patients with AEs grade ≥3 related to bevacizumab	95% Clopper Pearson exact confidence interval
50	10% (5 patients)	3% - 22%
50	20% (10 patients)	10% - 34%
100	10% (10 patients)	5% - 18%
100	20% (20 patients)	13% - 29%

STUDY PROCEDURES (summary)

Before the end of the P-trial (as defined in the P-trial protocol) the investigator will inform the study monitor of potential patients who are candidates for the E-trial. The monitor will then ensure that all relevant approvals are in place so patients can be enrolled into this E-trial with no interruption in treatment.

INFORMED CONSENT AND ENROLMENT

Written, informed consent must be obtained before patients undergo any E-trial-related procedures.

Enrolment: The investigator informs the monitor of potentially eligible patients (i.e. link to P-trial and characteristics). Blood sampling for serum pregnancy test (see Section 5.4.1) to determine eligibility in women patients of child-bearing potential (WOCP) will be done. After confirmation of eligibility, treatment with bevacizumab can continue.

Minimal patient characteristics will be collected, i.e. date of birth, gender, tumour type and P-trial protocol and patient number.

TREATMENT PERIOD

- Prior to each cycle of bevacizumab, patients will undergo assessments according to local standard of care. Weight will be recorded.
- AEs and SAEs as outlined in the protocol Section 7.2 will be documented at each visit.
- Tumour assessments as per local standard (the same method(s) as per P-trial are recommended).
- Treatment with bevacizumab can continue as per P-trial **until progression of disease**, withdrawal of consent, unacceptable toxicity (see also Section 6.1.1), death, or transition to another option for treatment with bevacizumab (e.g. licensed product or PTAP), whichever occurs first. Bevacizumab is administered as follows:
    - Bevacizumab 7.5 or 15 mg/kg IV on day 1 every 3 weeks or
    - Bevacizumab 5 or 10 mg/kg IV on day 1 every 2 weeks

Treatment interruptions of >42 days will result in permanent cessation of bevacizumab/P-trial IMP unless because of planned surgery needing bevacizumab interruption during P-trial. Restart of bevacizumab can be done only after Sponsor's medical monitor approval. Reason for treatment cessation will be captured.

- For patients on concurrent anti-cancer therapy as per the P-trial: Treatment with anti-cancer therapy should continue as stipulated in the P-trial, and as outlined in the protocol Section 6.4. Other P-trial IMP treatment will be stopped when bevacizumab is permanently discontinued.

SAFETY FOLLOW-UP VISIT
Patients will undergo a safety follow-up assessment as shown in Table 1. Date of, and reason for death will be documented.

Table 1: Schedule of mandatory* assessments

	Roll over from P-trial into E-Trial (Day -14 to Day 1)	**Treatment period Per cycle**	**Safety FU[§]**
Informed Consent	**X**		
Confirmation of eligibility	**X**		
Patient characteristics (Gender, date of birth, tumour type)	**X**		
Pregnancy test for WOCP[#]	**X**		
Weight		**X**	
Bevacizumab **Other P- trial anti-cancer IMP(s) if applicable****		**X[+]**	
Progression assessment		**Per local standard°**	
AE	**X** see Section **5.1**	**X**	**X**
Survival info		**X**	**X**
[§] (1) for patients who withdraw from the trial for reasons other than transition to another option for treatment with bevacizumab, 30 (± 3) days after the last dose of bevacizumab (or other P-trial IMP(s), if applicable) and (2) for patients who withdraw from the trial to transition to another option for treatment with bevacizumab, before administration of non-trial bevacizumab outside of the study.			

Pregnancy test: WOCP will have a serum pregnancy test no more than 7 days prior to the first trial treatment or no more than 14 days (with a confirmatory urine pregnancy test within 7 days prior to the first trial treatment).

*Additional assessments (as per local standard and clinical judgement of the investigator) will only be documented in the patients' source documents

The same method(s) as per P-trial are recommended

+ 1st bevacizumab dose in MO25757 E-trial to be within 42 days of last dose in P-trial

** classified as non-IMP in the E-trial, see also Section 6.4

PART I: TRIAL DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 Bevacizumab

Please refer to the current version of the bevacizumab Investigator's Brochure (IB) for further details.

Bevacizumab is a recombinant humanized monoclonal antibody to Vascular Endothelial Growth Factor (VEGF) composed of human IgG1 framework regions and antigen-binding complementary determining regions from a murine monoclonal antibody (muMAb VEGF A.4.6.1) that blocks the binding of human VEGF to all VEGF-A receptors.[1]

Bevacizumab recognizes and neutralizes isoforms of VEGF with a K_d of approximately 8 x 10^{-10} M. It does not recognize other peptide growth factors tested (fibroblast growth factor, epidermal growth factor, hepatocyte growth factor, platelet-derived growth factor and nerve growth factor). It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumour environment. Additional anti-tumour activity may be obtained via the effects of bevacizumab on tumour vasculature, interstitial pressure and blood vessel permeability, providing for enhanced chemotherapy delivery to tumour cells.[2] In addition, bevacizumab showed synergistic anti-angiogenic activity with docetaxel, as assessed by endothelial cell proliferation and tubule formation, *in vitro*.[3]

Anti-VEGF antibodies have shown benefit when combined with chemotherapy in preclinical models of different tumour types. Bevacizumab can block the growth of a number of human cancer cell lines grown in nude mice, including metastatic colorectal cancer (mCRC), non-squamous NSCLC, metastatic or locally recurrent breast cancer (BC), prostate cancer, head and neck cancer, metastatic renal cell carcinoma (mRCC) and ovarian cancer.[4-7]

Bevacizumab has been tested in many phase I to IV studies in a variety of solid tumours as monotherapy and in combination with chemotherapy. The combination of bevacizumab with chemotherapy improves PFS and/or OS in mCRC, [8-11] non-squamous NSCLC,[12-14] metastatic breast cancer (mBC),[15,16] mRCC,[17,18] ovarian cancer.[19,20,21] and brain cancer.[27]

Bevacizumab is currently approved in 133 countries worldwide (including the member states of the European Union (EU), and the United States of America) for the treatment of some forms of colorectal, breast, renal, lung, ovarian/cervical and brain cancers. Since the first marketed authorization (26 February 2004), the estimated cumulative market exposure to bevacizumab until 25 February 2018 is 3,099,396 patients in different indications. As of 25 February 2018, the estimated cumulative clinical trial exposure to bevacizumab is 34,789 patients patients have been exposed to bevacizumab as a marketed product or in clinical trials in different indications.

1.1.1 Safety of bevacizumab

In the Phase III trial programme conducted across several tumour types, bevacizumab has demonstrated a favourable safety profile with a low incidence of grade 3 or 4 AEs. Some AE of special interest (AESI) associated with the use of bevacizumab (either alone or in combination with chemotherapy) are as follows (see also Section 6.1.1):

- Hypertension
- Reversible posterior leucoencephalopathy syndrome (RPLS)
- Proteinuria
- Haemorrhage
- Thromboembolism
- Gastrointestinal perforation
- Fistulae
- Wound-healing complications
- Congestive heart failure (CHF)

For information regarding other side effects associated with the use of bevacizumab (either alone or in combination with chemotherapy), please refer to the current version of the IB. For specific information on a particular cancer setting, please refer back to the P-trial protocol.

1.1.2 Long-term exposure to Bevacizumab

The GOG-0218[19] trial is the first prospective controlled dataset assessing treatment duration. In GOG-0218[19] patients with previously untreated stage III–IV ovarian and other gynaecological cancers were randomized to different treatment durations with bevacizumab (24, 6 vs. 0 cycles, 15mg/kg q3w) in combination with carboplatin/paclitaxel chemotherapy.

The GOG-0218 trial met its primary endpoint of a statistically significant increase in PFS. Further, the data showed that continuing single-agent bevacizumab following combination treatment with up to 6 cycles of carboplatin/paclitaxel chemotherapy was necessary in order to gain the benefit. Overall, the safety profile of bevacizumab when used in addition to carboplatin/paclitaxel chemotherapy was as expected, based on the known toxicities of the individual components, except that the incidence of low-grade dysarthria (GOG-0218) was increased by more than previously seen in the bevacizumab-containing arms compared to comparator arms. In summary, the GOG-0218 trial shows a favourable risk benefit profile for the patients randomized to approx 16 months of bevacizumab vs. the control group. Please refer to the current version of the IB for more details.

Earlier clinical trials with bevacizumab had been designed to give bevacizumab until treatment progression, based on preclinical data showing that long-term, continued suppression of VEGF leads to benefit.

In clinical trials in patients with other cancer types, bevacizumab is usually given until progression of disease. This leads to very variable treatment durations per patient, with some patients being treated for more than 4.5 years[18]. Table 2 below gives an overview of treatment duration in various bevacizumab trials.

Table 2: Treatment duration with bevacizumab in selected trials

Study number	Author	Disease	N of patients on bevacizumab	Median treatment duration with bevacizumab	Maximum treatment duration with bevacizumab
AVF2107g	Hurwitz [8]	mCRC	402	40.4 weeks	NR
CALGB90206	Rini [18]	RCC	369	32.8 weeks	236 weeks
MO19390	Crino [22]	NSCLC	2212	21.3 weeks	132 weeks
E2100	Miller[15]	mBC	365	7.1 months	NR

NR = Not reported

Two extension studies AVF2540g and AVF0778g[23] in patients with solid tumours (please refer to IB for more details) suggest that bevacizumab can be given safely for long periods of time (up to 3 years in some cases - more than 1 year, in addition to the treatment received in the parent studies), both as single-agent and in combination with chemotherapy. No new incidents of gastrointestinal perforation, wound healing complications, congestive heart failure, or nephrotic syndrome were observed. However, patients do continue to be at risk of developing hypertension and proteinuria during treatment with bevacizumab.

Similar safety data are reported from the observational BRITE[24] study on 359 and 109 out of 1953 patients with mCRC who received continuous bevacizumab therapy for >12 and > 24 months respectively. The baseline characteristics for patients on long-term bevacizumab showed that these tended to be younger and had a more favourable performance score and fewer co-morbidities then the overall population. In this sub-population the occurrence of AESI was infrequent with long term exposure of bevacizumab. The risk of developing hypertension seemed continuous and related to overall exposure; however no SAEs were reported.

The SAiL[25] investigators assessed patients with NSCLC who continued to receive bevacizumab following chemotherapy cessation. Those 1332 patients received a median of 11 (interquartile range; 8-16) 3-weekly cycles of bevacizumab therapy on study. The 880 patients that were unable to receive continued maintenance therapy with bevacizumab following chemotherapy cessation, received a median of 3 (interquartile range; 2-5) 3-weekly cycles of bevacizumab. AEs that led to discontinuation for bevacizumab maintenance treatment were thromboembolism, gastrointestinal perforations, CHF and high grade bleeding. Hypertension, proteinuria and low grade bleedings occurred more frequently in the group with longer exposure

In a case report of 2 patients with mCRC, prolonged survival times of almost 5 and 6 years, respectively, were observed on bevacizumab combined with various chemotherapy[26]. Throughout most of their disease course, these patients tolerated bevacizumab generally

well in long term use and maintained a good quality of life, with some adjustments of chemotherapy doses because of side effects.

1.2 Trial Rationale

Bevacizumab is usually given until progression of the underlying cancer unless patients withdraw consent or experiences toxicities that lead to discontinuation. The time to progression is very variable from patient to patient (see Table 2).

Trials need to have a defined end. This is often event driven for comparative trials looking into PFS or OS. Single-arm trials often end after a prespecified time after last patient first visit. At their completion or closure some patients might still be on treatment with bevacizumab and benefit from the continuation of the therapy with bevacizumab as their cancer has not progressed. Roche/Genentech had committed to provide treatment for above mentioned patients in the P-trial.

This long-term E-trial was opened in 2012 to provide ongoing bevacizumab treatment to patients who were enrolled in Roche/Genentech clinical trials of bevacizumab that were ending but who would benefit from continuation of therapy as their cancer had not progressed. This study also ensured that all patients enrolled in the same trial had the chance to receive similar treatment (i.e. the first patient enrolled in a trial could benefit during enrollment and follow-up phase of a trial, while the last patient enrolled in a trial could benefit during follow-up phase and in this E-trial). At that time, no other option was available to provide access to bevacizumab while monitoring patient safety adequately.

In many countries bevacizumab has subsequently been authorised for treatment of solid tumours and is also available through the Post-Trial Access Program (PTAP). The current study protocol amendment allows for transition of patients from this E-trial to other treatment options available in their countries that are less burdensome to the patients. The extensive and favourable safety profile now available for bevacizumab supports the least restrictive follow-up for these patients.

1.3 Overall Risk and Benefit Assessment

The MO25757 E-trial is designed to ensure an optimal risk/benefit ratio. The study protocol includes the following measures to manage the risk:

- The Sponsor will assess each trial carefully before declaring it a “qualifying” P-trial and enrolling its eligible patients into this E-trial. For example, a trial that is prematurely stopped for safety issues related to bevacizumab, could not become a P-trial.
- Doses of study therapy have been chosen in accordance with SPC, and taking into account the available data on clinical studies as well as usual practices. Additionally the dose of bevacizumab in each patient will be the same dose the patient received during his/her therapy in the P-trial.
- Clear guidance on interruption and discontinuation for bevacizumab in case a patient develops severe side effects; this also takes into account side effects experienced during treatment in the P-trial.

- As this is an E-trial, all centres already have experience with the study treatment and have qualified and experienced specialists involved who are motivated to continue caring for the patients.
- Safety reporting will be carried out in compliance with Good Clinical Practice (GCP): clinical AEs will be monitored closely during the study. Moreover, a series of potential safety signals (AESI) already identified with bevacizumab will be specifically monitored.
- A formal interim safety analysis is planned 3 years after the first patient is enrolled. The study team will continuously monitor the safety of the patients as per usual standards.
- Side effects that appear to be related to the use of bevacizumab had been taken into account by defining in-/exclusion criteria in the P-trial aiming to avoid recruitment of patients with higher risk of developing such side effects. During the enrolment of potential patients for the E-trial, the investigator must reconfirm that patients are eligible for continuation.
- Clear clinical management guidelines to minimise AEs which may be expected to occur.
- Specifically prohibiting concomitant medications known and suspected to interact with the study medications.
- Providing clear directions as per the P-trial for modification of additional P-trial IMP dose and/or schedule to effectively manage expected AEs.
- Providing clear directions for interruption or permanent discontinuation of bevacizumab to effectively manage expected AEs.
- Scheduling safety evaluations as per local standard prior to each dose of bevacizumab and a final safety evaluation:

  (1) For patients who withdraw from the trial to transition to another option for treatment with bevacizumab, before administration of non-trial bevacizumab outside of the study

  (2) For other patients, 30 (± 3) days after the last dose of bevacizumab (or other P-trial IMP(s), if applicable)

Considering all available data and all the precautions taken, the potential risk and the expected benefit, the MO25757 study is considered acceptable for the treatment of patients with solid tumours.

2. OBJECTIVES

2.1 Primary Objectives

To provide continued bevacizumab therapy as single agent or in combination with an anti-cancer drug to patients with cancer who were previously enrolled in a Roche/Genentech - sponsored bevacizumab P-trial and who derived benefit from the therapy administered in the P-trial

To collect safety data with regard to long-term administration of bevacizumab.

2.2 Exploratory Objective

3. TRIAL DESIGN

3.1 Overview of Trial Design

Multicenter, open-label, single-arm phase IIIb/IV trial. Patients on bevacizumab at study end of the P-trial should be enrolled immediately thereafter into this E-trial. Patients will receive treatment with bevacizumab as during their P-trial until progression of disease, unacceptable bevacizumab toxicity, withdrawal of consent, death, or transition to another option for treatment with bevacizumab (e.g. licensed product or PTAP), (whichever occurs first).

3.1.1 Rationale for trial design

The primary aim is to provide continued bevacizumab therapy to cancer patients who benefit from the therapy administered in the P-trial until progression of their disease, therefore this is an open labelled, single arm, non comparative study.

3.1.2 Rationale for dose selection

Patients in MO25757 will receive bevacizumab at doses of 2.5 or 5 mg/kg/week every 2 or 3 weeks in line with the treatment schedule and dose as mandated by the P-trial, i.e.

- Bevacizumab 7.5 or 15 mg/kg IV on day 1 every 3 weeks or
- Bevacizumab 5 or 10 mg/kg IV on day 1 every 2 weeks

Treatment duration and dose modifications for bevacizumab are described in Section 6.1.1.

3.1.3 End of trial

This E-trial will end at the last safety FU visit (latest 30 days after last patient permanently discontinues bevacizumab treatment in this E-trial).

3.2 Number of Patients

The number of patients to be enrolled over the planned recruitment period of approximately 6 years is open.

3.3 Centres

This is a multi-national trial. The number of countries and centres is open.

4. TRIAL POPULATION

Under no circumstances are patients who are enrolled in this E-trial permitted to be re-enrolled in this E-trial.

4.1 Overview

Patients with solid tumours who derived benefit from bevacizumab therapy as single agent or in combination with an anti-cancer drug enrolled in a Roche/Genentech - sponsored bevacizumab P-trial and who meet all inclusion criteria and none of the exclusion criteria listed below.

4.2 Inclusion Criteria

1. Written informed consent must be obtained prior to any study-specific procedure.
2. Patient is treated with bevacizumab at the end of the Roche/Genentech sponsored P-trial and continues to have benefit as judged by the investigator
3. Eligible for continuation of bevacizumab treatment at the end of the P-trial, according to P-trial protocol
4. Able to comply with the E-trial protocol (MO25757)
5. Female patients should not be pregnant or breast-feeding. Female patients of childbearing potential (defined as <2 years after last menstruation or not surgically sterile) must use a highly effective contraceptive method (allowed methods of birth control, i.e. with a failure rate of less than 1 % per year, are implants, injectables, combined oral contraceptives, IUDs [only hormonspirals], sexual abstinence or vasectomised partner) during the E-trial and for a period of at least 6 months following the last administration of E-trial drug(s). Female patients with an intact uterus (unless amenorrhoeic for the last 24 months) must have a negative serum pregnancy test prior to first study treatment (see Section 5.4.1).
6. Fertile male patients must agree to use a highly effective contraceptive method (allowed methods of birth control, i.e. with a failure rate of less than 1 % per year, female partner using implants, injectables, combined oral contraceptives, IUDs [only hormonspirals], sexual abstinence or prior vasectomy) during the E-trial and for a period of at least 6 months following the last administration of E-trial drug(s).

4.3 Exclusion Criteria

7. Evidence of disease progression assessed according to P-trial protocol during the screening phase for this E-trial
8. Evidence of any AE potentially attributable to bevacizumab, for which the local label recommends permanent discontinuation.

9. A treatment interruption with bevacizumab of more than 42 days since the last administration of bevacizumab in the P-trial.

10. Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of the investigational drug(s) or puts the patient at high risk for treatment-related complications.

4.4 Concomitant Medication and Treatment

All relevant concomitant medication(s) and treatments at the time of an SAE must be reported.

All non-cancer therapies that the investigator feels are appropriate are allowed in the E-trial, unless specifically excluded in the P-trial.

Patients should receive full supportive care during and after the administration of bevacizumab. This includes, where required, transfusion of blood and blood products and/or the use of erythropoietin or G-CSF, anti-emetics, antibiotics for infective complications and anti-hypertensives for the management of hypertension. Anaphylaxis precautions should be observed during administration of bevacizumab as per local practice.

Any medication contraindicated with bevacizumab is not permitted and special warnings and precautions for bevacizumab treatment need to be strictly observed (see Section 7.3).

The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to local standards) and the patient has been on a stable dose of anticoagulants during the P-trial.

Prophylactic use of anticoagulation at baseline and during study treatment for maintenance of patency of permanent indwelling central venous access devices is permitted.

Prophylactic use of anticoagulation during study treatment for patients at high risk of venous thromboembolism is permitted. Bevacizumab or anticoagulation treatment will be stopped in case of

- any evidence of tumour invading major blood vessels on any prior CT scan.
- any evidence of CNS metastases

Due to a possible risk of bleeding during treatment with bevacizumab, patients should not take more than 325 mg of aspirin daily (or more than 75 mg of clopidogrel daily) at least until discontinuation of bevacizumab treatment.

Treatment with other concomitant medication or anti-tumour agents not defined in the respective P-trial or this E-trial protocol as study treatment, or other concurrent investigational agents of any type is not permitted in this E-trial.

Concomitant radiotherapy treatment, with the exception of palliative radiotherapy for pain control of pre-existing bone metastases, will be regarded as a new treatment and patients receiving radiotherapy will be withdrawn from study treatment.

4.5 Criteria for Withdrawal

Patients have the right to withdraw from trial treatment or from this E-trial at any time for any reason without affecting their right to an appropriate follow-up treatment.

Reasons a patient may discontinue **treatment** include, but are not limited to:

- Progression of disease
- Adverse event [a]
- Patient request (withdrawal of consent for further treatment) [b]
- Investigator request (with detailed documentation of reasoning) [c]
- Protocol violation
- Patient non compliance
- Trial termination by the sponsor [d]
- Death.

When a patient discontinues trial treatment or is withdrawn, the investigator will notify the Sponsor and, when possible, will perform the procedures indicated for the final visit 30 days after last bevacizumab administration, except for patients who withdraw from the trial to transition to another option for treatment with bevacizumab, for whom the final visit must be conducted before administration of non-trial bevacizumab outside of the study.

Patients may be discontinued from **this E-trial** for the following reasons:

- Patient request (withdrawal of consent for further FU) [b]
- Trial termination by the sponsor [d]
- Lost to follow-up [e]
- Death
- Transition to another option for treatment with bevacizumab (e.g. licensed product or PTAP) once available in a given country

[a] If the reason for removal of a patient from the trial is an AE, the principal specific event will be recorded on the eCRF. The patient should be followed until the AE has resolved, if possible. If the AE is deemed serious, it must be reported via the electronic SAE pages of the eCRF within 24 hours of becoming aware of the event.

[b] In the case that the patient decides to discontinue, he/she should be asked if he/she can still be contacted for further information i.e. the investigator needs to clarify the extent of withdrawal of consent (to treatment or to by followed up in the trial). The outcome of that discussion should be documented in both the medical records and in the eCRF. Consent withdrawal by the patient must be documented in writing by the patient or his/her legal representative.

[c] When applicable, patients should be informed of circumstances under which their treatment may be terminated by the investigator (e.g.. treatment failure, adverse event) without the patient's consent.

[d] The Sponsor has the right to terminate the trial at any time. Reasons may include, but are not limited to, the following: The incidence or severity of AE in this or other studies indicates a potentially negative benefit risk ratio for patients; patient enrolment is unsatisfactory; data recording is inaccurate or incomplete. See also Section 14.

[e] An effort must be made to determine why a patient fails to return for the necessary visits or is dropped from the trial. This information will be recorded in the medical record and on the patient's eCRF. Lost to follow-up is defined as 3 failed attempts by phone followed by one attempt of sending a letter that requires signature.

Patients withdrawn from trial treatment or from this E-trial will not be replaced, regardless of the reason for withdrawal.

4.6 Replacement Policy

4.6.1 For patients

Patients enrolled into the trial will not be replaced.

4.6.2 For centres

A centre may be closed for, though not limited to, the following reasons:

- Poor protocol adherence and/or repeated protocol violations.
- Repetitive late / inaccurate clinical data entry or failure to resolve data queries in the eCRFs.
- Non-compliance with International Conference on Harmonization (ICH) GCP guidelines.

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Please refer to Table 1 detailing the schedule of assessments.

5.1 Screening Examination and Eligibility

All patients must provide written, informed consent before any E-trial-specific assessments or procedures are performed.

A screening examination ("baseline") should be performed between 14 days and 1 day before the first dose of treatment in this E-trial (for specific timelines see Table 1), which will include the following procedures (unless the procedures have already been conducted during this time period as part of the patient's routine clinical care:

– Eligibility (inclusion and exclusion criteria, as listed in Section 4.2 and Section 4.3, respectively)

– Minimal patient characteristics will be collected, i.e. date of birth, gender, tumour type P-trial protocol and patient number

– Blood sampling for serum pregnancy test (see Section 5.4.1)

The following procedures **are recommended**, and will usually be part of the patient's routine care. Data should be documented in the patient's chart (source documents).

– Complete physical examination and measurement of vital signs (including BP).

– Assessment of laboratory parameters and Urinalysis (see Section 5.4).

– Tumour assessment (see Section 5.3.1).

AEs: After informed consent signature, but prior to the first dose of study therapy in the E-trial (bevacizumab or if applicable other P-trial IMP), AEs should be reported in the P-trial following the P-trial's guidelines for AEs reporting, and only SAEs caused by an E-trial-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as blood draws).

Patients who fulfil all of the inclusion and none of the exclusion criteria will be included into the E-trial.

The investigator's assessment of each screened patient with regard to the E-trial's inclusion and exclusion criteria is to be documented in the patient charts.

A screen failure log must be maintained by the investigator.

5.2 Procedures for Enrolment of Eligible Patients

Patients where written informed consent has been obtained and who satisfy all eligibility criteria can be enrolled into this E-trial. As eligibility will not be confirmed centrally, it is the responsibility of the investigator to ensure that each patient meets all eligibility criteria. In the event there are any questions or doubts about a patient's eligibility, the Investigator site should contact the study monitor before enrolling the patient.

The Investigator site will be provided with a unique E-trial patient identification number via the eCRF, at the time of individual patient enrolment. The patient numbers will be allocated sequentially in the order in which the patients are enrolled.

Each patient will also be identified by their designation of the P-trial (i.e. patient number and P-trial protocol number) in the eCRF.

A Patient Enrolment and Identification Code List must be maintained by the investigator.

5.3 Clinical Assessments and Procedures

This E-trial protocol mandates a minimal number of assessments see Table 1. Patients should undergo routine clinical care as per the local standards. All assessments will be scheduled as indicated in Table 1. Additional assessments may be performed as clinically indicated.

All material used for the baseline assessment and assessment of follow-up of patients, or for the investigation of AEs, may be duplicated and made available to the Sponsor for review on request, e.g., for further assessment of the safety profile of the trial treatment, quality assurance purposes etc.

5.3.1 Tumour assessments and progression criteria

The baseline for the tumour evaluation (i.e. determination of progressive disease) is as per the P-trial.

Tumour assessments in this E-trial will be performed according to local standards. It is **recommended** to continue using the same imagery technique (CT-scans, X-rays or MRIs) and the same tumour evaluation criteria (example RECIST v1.0 or V1.1) as in the P-trial throughout this E-trial. The same investigator should make measurements for all assessments for each patient.

- Patients known to have bone metastases at baseline, or with signs or symptoms suggestive of bone metastasis, should undergo an isotope bone scan (this procedure is not mandatory if an 18-FDG PET scan has already been performed).
- CT/MRI scan of the brain is not mandatory, but should be performed as soon as possible if there is a clinical suspicion of CNS metastasis (see also next section).
- If a patient inadvertently misses a prescribed tumour evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next prescribed assessment, unless signs of clinical progression are present. If there is suspicion of new PD based on clinical or laboratory findings before the next prescribed assessment, an earlier assessment should be performed.
- Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumour measurements. Additionally, the PD may be so evident in some cases that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression will be based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy with appropriate imaging.

5.3.2 Clinical safety assessments

Patients should be assessed according local standards. All mandatory assessments will be scheduled as indicated in the Schedule of Assessments (Table 1). Additional assessments may be performed as clinically indicated.

Clinical assessments may include a CT / MRI scan of the brain (only in patients with new symptoms/signs suggestive of CNS involvement or other unexplained neurological symptoms) or follow-up of existing stable brain metastasis (see also previous section).

A symptom-directed physical examination should be performed at each visit or as indicated, including measurement of vital signs (weight and BP).

The NCI CTC-AE will be used to evaluate the clinical safety of the treatment in this E-trial (see page 64). Version 4.0 is recommended. However the investigator may continue using the NCI CTC-AE version of the P-trial.

Patients will be assessed for AEs and SAEs, at each clinical visit and as necessary throughout the trial. All AEs and SAEs will be recorded into the eCRF pages. Further details on definition, collection and reporting of AEs are provided in Section 7.

Safety assessments in line with local standard of care or those that are symptom-directed should be undertaken at the discretion of the treating physician. If the P-trial indicated specific safety assessments for certain patient populations, it is recommended that they are continued to ensure the patient's safety in this E-trial.

Patients will undergo a final safety follow-up assessment for AEs:

(1) For patients who withdraw from the trial for reasons other than transition to another option for treatment with bevacizumab, 30 (± 3) days after the last dose of bevacizumab (or other P-trial IMP(s), if applicable) and

(2) For patients who withdraw from the trial to transition to another option for treatment with bevacizumab, before administration of non-trial bevacizumab outside of the study.

5.4 Laboratory Assessments

Laboratory tests should be performed as per local standard of care.

In order to determine a patient's eligibility for the E-trial, a serum pregnancy test for WOCP must be performed (see Table 1, and see next section) and recorded in the Screening section of the eCRF.

Local laboratories will be used for all laboratory tests, with abnormal test results for the laboratory test recorded in the AE/SAE section of the eCRF Section 7.1.3 if appropriate. Sample handling procedures should comply with Good Laboratory Practices.

5.4.1 Safety laboratory assessments

Regular safety assessments should be taken in accordance with local standard of care, and are recommended to include:

- Haematology: haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count
- Coagulation tests (INR and aPTT)
- Biochemistry: serum chemistry (including total protein [or albumin only], ALP, AST/SGOT, ALT/SGPT, total bilirubin, creatinine, estimated CrCl)
- Urinalysis by dipstick. In case proteinuria ≥ 2+ is detected by the dipstick method, a 24-hour urine collection is needed to confirm renal function is within acceptable limits (< 1 g per day).

Pregnancy test: WOCP will have a serum pregnancy test no more than 7 days prior to the first trial treatment or no more than 14 days (with a confirmatory urine pregnancy test within 7 days prior to the first trial treatment). This test will be repeated if there is any likelihood that a female patient may be pregnant (not required for women who have undergone, and have documentation of a hysterectomy).

5.5 Post Trial Provision of Care

Patients will receive post E-trial treatment for their cancer at the investigator's discretion. Any ongoing SAEs at the time of Database lock must be followed up until resolution. All SAEs (see Section 7.1.2.3) will be reported indefinitely regardless of the relationship to the study drug. See Section 7.2.4 for further details on collection of AEs post-study). No other data will be collected after E-trial end for these patients except for patients who subsequently receive Continued Access to bevacizumab via a PTAP. See safety reporting requirements from SRD-0120796 Global: Post-Trial Access Safety Data Exchange Agreement Template.

5.6 Continued Access to Bevacizumab

The Sponsor will offer continued access to Roche IMP (bevacizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below. The option of Continued Access will be country-specific and will depend on the bevacizumab marketing authorisation for given indications and/or local regulations.

A patient will be eligible to receive Roche IMP (bevacizumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive Roche IMP (bevacizumab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for cancer.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for cancer.
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

6. DOSING AND SCHEDULING

For "Pharmaceutical Particulars of Bevacizumab" see Appendix 2.

6.1 Dose and Schedule of Bevacizumab

The dose of 2.5 or 5 mg/kg/week of bevacizumab will be administered intravenously every 2 (+/- 3 days) or 3 weeks (+/- 5 days). The dose and schedule of bevacizumab will be the same as during treatment in the P-trial and must be continued for the duration of the E-trial in any given patient. Weight at the start of the E-trial (baseline weight) will be used to calculate the starting dose in this E-trial.

Treatment with bevacizumab will continue until disease progression or unacceptable toxicity (see also following sections), withdrawal of consent, death, or transition to another option for treatment with bevacizumab (e.g. licensed product or PTAP), (whichever occurs first).

At each cycle, bevacizumab must be administered before concurrent anti-cancer therapy treatment at the same clinic visit, for oral agents the patients are allowed to follow their normal schedule. Rationale for dose selection is given in Section 3.1.2. The first dose of bevacizumab will be administered in a similar way to treatment at the end of the P-trial. If this is not known, the investigator should follow the standard instructions for first time administration (see Appendix 2).

6.1.1 Dose modifications and delays

Bevacizumab dose will not be reduced for reasons other than a >10% change (loss or gain) in weight from baseline (at rollover assessment). Missed doses will not be administered subsequently. Treatment should not be omitted for more than 42 days unless because of planned surgery requiring bevacizumab interruption during P-trial. Bevacizumab can be restarted only after Sponsor's medical monitor approval.

Baseline body weight is used to calculate required doses. For bevacizumab, dose adjustments for body weight changes are not required unless the patient's body weight changes by at least 10% from baseline.

Bevacizumab treatment can be continued as single agent in the case the concurrent anti-cancer therapy is stopped permanently. If bevacizumab is stopped permanently, the patients should have their final study visit 30 days (+/- 3 days) after their last dose.

In cases of toxicity, please refer to the current version of the bevacizumab IB for guidance.

6.1.1.1 General Remarks on Grade 3 or 4 Bevacizumab-Related Events

If the first occurrence was during treatment in the P-trial, this should be counted. Please see also Section 5.1 for guidance of reporting those AEs.

First occurrence:

- Hold bevacizumab until toxicity has resolved to baseline or at least improved to CTCAE grade ≤ 1 (with exception of the special cases outlined below).

Second occurrence upon reintroduction:

- If grade 3 toxicity recurs upon reintroduction of bevacizumab, the investigator should consider the individual benefit versus the risk of continuing the bevacizumab therapy. If the event occurs again upon a second reintroduction of bevacizumab, bevacizumab treatment should be permanently discontinued.
- If a second episode of grade 4 toxicity occurs, permanently discontinue treatment.

In any patient who experiences one of the events listed below, bevacizumab therapy should be held or permanently discontinued as stated in Sections 6.1.1.2-6.1.1.8.

- RPLS, see 6.1.1.2
- Grade 1-4 Gastro-intestinal perforation and ≥ 2 fistula, see 6.1.1.3
- Major surgery and wound healing complications, see 6.1.1.4
- Grade 4 Hypertension (hypertensive crisis), see 6.1.1.5.
- Grade 4 Proteinuria (nephrotic syndrome), see 6.1.1.6.
- Grade 3/4 Venous thrombosis/embolism (VTE), see 6.1.1.7
- Grade 1-4 Arterial thrombosis/embolism (ATE), see 6.1.1.7
- Grade 3/4 Haemorrhagic events, see 6.1.1.8
- Grade 3/4 Left ventricular dysfunction (CHF), see 6.1.1.9

6.1.1.2 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known. Adequate brain imaging using MRI must be performed as a follow-up measurement for patients with RPLS.

6.1.1.3 Gastrointestinal Perforation and Fistula

Bevacizumab has been associated with serious cases of gastrointestinal perforation in patients with metastatic carcinoma of the colon or rectum. The presentation of these events has varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. The common feature among these cases was intra-abdominal inflammation,

either from gastric ulcer disease, tumour necrosis, diverticulitis or chemotherapy-associated colitis. Nevertheless, a causal association of an intra-abdominal inflammatory process and gastrointestinal perforation to treatment with bevacizumab has not been established. However, caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab.

Gastrointestinal perforations have been reported in clinical studies with an incidence of < 1% in patients with mBC or non-squamous NSCLC, and up to 2% in mCRC patients. Fatal outcome was reported in approximately one-third of serious cases of gastrointestinal perforations, which represents between 0.2% - 1% of all bevacizumab treated patients.

Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the gastrointestinal tract are common in patients with mCRC, but uncommon or rare in other indications. Fistulae that involve areas of the body other than the gastrointestinal tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly in patients receiving bevacizumab in clinical studies and post-marketing reports.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistula or any grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

6.1.1.4 Surgical procedures and wound healing complications

Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld for an interval of at least two half lives (approximately six weeks) before conducting major elective surgery. Emergency surgery should be performed as appropriate without delay after a careful risk benefit assessment.

Continuation of trial treatment in patients who have had bevacizumab treatment delayed for more than 2 treatment cycles due to surgical procedures or wound healing must also be discussed with the Roche medical monitor or his/her designee.

6.1.1.5 Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent.

Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy.

Blood pressure should to be assessed before each bevacizumab administration. In most cases hypertension is controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient.

Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

6.1.1.6 Proteinuria

In clinical studies, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria (nephrotic syndrome) was uncommon in patients with bevacizumab.

Proteinuria, reported as an AE with bevacizumab treatment has ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome with the great majority as Grade 1 proteinuria. The proteinuria seen in bevacizumab clinical trials was not associated with renal dysfunction and rarely required permanent discontinuation of bevacizumab therapy. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab.

Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during bevacizumab treatment. Proteinuria should be assessed within 48 hours before each bevacizumab treatment by dipstick method unless assessed by 24-hour urine collection.

An algorithm for the appropriate management following a positive dipstick result with corresponding bevacizumab treatment management guidance is provided below.

Table 3: Bevacizumab treatment management for proteinuria

NCI CTC-AE v3.0 or v4.0	Urinalysis	Treatment action
Grade 1	1+ proteinuria urinary protein < 1.0 g/24 hrs	No bevacizumab dose modifications
Grade 2	2+ proteinuria urinary protein 1.0 - 3.4 g/24 hrs	Suspend bevacizumab for urine protein level ≥ 2 g/24 hrs and resume when proteinuria is < 2 g/24 hours For 2+ dipstick: may administer bevacizumab; obtain 24-hour urine prior to next bevacizumab dose For 3+ dipstick: obtain 24-hour urine prior to bevacizumab administration
Grade 3	Urinary protein ≥ 3.5 g/24 hrs	Suspend bevacizumab. Resume when proteinuria is < 2 g/24 hrs, as determined by 24-hrs urine collection < 2.0 g.
Nephrotic syndrome		Discontinue bevacizumab permanently.

6.1.1.7 Thrombosis/Embolism

Arterial thrombosis/embolism

Bevacizumab should be discontinued in patients who develop ATE (any grade).

A history of ATE or age greater than 65 years has been associated with an increased risk of ATE during bevacizumab therapy. Patients receiving bevacizumab plus chemotherapy with a history of ATE and age greater than 65 years have a higher risk. Caution should be taken when treating these patients with bevacizumab.

Venous thrombosis/embolism

Grade 3 VTE: Hold study drug treatment for ≥ 3 weeks. Bevacizumab may be resumed during the period of therapeutic-dose anticoagulant therapy if the patient is on a stable level of anticoagulation prior to restarting study drug treatment:

- Patients on heparin treatment should have an aPTT between 1.5-2.5 x ULN (or patient value before starting heparin treatment)
- Patients on full dose low molecular weight heparins should receive the appropriate dose based on the weight of the patient according to package insert.
- Patients on coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1-4 days apart.

Recurrent grade 3 VTE: discontinue the patient from study drug.

Bevacizumab should be discontinued in patients with life-threatening (Grade 4) pulmonary embolism.

6.1.1.8 Haemorrhage

An increased incidence of bleeding events was observed in patients treated with bevacizumab as compared to control treatment arms. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage.

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomized clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding of any grade.

Pulmonary haemorrhage/haemoptysis has been observed across indications. Serious and in some cases fatal pulmonary haemorrhage/haemoptysis has been observed in patients with advanced or recurrent NSCLC treated with bevacizumab. Patients with a history of grade ≥2 haemoptysis, or with history or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding, should be excluded from participation in this trial (see Section 4.3).

Bevacizumab should be permanently discontinued for:

- Any grade of CNS bleeding: permanently discontinue bevacizumab. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding of any grade.
- Grade ≥ 2 haemoptysis.
- Grade 3 or 4 bleeding of any other kind.

If hemorrhagic complications occur in patients on full dose anticoagulation treatment, permanently discontinue bevacizumab treatment and follow guidelines of the institution. Standard procedures such as antagonisation with protamine or vitamin K, infusion of vitamin K dependent factors or insertion of a vena cava filter should be considered dependent on the severity of the bleeding and thrombotic events and the organ affected.

6.1.1.9 Congestive Heart Failure (CHF)

Events consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF, requiring treatment or hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.
Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, concomitant cardiotoxic therapy or congestive heart failure with bevacizumab.
Bevacizumab should be permanently discontinued in patients with ≥ grade 3 CHF.

6.1.1.10 Dose interruption due to infusion-associated reactions

For administration guidelines, see Appendix 2.

- In case of an infusion-related reaction a 90-minute infusion or up to 24 hours later, the next infusion must be administered over at least 120 minutes. If the 120 minute infusion is well tolerated, the next infusion and all subsequent infusions may be delivered over 120 minutes.
- If any infusion-related reaction occurs during a 60 minute infusion or up to 24 hours later, the next infusion must be administered over 90 minutes. If the 90 minute infusion is well tolerated, the next infusion and all subsequent infusions may be delivered over 90 minutes.
- If an infusion-related reaction occurs during a 30-minute infusion or up to 24 hours later, all subsequent infusions may be delivered over 60 minutes or longer.

6.2 Formulation, Packaging, Labelling, Preparation and Administration of Bevacizumab

For details regarding the formulation, packaging, labelling, preparation and administration of bevacizumab, see Appendix 2.

6.3 Dose and Schedule of other IMP Treatment

Not applicable

6.4 Dose and Schedule of non-IMP Treatment

Anti-cancer therapy given as IMP (supplied by the Sponsor in the P-trial "P-trial IMP") together with bevacizumab in the P-trial will be administered as per instructions in the P-trial, but classified as **Non-IMP** in this E-trial. The Sponsor will continue to provide those anti-cancer therapies until bevacizumab is permanently discontinued. If bevacizumab is permanently stopped, other P-trial IMP treatment given until progression has to be permanently stopped.

Management (i.e. handling, storage, administration, accountability and disposal) of those anti-cancer drugs will be in accordance with instruction defined in the P-trial.

Investigators can prescribe non-IMP in accordance with their local label and standard of care (see also Section 4.4). Their use will be in accordance with the relevant local guidelines and SPC. Management (i.e. handling, storage, administration and disposal) will be in accordance with GCP and local guidelines.

- Use commercial stock in keeping with the usual practice of the institution. They will not be provided by the Sponsor.
- There are no special accountability arrangements.

6.5 Blinding and Unblinding

Not applicable; this trial is open-label.

6.6 Accountability of Bevacizumab and Assessment of Compliance

6.6.1 Accountability

A pre-printed Drug Dispensing Log will be provided by the Sponsor.

The investigator is responsible for the control of drug under investigation. Adequate records for the receipts (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the trial drug must be maintained. Accountability and patient compliance will be assessed by maintaining adequate drug storage, drug dispensing, drug inventory, and drug destruction records.

Accurate records must be kept for each trial drug vial provided by the Sponsor. These records must contain the following information:

- documentation of drug shipments received from the sponsor (date received, quantity and batch identity)
- documentation of continuous drug storage within 2-8° C (bevacizumab) or other appropriate temperature range
- disposition of unused trial drug not administered to a patient

The Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the patient to whom the trial drug was dispensed

- the date(s), quantity and batch identity of the trial drug administered *to* the patient

This inventory must be available for inspection by the Monitor at every visit. All supplies, including partially used or empty containers and copies of the dispensing and inventory logs, must be returned to the Monitor before the end of the trial, unless alternate destruction has been authorized by the Sponsor, or required by local or institutional regulations.

Any temperature excursions outside of appropriate range must be quarantined from the usable stock. The event should be recorded on the temperature excursion log, and sent to sponsor for review. Sponsor will inform the site if excursion was within limits and can be returned to usable stock.

6.6.2 Assessment of Compliance

Patient compliance will be assessed by maintaining adequate trial drug dispensing records. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator and the Sponsor.

6.7 Destruction of Bevacizumab

Local or institutional regulations may require immediate destruction of used trial drug. In these cases, it may be acceptable for investigational site staff to destroy dispensed trial drug before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the sponsor at trial start up before destruction.

Written documentation of destruction must contain the following:

– Identity (batch numbers and dispensed patient numbers) of trial drug(s) destroyed

– Quantity per type (100mg and 400mg vials) of trial drug(s) destroyed

– Date of destruction (date discarded in designated hazardous container for destruction)

– Method of destruction (the site must provide the sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)

– Name and signature of responsible person who discarded the trial drug in a hazardous container for destruction.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Adverse event reporting period

Investigators will seek information on adverse events at each patient contact. All adverse events, 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 study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 7.2.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.5.

7.1.2 Clinical adverse events

This trial will comply with all local regulatory requirements. According to the ICH guideline for GCP, 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 Section 7.1.2.7 and Section 7.1.2.8 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)

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event 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?"

7.1.2.1 Intensity

Intensity of all AEs will be graded according to the NCI CTC-AE on a five-point scale (Grade 1 to 5). Version 4.0 is recommended. All AEs and SAEs will be reported in detail on the eCRF.

Table 4: Grading of adverse events not listed on the NCI CTC-AE v4.0

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life threatening / disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

7.1.2.2 Drug – adverse event relationship

The causality relationship of trial drug to the AE will be assessed by the investigator as either:

Yes or No

If there is a reasonable suspected causal relationship to the trial drug, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**.

The following criteria should be considered in order to assess the relationship as **Yes:**

– Reasonable temporal association with drug administration

– It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of treatment administered to the patient.

– Known response pattern to suspected drug

– Disappears or decreases on cessation

– Reappears on rechallenge

The following criteria should be considered in order to assess the relationship as **No**:

– It does not follow a reasonable temporal sequence from administration of the drug.

– It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of treatment administered to the patient.

– It does not follow a known pattern of response to the suspected drug.

– It does not reappear or worsen when the drug is readministered.

7.1.2.3 Serious adverse events (immediately reportable to the Sponsor)

A SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. These must be reported to The Sponsor immediately (at least within 24 hours of the investigator becoming aware of the event) through the eSAE page in the eCRF. It is any AE that at any point fulfils at least one of the following criteria:

– is fatal (results in death; NOTE: death is an outcome, not an event)

– is Life-Threatening (NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).

– required in-patient hospitalization or prolongation of existing hospitalization;

– results in persistent or significant disability/incapacity;

– is a congenital anomaly/birth defect;

– is medically significant or requires intervention to prevent one or other of the outcomes listed above.

****The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably**.

The trial will comply with all local regulatory requirements and adhere to the full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2**.

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 7.1.2.1; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.2.2 for reporting instructions).

7.1.2.4 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 7.1.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 7.2.2). This includes death attributed to progression of cancer.

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 to progression of cancer, “cancer 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 7.2.4.

7.1.2.5 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 7.1.2.3), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- 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 experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

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

7.1.2.6 Adverse Events of Special Interest

Some AEs have been reported as associated with the use of bevacizumab treatment. Further details are provided in the IB. Considering the extensive clinical use acquired with bevacizumab across its indications in over 1,000,000 patients, only the most clinically relevant will be considered as AESIs for this trial, and will undergo specific reporting.

- Hypertension
- RPLS
- Proteinuria
- Haemorrhage, with a focus on haemoptysis and CNS bleeding
- Arterial and venous thromboembolic events
- Wound healing complications
- Gastro-intestinal perforation
- Fistulae
- CHF

7.1.2.7 Progression of underlying malignancy

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST v1.1 criteria (recommended), or other criteria as determined by the P-trial protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under trial.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumour measurements. Or, the PD is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an AE being due only to the disease under trial, it should be reported as an AE or SAE.

7.1.2.8 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 eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When

recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

7.1.3 Treatment and follow-up of adverse events

7.1.3.1 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 until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 7.2.3.

After the last bevacizumab infusion, continue to report AEs as follows:

The final outcome of each AE must be recorded on the eCRF (prior to database lock).

Ongoing SAEs have to be followed and new information needs reporting using the eCRF (prior to database lock) and as agreed with the study monitor thereafter – all SAEs have to be reported **after study end** (see Section 5.5 Post Trial Provision).

7.1.3.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

7.1.4 Laboratory Test Abnormalities

Local laboratories will be used for all laboratory tests, for details see Section 5.4.1.

Laboratory test value abnormalities should only be recorded in the AE section of the eCRF as AEs, if they are considered clinically significant, as defined below.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions should be recorded as a single diagnosis on the AE page in the eCRF:

– Accompanied by clinical signs and symptoms

– Leading to a change in trial drug (e.g. dose modification, interruption or permanent discontinuation)

– Requiring a change in concomitant treatment (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication or treatment)

– Is clinically significant in the investigator's judgment

Note: For oncology trials, certain abnormal values may not qualify as adverse events.

Any laboratory result abnormality fulfilling the criteria for a SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

It is the investigator'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 adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether 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 adverse event. 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 7.1.4 for details on recording persistent adverse events).

7.1.4.1 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × 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, Investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
- Treatment-emergent ALT or AST > 3 × 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 and reported to the Sponsor immediately (i.e. no more than 24 hours after learning of the event), either as an SAE or a non-serious AESIs (see Section 7.2.1).

7.1.5 Follow-up of abnormal laboratory test values

In the event of a medically significant, unexplained abnormal laboratory test value, the test should be repeated and followed until it has returned to the normal range, baseline value and/or an adequate explanation of the abnormality is found. For events recorded in the eCRF according to Section 7.1.4 for which a clear explanation is established it should be recorded on the eCRF.

7.1.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event 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 investigator's judgment

It is the investigator'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 adverse event.

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 on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 7.2.1.2 for details on recording persistent adverse events).

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 7.1.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 7.2.2).

7.2 Handling of Safety Parameters

7.2.1 Reporting of adverse events

All AEs and SAEs, regardless of the relationship to trial drug, will be recorded in the eCRF. AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to trial drug, action taken with the trial drug, outcome, and whether the AE is classified as serious.

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.

AEs (either related to trial specific procedures or otherwise) experienced after the patient has signed the Informed Consent form but before they have received trial treatment, should be recorded for the P-trial, as per guidance on AE reporting for the P-trial.

Progression of underlying malignancy see Section 7.1.2.7 **is not to be reported as an (S)AE**

Signs and symptoms of the underlying cancer should only be reported if:

- Newly emergent (i.e. not present at baseline as per the P-trial) and the association with the underlying malignancy and old/new metastatic lesions is unclear and/or
- The investigator attributed deterioration of the underlying malignancy's signs and symptoms directly to the trial drug

Should there be any uncertainty regarding the attribution of the underlying cancer to the AE, it should be reported as an AE or a SAE accordingly.

A medical condition (e.g. elevated laboratory value) already existent before first treatment should not be reported as an AE unless the condition worsens.

If the AE increases in severity, the investigator must re-assess the event to determine if an AE must be reported (determine attribution).

If the AE resolves and then recurs, the investigator should re-assess the event in case the second AE occurred more than 3 days after the end date of the preceding AE. In case of a shorter interval, the AE should not be reported separately.

7.2.1.1 Adverse Events That Are Secondary to Other Events

In general, adverse events 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 adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event 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 consequent 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 adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

7.2.1.2 Persistent or Recurrent Adverse Events

A persistent adverse event 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 adverse event 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 after learning that the event became serious; see Section 7.2.2 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 adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

7.2.2 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 7.1.2.3)
- Adverse events of special interest (defined in Section 7.1.2.6)
- Pregnancies (see Section 7.2.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events 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.

7.2.2.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide

medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

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 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., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning 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., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 28 days after the final dose of study treatment are provided in Section 5.5.

7.2.3 Pregnancy

Bevacizumab has been shown to be embryo-toxic and teratogenic when administered to rabbits. Angiogenesis has been shown to be critically important to foetal development. The inhibition of angiogenesis following administration of bevacizumab could result in an adverse outcome of pregnancy. Therefore, bevacizumab should not be used during pregnancy. Female patients with childbearing potential or amenorrhoeic for < 24 months must have a negative serum pregnancy test (see Section 5.4.1) prior to starting the trial and agree to use an effective method of contraception during the trial, and for a period of 6 months following the last administration of bevacizumab.

A female patient must be instructed to stop taking the trial drug and immediately inform the investigator if she becomes pregnant during the trial or within 6 months after the final

dose of study drug. The investigator must report all pregnancies within 24 hours of becoming aware of the pregnancy to the sponsor. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 6 months after the completion of bevacizumab must also be reported to the investigator.

Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel 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 serious adverse events 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 Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Male patients should not father a baby whilst on trial treatment. Fertile male patients participating in the trial must practice an acceptable method of effective birth control while on treatment and for 6 months following the last administration of bevacizumab. Pregnancy occurring in the partner of a male patient participating in the trial should be reported to the investigator and the Sponsor. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

7.2.3.1 Abortions

Any spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e. no more than 24 hours after learning of the event; see Section 7.2.2).

7.2.3.2 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male 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. no more than 24 hours after learning of the event; see Section 7.2.2).

7.2.4 Post-Study Adverse Events

At the safety follow-up visit, the Investigator should instruct each patient to report to the Investigator any subsequent adverse events.

After study closure, the Sponsor should be notified if the investigator becomes aware of any death, SAE and AESI occurring at any time after a patient has discontinued study participation regardless of the relationship to the study drug treatment.

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.

The investigator is not required to actively monitor patients after the study has ended.

7.3 Warnings and Precautions

7.3.1 Warnings and precautions relating to bevacizumab

No evidence available at the time of the approval of this trial protocol indicated that special warnings or precautions were appropriate with regards to bevacizumab treatment, other than those noted in the current version of the IB.

The evaluation is based on information from clinical studies with bevacizumab as well as from the use of the marketed product, including compassionate use and expanded access programs (as described in the Investigator's Brochure). AEs that have been recognised in the core data sheet as adverse drug reactions, for which guidance is provided in previous sections (6.1.1.2 -6.1.1.8) are:

- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): 6.1.1.2
- Gastrointestinal Perforation: 6.1.1.3
- Wound Healing: 6.1.1.4
- Hypertension: 6.1.1.5
- Proteinuria: 6.1.1.6
- Thrombosis/Embolism: 6.1.1.7
- Haemorrhage: 6.1.1.8
- Congestive heart failure: see below

Congestive Heart Failure/Cardiomyopathy: In a phase III controlled clinical trial of metastatic breast cancer, CHF/cardiomyopathy was reported in 3% of the bevacizumab-treated patients compared with 1% in the controlled group. These events varied in severity from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF requiring hospitalization and treatment. All the bevacizumab-treated patients were previously treated with anthracyclines (doxorubicin cumulative dose range 240–360 mg/m^2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.

There was no information on patients with pre-existing CHF (New York Heart Association (NYHA) II-IV) at the time of initiating the therapy, as these patients were excluded from

studies. In patients with metastatic cancer of the colon or rectum, including study AVF2192g, there was no significant increase in the incidence of CHF in bevacizumab-treated patients.

Elderly Patients: Data from 5 randomised clinical trials showed that age > 65 years was associated with an increased risk of developing ATE including cerebrovascular accidents (CVAs), TIAs and MIs when treated with bevacizumab. No increased incidence of bevacizumab-related events including gastrointestinal perforation, wound healing complications, hypertension, proteinuria and haemorrhage was observed in elderly patients (> 65 years) with metastatic cancer of the colon or rectum receiving bevacizumab compared to those aged ≤ 65 years treated with bevacizumab.

7.3.2 Warnings and precautions relating to anti-cancer therapy classified as non-IMP, if applicable

Please refer to the manufacturer's prescribing information or the information provided for the P-trial.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary variables

8.1.1 Primary Variables

The primary objective of this E-trial is to evaluate the continuation of bevacizumab therapy as single agent or in combination with an anti-cancer drug to cancer patients who were previously enrolled in a Roche/Genentech sponsored bevacizumab P-trial and who derived benefit from the therapy administered in the P-trial.

The summary will be presented for the safety population that will include all enrolled patients in the E-trial who received at least one dose of bevacizumab.

The primary variables will be based on following safety endpoints: AE grade ≥3 related to bevacizumab, SAEs and cause of death.

8.2 Hypothesis Testing

No formal statistical hypothesis testing is planned.

8.2.1 Types of Analyses

8.2.1.1 Efficacy Analysis

Progression free survival and overall survival will be summarised using Kaplan-Meier approach. Data may be pooled with the appropriate P-trial database to analyse scientific questions of interest. More details will be written in the Statistical Analysis Plan (SAP).

8.2.1.2 Interim Analysis

No formal efficacy interim analyses are planned for this E-trial.

However, there will be a safety review of data approximately 3 years after the enrolment of the first patient in this E-trial. An abbreviated study report will summarise safety results for patients who have completed or discontinued from the treatment or died, whichever occurs first.

8.2.2 Safety Analysis

Descriptive statistics will be presented for cumulative bevacizumab doses and duration of exposure. The number and percentage of patients discontinued from bevacizumab with corresponding reason for discontinuation will be summarized and listed.

The incidence, type and severity of AEs grade ≥3 related to bevacizumab will be summarized according to the primary System organ class (SOC) and within each SOC, by MedDRA preferred term. AESI as defined in the Section 6.1.1, and SAEs will be analysed in a similar way to AEs grade ≥3 related to bevacizumab. Time to onset of AESIs may also be estimated and presented graphically.

Cause of death will be summarised by frequency tables and listed.

All summaries will be presented for the safety population as defined above.

Concurrent anti-cancer therapies will be summarized for the safety population and presented by frequency tables and percentages.

8.2.3 Other Analyses

Patient characteristics, such as demographics, will be also summarised for the safety population.

8.2.3.1 Subgroup Analyses

Exploratory subgroup analyses may be performed e.g. by indication (cancer type). Details will be specified in the SAP.

No adjustment for multiplicity within subgroup comparison will be applied.

8.3 Sample Size

This is an E-trial. Patients will be enrolled from qualifying P-trials. The formal estimation of sample size is not possible.

The table below presents a few possible scenarios for percentage of AEs grade ≥3 related to bevacizumab with corresponding 95% Clopper-Pearson exact confidence intervals

Table 5: Scenarios for Percentage and Number of Patients with AEs grade ≥3 related to bevacizumab and corresponding Confidence Intervals

Sample Size	Percentage and Number of Patients with AEs grade ≥3 related to bevacizumab	95% Clopper Pearson exact confidence interval
50	10% (5 patients)	3% - 22%
50	20% (10 patients)	10% - 34%
100	10% (10 patients)	5% - 18%

100	20% (20 patients)	13% - 29%

It is difficult to estimate at this stage how many patients will be enrolled in this study. Assuming a sample size of 100 patients then the percentage of patients with at least one AEs grade ≥3 related to bevacizumab could be estimated to be within 5%-18% with a probability of 95% and assuming observed rate of patients with at least one AEs grade ≥ 3 of 10%.

The sample size was estimated using SAS Version 9.2 and nQuery Version 6.

9. DATA QUALITY ASSURANCE

The overall procedures for quality assurance of clinical trial data are described in the Sponsor Standard Operational Procedures.

Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the investigator's records by the trial monitor (source document verification), and the maintenance of a drug–dispensing log by the investigator.

Data for this trial will be recorded via an EDC system using eCRFs. Patient data will be transcribed by the site from the paper source documents onto the eCRF. (In no case is the eCRF to be considered as source data for this trial.)

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Sponsor database will verify the data and discrepancy reports will be generated accordingly and transferred electronically to the eCRF at the site for resolution by the investigator.

The result of the analysis must not be released with individual identification of the patient until the database is closed.

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.

eCRFs 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.

9.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

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 GCP 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.

10. TRIAL COMMITTEES

No Roche external trial committees are planned.

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PART II: ETHICS AND GENERAL TRIAL ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline [January 1997] or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the USA or under US IND, the investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

In other countries where "Guideline for Good Clinical Practice" exist Roche and the investigators will strictly ensure adherence to the stated provisions.

12.2 Informed Consent

Written Informed Consent from Patients:

12.2.1 Main study Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator [if acceptable by local regulations], to obtain signed informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The Case Report Forms (CRFs) for this study contain a section for documenting patient informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

For the patient not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

12.2.2 Death or Loss of Competence of Participant who has donated a specimen(s) that is stored in the RCR

For patients giving specimen during the P-trial:

In case the Informed Consent Form and/or the Study Protocol do not provide any specific provisions for death or loss of competence, specimen and data will continue to be used as part of RCR research.

In the event of the death of a participant of a Roche Clinical Trial or Experimental Medicine Research study or if a participant is legally incompetent at the time of the specimen and data procurement, or becomes legally incompetent thereafter, applicable provisions as stated for such situations in the respective Informed Consent Form and/or the Study Protocol shall become effective and be followed accordingly.

Additional procurement of assent from legally incompetent persons and minors shall take place according to local laws and international best practice, as it applies to the specific case.

12.3 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 13).

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.

12.4 Financial Disclosure

The investigator(s) will provide the Sponsor with sufficient accurate financial information (PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the sponsor and the investigator (investigator representative[s] in the case of a multicenter trial, i.e. the Steering Committee). Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the International Medical Leader and Biostatistician.

All protocol modifications must be submitted to the appropriate IEC or IRB for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change[s] involves only logistical or administrative aspects of the trial (e.g. change in monitor[s], change of telephone number[s]).

14. CONDITIONS FOR TERMINATING THE TRIAL

Both the Sponsor and the investigator reserve the right to terminate the trial at any time. Should this be necessary, both parties will arrange the procedures on an individual trial basis after review and consultation. In terminating the trial, Roche and the investigator will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IRB/IEC and Regulatory Agencies should be informed accordingly.

15. TRIAL DOCUMENTATION, eCRFs AND RECORD KEEPING

15.1 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).

15.2 Investigator's Files / Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. These documents should be classified into two different separate categories [1] Investigator's Trial File, and [2] patient clinical source documents.

The Investigator's Trial File will contain the protocol/amendments, Case Report and Query Forms, IEC/IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition at the end of the trial the investigator will receive the patient data, which includes an audit trail containing a complete record of all

changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's Trial File.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, CT, MRI, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrolment logs. The investigator must keep these two categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the trial. After that period of time the documents may be destroyed, subject to local regulations.

Should the investigator wish to assign the trial records to another party or move them to another location, Roche must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

ICH GCP guidelines require that investigators maintain information in the trial patient's records which corroborate data collected on the eCRF(s). Completed eCRF will be maintained by Roche.

15.3 Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the trial documentation or clinic records. This is particularly important when eCRFs are incoherent or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected.

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 15.1.

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.

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.

15.4 Audits and Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Roche or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

15.5 Electronic Case Report Forms

Data for this trial might be captured via an EDC system by using an online eCRF. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each patient enrolled, an eCRF must be completed and electronically signed by the Principal investigator from the trial staff. This also applies to records for those patients who fail to complete the trial (even during a pre-enrolment screening period if an eCRF was initiated). If a patient withdraws from the trial, the reason must be noted on the eCRF. If a patient is withdrawn from the trial because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

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.

16. MONITORING THE TRIAL

It is understood that the responsible Roche Monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (eCRFs, source notes, and other pertinent data) provided that patient confidentiality is maintained in accord with local requirements.

It will be the Monitor's responsibility to inspect the eCRFs and patients study files/source notes at regular intervals throughout the trial, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The Monitor should have access to laboratory test reports and other patient records needed to verify the entries on the eCRF. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrolment log showing codes, names and addresses. The investigator should maintain documents not for submission to Roche, e.g., patients' written consent forms, in strict confidence.

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.

18. CLINICAL STUDY REPORT (CSR)

A clinical study report will be written and a summary or a full report distributed to Health Authorities as required by applicable regulatory requirements.

19. PUBLICATION 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 of the U.S. National Institutes of Health and the European Medicines Agency, 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, and redacted clinical study reports and other summary reports will be provided upon request (see Section 17 for more details). 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.

20. APPENDICES

Appendix 1 : National Cancer Institute-Common Toxicity Criteria for Adverse Events v4.0

The Common Terminology Criteria for Adverse Events v4.0, updated June 14, 2010, is available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix 2: Pharmaceutical Particulars, Preparation and Administration of Bevacizumab

1. List of Excipients

- Trehalose dihydrate
- Sodium phosphate
- Polysorbate 20
- Water for injections

2. Incompatibilities

No incompatibilities between bevacizumab and polyvinyl chloride or polyolefin bags have been observed. A concentration-dependent degradation profile of bevacizumab was observed when diluted with dextrose solutions (5%).

3. Stability

Bevacizumab should not be used after the retest date shown on the pack.

4. Special Remarks

4.1 Special Precautions for Storage

Bevacizumab is supplied as a clear to slightly opalescent, colourless to pale brown, sterile liquid for intravenous (i.v.) infusion in single-use vials which are preservative-free.

Bevacizumab will be supplied in 5 mL glass vials with a 4 mL fill (100 mg, 25 mg/mL) and/or in 20 mL glass vials with a 16 mL fill (400 mg, 25 mg/mL). The formulation contains sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI) in addition to bevacizumab active ingredient.

VIALS ARE FOR SINGLE USE ONLY. Vials used for one patient may not be used for any other patient. Vials should not be used after the re-test date shown on the pack.

The labelling of bevacizumab will be in accordance with all local legal requirements and conducted according to Good Manufacturing Practice.

Store vials in a refrigerator at 2°C-8°C (36°F -46°F). Keep vial in the outer carton due to light sensitivity. **DO NOT FREEZE. DO NOT SHAKE. Protect from light.**

Bevacizumab does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C (36°F-86°F) in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (36°F-46°F), unless dilution has taken place in controlled and validated aseptic conditions.

4.2 Instructions for Use, Handling and Disposal

Bevacizumab should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab for a dose of 7.5 or 15 mg/kg of body weight and dilute in a total volume of 100 mL of 0.9% sodium chloride injection, United States Pharmacopeia (USP). **Bevacizumab infusions should not be administered or mixed with dextrose or glucose solutions.** In case of administering a total dose exceeding 1000 mg, dilute the calculated dose of bevacizumab with a sufficient amount of 0.9% sodium chloride injection to keep final concentration between 1.4 mg/mL and 16.5 mg/mL. Keep 100 mL as the minimal volume to administer and limit the infusion volume as much as possible. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. **Diluted bevacizumab should be used within 8 hours (USP).**

5. Administration

Administration will be as a continuous i.v. infusion. Anaphylaxis precautions should be observed during trial drug administration.

The first dose of bevacizumab will be administered over 90 minutes. If the first infusion is well tolerated (without infusion-related reaction e.g. fever and/or chills), the 2nd dose will be administered over 60 minutes. If the 2nd dose is also well tolerated without an infusion reaction, all subsequent doses will be administered over 30 minutes).

- In case of an infusion-related reaction during the first cycle (during the 90-minute infusion or up to 24 hours later), the next infusion must be administered over at least 120 minutes. If the 120 minute infusion is well tolerated, the next infusion and all subsequent infusions may be delivered over 120 minutes.
- If any infusion-related reaction occur during the second cycle (during the 60 minute infusion or up to 24 hours later), the next infusion must be administered over 90 minutes. If the 90 minute infusion is well tolerated, the next infusion and all subsequent infusions may be delivered over 90 minutes.
- If an infusion-related reaction occurs during a 30-minute infusion or up to 24 hours later, all subsequent infusions may be delivered over 60 minutes or longer.

A rate-regulating device should be used for all trial drug infusions. When the trial drug i.v. bag is empty, 50 mL of 0.9% sodium chloride solution, USP?, will be added to the i.v. bag or an additional bag will be hung, and the infusion will be continued for a volume equal to that of the tubing to ensure complete delivery of the trial drug. The total infusion time, therefore, should always be either 90, 60, or 30 minutes. If more saline is infused, the extent of saline infusion does not factor into the trial drug infusion time.

Should extravasation of the trial drug infusion occur, the following steps should be taken:

- Discontinue the infusion. Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent. If a significant volume of the trial drug infusion remains, restart the infusion at a more proximal site in the same limb or on the

other side. Treat the infiltration according to institutional guidelines for infiltration of a non-caustic agent.

In the event of a suspected anaphylactic reaction during trial drug infusion:

- Stop the trial drug infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of trial drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer antihistamines, corticosteroids, epinephrine, or other medications as required.
- Continue to observe the patient, document observations and administer further treatment as required.

The above events should be reported as AEs.