STATISTICAL ANALYSIS PLAN

1302.3 INVICTAN®-3

A SINGLE ARM, OPEN-LABEL, MULTICENTER, MULTINATIONAL, SAFETY AND EFFICACY PHASE IIIB TRIAL OF BI 695502 PLUS MFOLFOX6 IN SUBJECTS WITH PREVIOUSLY UNTREATED METASTATIC COLORECTAL CANCER

AUTHOR:

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V5.0 (Dated 13DEC2018) for Protocol 1302.3.

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OUTPUT TEMPLATES SIGNATURE PAGE

Please refer to Output Templates V4.0 (Dated 07NOV2018) for Protocol 1302.3 INVICTAN®-3.

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	23MAR2017		Not Applicable – First Version
1.0	24APR2017		Update based on sponsor comments received on 1302.5 dry run 1.
1.1	08JUN2017		Update based on sponsor comments received on TSAP 1302.5 and comments received on dry run 1
2.0	04AUG2017		Update based on sponsor comments after reviewing TSAP version 1.1 and comments received on 1302.5 dry run 2.
3.0	08JUN2018		Update based on the protocol amendments version 6.0 - Switch of all subjects on trial medication to Avastin®, Update to Appendix 7 based on review by medical advisor, Inclusion of applicable comments received on TSAP 1302.5 version 4.0.
4.0	07NOV2018		Update based on comments received from dry run TFL delivery
5.0	13DEC2018		Update definition of dose increase and dose decrease in section 13 and update appendix 7.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5FU	5-fluorouracil
30-day FU	Follow-up visit 30 days after the last trial drug administration
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BIcMQ	Boehringer Ingelheim-customised MedDRA query
BLQ	Below the lower Limit of Quantification
BMI	Body Mass Index
BSA	Body Surface Area
BP	Blood Pressure
CI	Confidence Interval
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of Variation
DBL	DataBase Lock
DOR	Duration Of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOI	End of Infusion
gCV	geometric Coefficient of Variation

GI	Gastrointestinal
gMean	geometric Mean
HIV	Human Immunodeficiency Virus
KM	Kaplan-Meier
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	Leucovorin/5-Fluorouracil/Oxaliplatin
NA	Not Applicable
NE	Not Evaluable
nADA	Neutralizing Anti-Drug Antibody
NCI CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NTP	Non-Treatment Period
OR	Objective Response
OS	Overall Survival
P10	10% percentile
P90	90% percentile
PD	Progression Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PKS	Pharmacokinetic Analysis Set
PR	Partial Response
PT	Preferred Term
Q1	25th percentile
Q3	75th percentile
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Residual Effect Period
SAE	Serious Adverse Event
SCR	Screened set

SD	Stable Disease
SFU	Safety Follow-up
SI	System International
SMQ	Standardized MedDRA Query
SOC	System Organ Class
Std Dev	Standard Deviation
SWS	Switched Set
TB	Tuberculosis
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TFL	Table Figure Listing
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TTP	Time To Progression
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
US	United States of America
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, immunogenicity data for Protocol 1302.3 **INVICTAN®-3**. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

The document pertains to:

- Preliminary analysis: the analysis that will be performed at the time point of the primary analysis of trial 1302.5,
- Final analysis: the final analysis at the end of the trial.

This trial statistical analysis plan (TSAP) is based on Protocol version 6.0, dated 17 January 2018, following the recommendation of the sponsor on 21 DEC 2017 that all subjects should be switched from BI 695502 to the reference product bevacizumab (commercially available Avastin®, hereafter referred to as Avastin®) as soon as it is available at the respective clinical site. Limited safety data (adverse events, immunogenicity) will be analysed for the post-switch period.

2. TRIAL OBJECTIVES

2.1. Primary Objective

The primary objective of this trial is to evaluate the safety and tolerability of BI 695502 in combination with leucovorin/5-fluorouracil/oxaliplatin (mFOLFOX6) and as maintenance therapy (when applicable).

2.2. Secondary Objectives

The secondary objectives are to evaluate the following efficacy parameters:

- Progression-free survival (PFS),
- Objective response (OR) rate (proportion of subjects with complete response [CR] or partial response [PR]),
- Overall survival (OS),
- Duration of response (DOR),
- Time to progression (TTP).

2.3. Further Objectives

The other objectives of the trial are:

- To evaluate the presence of anti-drug antibodies (ADAs) and neutralizing antidrug antibodies (nADA).

3. TRIAL DESIGN

3.1. General Description

This is a Phase IIIb, open-label, multicenter, multinational, single-arm trial. The trial will investigate the safety, efficacy, immunogenicity of BI 695502 (corresponding to the trial medication) in subjects with previously untreated metastatic colorectal cancer (mCRC), who will receive BI 695502 in combination with mFOLFOX6 chemotherapy every 2 weeks until disease progression, death, unacceptable toxicity or the end of the trial (See protocol Section 8.6 for 'end of the trial' definition), whichever occurs earliest. Based on subject tolerability, at least 8 cycles of mFOLFOX6 should be given to all subjects. If the investigator decides to stop Oxaliplatin at any time during the trial, subjects should continue to receive infusional 5-Fluorouracil (5FU) +leucovorin with BI 695502 until progression, unacceptable toxicity or withdrawal of consent, whichever occurs first. The efficacy analysis will be based upon the evaluation of tumor imaging as per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [1] and as assessed by central imaging review.

Per the sponsor's 21 Dec 2017 recommendation, subjects should be switched from BI 695502 to the reference product, bevacizumab (commercially available Avastin®, hereafter referred to as Avastin®), as soon as it is available at the respective clinical site. The Switch Visit is defined in Section 6.5. If Avastin® is not immediately available, the investigators may temporarily allow continuation on BI 695502.
Each subject will continue the study with the same visit schedule as described in the protocol.

Subjects who discontinue treatment with chemotherapy or BI 695502 or Avastin®, but do not have disease progression and have not started a new anticancer therapy, will continue in the trial in the non-treatment period until disease progression or initiation of a new anticancer therapy, whichever occurs first.

All subjects who receive at least one infusion of BI 695502 will attend a Follow-up visit 30 days (30-day FU) after the last BI 695502 dose or last Avastin® dose is administered whichever occurs later.

Subjects will attend a long-term Safety Follow-up (SFU) visit 18 weeks after the last administration of trial medication prior to the switch visit. If the subject continues to receive treatment with Avastin® beyond 18 weeks post last BI 695502 dose, then no SFU visit will be performed.

After the long-term SFU visit or discontinuation of Avastin® (whichever occurs later), all subjects will be monitored for survival every 3 months via telephone call until death, withdrawal of consent for the study or until the trial is closed, whichever occurs earlier.

The trial will be closed when all screened and treated subjects have either died, are lost to follow-up, have withdrawn consent for the study, or when a maximum of 12 months after the last subject assigned to trial medication has the 30-day FU visit has elapsed, whichever occurs earlier.

Further details of the trial design can be found in the protocol Section 3.1.

3.2. Schedule of Events

Schedule of events can be found in Sections “Flow Chart 1.1 – Cycle 1 to Cycle 13” and “Flow Chart 1.2 – Cycle 14 Onwards” of the protocol.

3.3. Changes to Analysis from Protocol

The protocol Section 7.3.2.1 defines that a sensitivity analysis for the objective response (OR) secondary efficacy endpoint will be performed using the investigator-assessed OR. As the OR rate based on the investigator assessment is not defined as an endpoint in protocol Section 5.1 it will be defined as an other efficacy endpoint.
In addition, “further” safety endpoints are defined in protocol Section 5.1.3. These endpoints will be renamed to “other” safety endpoints.

In protocol Section 7.3, only the treated set, all subjects treated with at least one dose of trial medication, is defined.

Observed value thresholds that define observed dose reductions and increases for Oxaliplatin, Leucovorin and 5FU were specified and any dose classified per the definition will be classified as an important protocol violation (See section 13).

Censoring rules for PFS are defined in protocol Table 7.5.1:1. For harmonization with 1302.5 analysis, a more detailed version of censoring rules table will be used compared to the table available in the protocol (see Section 15.2.1.1). This more detailed version of the censoring rules table will lead to some deviations from the protocol:

- In case of no baseline assessment: per protocol, the subject’s PFS time should be censored at the date of first administration of trial medication. However, if the subject died on or before the second planned tumor assessment, e.g. on or before the assessment of a progressive disease would have been possible if a baseline assessment would have been available, then the subject’s PFS time won’t be censored and the date of death will be the date of the event.
- In case of consecutive missed radiological assessments: per protocol, the subject’s PFS time should be censored at the date of last radiological assessment of measured lesions. For the purpose of the analysis, “consecutive missed radiological assessments” will be defined as two or more consecutively missed tumor radiological assessments. In addition, for the censoring date, the date of last

radiological assessment prior to missed tumor assessments will be used.

- In case of new anticancer therapy started: per protocol, the subject's PFS time should be censored at the date of last radiological assessment of measured lesions. However, the subject's PFS time will be censored only if the new anticancer therapy is initiated before PD and the date of last tumor assessment before initiation of new anti-cancer therapy will be used as censoring date.

Per protocol Section 5.1.1, the AEs selected for primary safety endpoint include the category "All haemorrhages and pulmonary haemorrhages". For more clarity, this category will be renamed as "All haemorrhages including pulmonary haemorrhages.

In the protocol, the definition of enrolled subjects is not clear. Per the first paragraph of the protocol Section 3.3, enrolled subjects are subjects who have signed informed consent, while in the second paragraph, it is stated that subjects considered screen failures won't be enrolled in this trial. However, screen failures subjects should also have signed an informed consent. Due to this contradiction in the protocol and to avoid any confusion in the analysis, the wording "screened" will be used for subjects who have signed an informed consent.

The following additional analyses will be performed, compared to the analyses planned in the protocol:
- Section 4.1: Preliminary analysis (selected safety parameters).

4. PLANNED ANALYSES

The following analysis will be performed for this trial:

- Preliminary Analysis
- Final Analysis

The preliminary analysis and final analysis described in this TSAP will be performed by Biostatistics following Sponsor Authorization of this TSAP, Sponsor Authorization of Analysis Sets and after Data Snapshot/Database Lock (DBL) takes place.

4.1. Preliminary Analysis

The preliminary analysis that will include an analysis of selected safety data (Adverse Events) as well as some important background information. The analysis will be based on treated set (TS) and will be indicated specifically in the table of contents of the output shells.

This preliminary analysis will take place at the time point of 1302.5 primary analysis, and the data cut-off for this supportive analysis will coincide with the data cut-off for the primary analysis of 1302.5. Details of the cut-off date used for 1302.3 can be found in APPENDIX 5.

For the purposes of this supportive analysis, all safety data observed prior to the cut-off date will be cleaned.

No Clinical Trial Report (CTR) will be produced for this preliminary analysis, rather a selection of displays that will be identified in the table of contents.

4.2. Final Analysis

The final analysis will be performed at the end of the trial.

This final analysis will include all analyses specified in the TSAP on the global population. That is to say, the analyses of the primary safety, as well as, all secondary and other efficacy endpoints and safety, immunogenicity, background information data. The analysis will be based on the TS, SWS

The final analysis will take place after the last treated subject in the trial will have received his/ her last treatment and completed the relevant follow-up, e.g. at time of last subject last planned visit (including non-treatment period [NTP] and follow-up visits).

For efficacy analysis, data for switched subjects will be considered censored at the switch visit. There will be no analysis of efficacy or laboratory data post-switch.

Post-switch data will only be tabulated where specified in the relevant sections below. All availabe post-switch data will be listed.

For safety analysis post-switch, AEs that started on the Switch Visit up to the 30-day follow-up visit will be handled as treatment emergent.

All data will be cleaned and evaluated and the results summarized in the CTR.

5. ANALYSIS SETS

A data review meeting will be set up to decide on the final allocation rules to assign subjects to the analysis sets.

5.1. Screened Set [SCR]

The screened (SCR) set will contain all subjects who provide informed consent for this trial.

5.2. Treated Set [TS]

The treated set (TS) will contain all subjects who signed informed consent and who receive at least one dose of trial medication.

If there is any doubt as to whether a subject was treated or not (for example, a subject with date of administration of trial medication and/or start dose available but the information on the total dose administered is missing), he/she will be assumed treated for the purposes of analysis.

5.3. Switched Set [SWS]

The Switched Set (SWS) will contain all subjects who provided verbal informed consent to switch to commercial Avastin® and who received at least one dose of Avastin® post-switch.

The SWS is applicable for the post-switch period (see Section 6.7 for definition) analyses.

Note that data for subjects who had completed treatment, or were no longer in the study at the time of the switch will be analysed to the extent available. These subjects will not have performed a Switch Visit, and to distinguish from the Switched Set are referred to as 'non-switched' subjects. Data for 'non-switched' subjects will be analyzed to the extent available and corresponds to the pre-switch period only (see Section 6.7 for definition).

6. GENERAL CONSIDERATIONS

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

For the pre-switch period, the reference start date (Study Day 1) is defined as the date of the first dose of trial medication. For subjects assigned to trial medication but not treated, it is the day of assignment to trial medication (as recorded on electronic Case Report Form [eCRF] page "Eligibility"). This will be applied for all endpoints except for DOR where the first documented CR or PR date will be used as reference start date.

For the post-switch period (see Section 6.7 for definition), the reference start date (Study Day 1) is defined as the day of first dose of Avastin® post-switch. This is applicable for SWS.

Reference start date or study day will appear in every listing where an assessment date or event date appears.

If the start date of the event is on or after the reference start date then:

- Study Day = (start date of event – reference start date) + 1.

If the start date of the event is prior to the reference start date then:

- Study Day = (start date of event – reference start date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations, will appear as partial or missing in the listings. For tables, the imputation rules from APPENDIX 2 will be used.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement (date and time, whenever time is recorded) and the reference start date/time coincide, then that measurement will be considered as baseline. Adverse Events (AEs) and medications commencing on the reference start date will be considered as happening on-treatment.

For the post-switch period (see Section 6.7 for definition), the Switch Visit (see Section 6.5) will form the post-switch baseline.

6.3. Retests, Unscheduled Visits and Early Termination

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit table summaries and by-visit graphs, but will be presented in the listings, individual data graphs and hepatic injury / Hy's Law by visit tables.

Unscheduled tumor assessments will be used for the derivation of all efficacy endpoints, and in the re-calculation of cycles for by-visit table summaries.

In the case of a retest (recorded as unscheduled visit), the latest available measurement within 3 days after the planned assessment will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. Windowing Conventions

This section describes the windows used for the statistical analysis of tumor assessment in this trial.

For the analysis of PFS, TTP, DOR and ORR the following windows will be used:

Tumor Assessment Windows:

Assessment Number	Window
Tumor assessment 1 (Cycle 5)	from Day 1* to Day 84
Tumor assessment 2 (Cycle 9)	from Day 85 to Day 140
Tumor assessment 3 (Cycle 13)	from Day 141 to Day 196
Tumor assessment 4 (Cycle 17)	from Day 197 to Day 252
Tumor assessment 5 (Cycle 21)	from Day 253 to Day 308
Tumor assessment 6 (Cycle 27)	from Day 309 to Day 392
…	…

From Cycle 28 onwards, the tumor assessments should be performed at every 12 weeks (meaning every 84 days).

*First administration of trial medication date.

These windowing conventions will apply for reporting in the pre-switch period (See Section 6.7 for

definition). Thereafter, PFS, TTP, DOR or ORR will not be presented for the post-switch period (See Section 6.7 for definition).

6.5. Switch Visit

The Switch Visit is defined as the visit on which commercial Avastin® was administered for the first time.

The assessments to be performed at the switch (prior to Avastin® administration) are specified in the Protocol (Flow Chart 1.2).

6.6. Safety Follow Up Visit

All subjects are required to return for a Safety Follow Up (SFU) Visit 18 weeks after their last administration of trial medication. For the SWS, the 18 week period will commence from the last administration of trial medication prior to the Switch Visit.

If a switched subject continues to receive treatment with Avastin® beyond 18 weeks after the last dose of trial medication in the pre-switch period (See Section 6.7 for definition), then no SFU will be performed.

After the SFU Visit or discontinuation of Avastin® (whichever occurs later) subjects will be monitored for survival every 3 months until death or end of trial, whichever is earlier.

The last survival information is retrieved from the eCRF page “Survival Information” for the last visit performed in the Survival period.

6.7. Definition of Pre-switch and Post-switch Period

The pre-switch period is defined as the period up until the Switch Visit. For non-switched subjects, this corresponds to the whole trial, up until the end of the study.

The post-switch period is defined as the period at and after the Switch Visit (see Section 6.5) and is applicable to the Switched Set only (Section 5.3). The post-switch time period is defined as the Switch Visit until the end of the study. For this period, the Switch Visit will form the post-switch baseline, and treatment cycles will be renumbered post-switch Cycle 1 and so on until last cycle.

6.8. Statistical Tests

No formal hypothesis testing will be performed. However, confidence intervals (CIs) are presented and will be interpreted in an exploratory fashion only.

6.9. Common Calculations

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Test Value.

For quantitative measurements, percentage change from baseline will be calculated as:

- $\left(\frac{\text{Test Value at Visit x– Baseline Test Value}}{\text{Baseline Test Value}}\right) \text{X } 100$

6.10. Software Version

All analyses will be conducted using SAS® version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. Adjustments for Covariates and Factors to be Included in Analyses

No adjustments for covariates will be performed for this trial and no factors will be included in analyses.

7.2. Multicenter Studies

This trial will be conducted by multiple investigators at multiple centers internationally (approximately 50 clinical sites). Few subjects are expected to be recruited per site.

7.3. Missing Data

Missing safety data will not be imputed, unless otherwise specified in Section 16.

Missing efficacy data will be handled as described in Section 15.2.2 of this analysis plan.

7.4. Multiple Comparisons/ Multiplicity

No multiplicity-adjustment will be performed.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The shells provided with this TSAP describe the presentations for this trial and therefore the format and content of the summary tables, figures and listings to be provided by Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this trial. The number of subjects included in each analysis set will be summarized overall.

The following subject disposition and withdrawals will be presented for the SCR.

Relevant dispositions and withdrawals for the post-switch period will also be presented for the SWS

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The subject disposition and withdrawals will be presented by site for the SCR:

The REP (Residual Effect Period) is defined as the 18 week (126 days) period after the last dose date of trial medication (the last date of trial medication + 18 weeks (126 days) inclusive).

Subjects who discontinue treatment with chemotherapy or BI 695502 or both, but do not have disease progression and have not started a new anticancer therapy, will continue in the trial in the non-treatment period until disease progression, initiation of a new anti-cancer therapy, withdrawal of consent for the study or the end of the trial, whichever occurs first.

The final list of important protocol violations will be confirmed at the data review meeting before the database lock or data snapshot, at the time of each analysis which includes the important protocol violations data.

Important protocol violations, as defined in APPENDIX 6, will be presented for the treated set.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data, baseline disease characteristics and other baseline characteristics will be presented for the TS.

The 1 baseline disease characteristics will be reported:

The f other baseline characteristics will be reported:

Accountability for missing data will be displayed in case of any missing entries.

10.1. Derivations

- Age (years) = (date of informed consent– date of birth)/365.25. The lower integer will be used. For example, if age (years) = 42.68 then age will be displayed as 42.

In the case where the date of birth is partial (only year is available), the corresponding age will be presented based on the imputations specified in APPENDIX 2.

- Grading of hypertension [the worst case (highest grade) will be used in the corresponding summaries] according to CTCAE v 4.03:
  - Grade 0: systolic blood pressure (BP) < 120 mmHg and diastolic BP < 80 mmHg
  - Grade 1: systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg
  - Grade 2: systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg
  - Grade 3: systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg

In the case where the date of event is partial (only year is available), the corresponding date will be presented based on the imputations specified in APPENDIX 2.

11. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History information will be presented for the TS.

Medical History and Surgeries/Procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or higher if available at the time of the data cut-off.

11.1. MEDICAL HISTORY AND PREVIOUS SURGICAL PROCEDURES

Medical History and Previous Surgical Procedures as well as Active Medical History and Concomitant Surgical procedures will be presented by System Organ Class (SOC) and Preferred Term (PT).

SOCs will be sorted by internationally agreed European Medicines Agency (EMA) SOC order (refer to APPENDIX 4). PTs will be sorted by decreasing frequency within SOCs based on total count.

11.2. PRIOR RADIOTHERAPY

Prior radiotherapy, as reported in the eCRF, will be presented by anatomic site by decreasing frequency based on total count.

12. MEDICATIONS

Medications will be presented for the TS and coded using WHO Drug Dictionary (WHO-DD) version SEP2016 or higher. No Anatomical Therapeutic Chemical (ATC) class coding will be performed. The medical terms will be summarized by WHO-DD Preferred Name.

The WHO-DD Preferred Names will be sorted by decreasing frequency based on total count.

12.1. PRIOR ANTI-CANCER DRUG THERAPIES

Prior anti-cancer drug therapies, as reported in the eCRF, will be presented using WHO-DD preferred names.

12.2. PREVIOUS, CONCOMITANT AND POST-TRIAL MEDICATION THERAPY

See APPENDIX 2 for handling of partial dates for medications. In the case where it will not be possible to define a medication as prior, concomitant or post, the medication will be classified by the worst case; i.e. concomitant. Concomitant medications will also be reported separately for the SWS for the post-switch period.

12.3. CONCOMITANT ANTI-HYPERTENSIVE MEDICATION

The information on anti-hypertensive medications will be reported for the Pre-Switch Period:

Identification of these anti-hypertensive medications will be based on pre-specified WHO-DD preferred names according to medical input. The following process will be used by the medical advisor:

13. TRIAL MEDICATION EXPOSURE

Trial medication is defined as BI 695502. Some subjects were switched from BI 695502 to Avastin® at their Switch Visit. So, the post-switch period exposure to Avastin® will be presented and listed seperately for the SWS.

Exposure to trial medication and exposure to Avastin® will be presented for the TS and the SWS.

A descriptive table will present the dose intensity and relative dose intensity (as defined in Section 14) for each cycle, as well as, for the following periods of interest:

- Cycle 1 to Cycle 4;
- Cycle 1 to Cycle 8;
- Prior to Switch Visit (Cycle 1 to last cycle performed prior to the Switch Visit (if applicacle)).

For the post-switch period, the Switch Visit is redefined as the baseline Switch Visit, and each cycle post-switch incrementally numbered starting from Cycle 1 post-switch, regardless of the number of cycles performed pre-switch.

All screened subjects assigned to trial medication (as defined in Section 9) who should have completed the pre-specified visit are considered as subjects expected to be treated at pre-specified visit.

The frequency and percentage of subjects treated compared to the number of subjects expected to be treated at each scheduled visit until all cycles done will be presented for trial medication, Avastin®, Oxaliplatin, Leucovorin and 5FU.

In addition, the frequency and percentage of subjects treated at each scheduled visit, for all cycles, will also be presented for trial medication, Oxaliplatin, Leucovorin and 5FU.

A descriptive table will present the dose intensity and relative dose intensity (as defined in Section 14).

The amount of trial medication, Oxaliplatin, Leucovorin and 5FU will be calculated at site

A dose delay will be defined based on the duration between the start date/time of the infusion of trial medication and the start date/time of the next infusion of trial medication: (

14. DOSE INTENSITY AND RELATIVE DOSE INTENSITY

The dose intensity and the relative dose intensity for the trial medication, Oxaliplatin, Leucovorin and 5FU will be calculated for each 2 week cycle.

14.1. Derivations

- **Dose Intensity**

The dose Intensity is defined as the total dose of trial medication given in a fixed time period.

- **Relative Dose Intensity**

The relative dose intensity (%) is defined as the dose intensity (in mg/kg/week) divided by the protocol planned dose (in mg/kg/week) X 100.

15. EFFICACY OUTCOMES

15.1. Primary Efficacy

No primary efficacy analysis will be performed for this trial.

15.2. Secondary Efficacy

The secondary efficacy analyses will be performed on the TS for the pre-switch period. Subjects data will be censored at or prior to the Switch visit. Post-switch period data will not be used in the secondary efficacy analyses.

Secondary efficacy analyses will be based on the central imaging review. The imaging charter describes the central imaging assessment. RECIST 1.1 is the basis for the central imaging review.

15.2.1. Secondary Efficacy Variables & Derivations

To analyze tumor response, one may need to determine the date of tumor assessment. If there are more than one tumor assessment in a given tumor assessment window, then the data for the scan with the most recent date, i.e., the last tumor assessment in that window will be used.

The date of disease progression is defined as the date of radiological diagnosis of PD for subjects progressed according to central review assessment.

15.2.1.1. PROGRESSION-FREE SURVIVAL

Progression-free survival (PFS) time is defined as the time from first administration of trial medication until disease progression as assessed by central imaging review according to RECIST 1.1 or death from any cause for the Pre-Switch Period (as collected on 'End of Treatment', 'Safety Follow-up' and 'Survival Information' pages of eCRF), whichever occurs first.

For non-switched subjects, PFS time will be censored on the date of the last adequate tumor assessment for subjects who do not have an event (PD or death) or for subjects with an event after two or more subsequent missing response assessments.

For the SWS, PFS time will be censored at the last tumor assessment at or prior to the Switch Visit for subjects who do not have an event (PD or death) for the pre-switched period.

Subjects who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessment will have PFS time censored at first administration of trial medication time unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered as an event.

15.2.1.2. OBJECTIVE RESPONSE RATE

The objective response of each subject will be classified according to the following RECIST 1.1 categories based on independent central review, irrespective of protocol violations or missing data:

- Complete response (CR),
- Partial response (PR),
- Stable disease (SD),
- Progressive disease (PD),
- Not applicable (NA),
- Not evaluable (NE).

The OR rate is defined as the proportion of subjects achieving an unconfirmed CR or PR after the start of treatment.

OR will be evaluated for each subject separately from the date of first administration of trial medication (i.e. Study Day 1) until either:

- Progression according to RECIST 1.1 based on independent central review,
- Unacceptable toxicity defined by end of treatment due to adverse event as reported in the eCRF
- Death as reported in the eCRF
- Switching treatment
- End of trial without switching treatment,

whichever occurs first.

Unscheduled assessments recorded after the first administration of trial medication will be taken into

account.

The date of End of Treatment' due to an adverse event corresponds to date of the last infusion. However, in cases where the start date of the adverse event leading to study drug discontinuation is after the last infusion date the following definition will apply:

The date of End of Treatment due to the adverse event is imputed as the date of the AE with the earliest start date among the subject's AEs with start dates after the subject's last infusion date. The time to OR is considered as censored at this imputed End of Treatment Date.

A swimmer plot of the objective response at each cycle (as assessed by central imaging review), over the whole treatment duration in days, will be produced on the TS. Subjects will be categorized as OR= Yes/No.

15.2.1.3. DURATION OF RESPONSE

Duration of response (DOR) is defined as the time from first documented CR or PR until time of progression as assessed by central imaging review for the Pre-Switch Period.

This definition above applies only to subjects who experienced CR/PR.

15.2.1.4. TIME TO PROGRESSION

Time of progression (TTP) is defined as the time from first administration of trial medication to the date of tumor progression, as assessed by central imaging review for the Pre-Switch Period.

15.2.1.5. OVERALL SURVIVAL

Overall survival (OS) time is defined as the time from first administration of trial medication until death from any cause for the Pre-Switch Period (as collected on 'End of Treatment', 'Safety Follow-up' and 'Survival Information' pages of eCRF).

For subjects alive, the overall survival will be censored at the last date known to be alive for the Pre-Switch Period.

15.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

For the purpose of OR rate analysis, a secondary endpoint, subjects who do not have documented CR or PR at a specific time point will be considered as non-responders at this time point. Missing or non-

evaluable response assessments will not be imputed and the subject will be considered as a non-responder.

The imaging charter (Section 6.2.2, criterion 13.D) details the criteria needed to handle missing assessments in the central independent review.

If there is no post baseline assessment at all then the subject will be considered as a non responder.

15.2.3. Analysis of Secondary Efficacy Variables

15.2.3.1. ANALYSIS OF OBJECTIVE RESPONSE RATE

The number and percent of subjects with a CR or PR and the OR rate will be summarized in a descriptive table, together with a Wilson score 95% CI for the OR rate. Additionally, the response categories will be analyzed descriptively and displayed by cycle in the same summary table.

For unscheduled visits, the study day will be attributed to the corresponding cycle according to the rule defined in Section 6.4. For the subjects with progression of disease or treatment stopped due to unacceptable toxicity, or death or end of trial, their study day will also be evaluated in order to determine the corresponding cycle according to the rule defined in Section 6.4.

Number and percent of subjects with at least one lesion (nodal, non-nodal) will be presented per tumor assessment visit (baseline, Cycle 5, Cycle 9, …), as well as, the location of each lesion.
The following characteristics will also be reported:

- For target lesions:
  - Response (Complete Response, Partial Response, Stable Disease, Progressive Disease, Not Evaluable)
  - Sum of the diameters (mm)
- For non-target lesions:
  - Response (Complete Response, Non CR/ Non PD, Progressive Disease, Not Evaluable)
  - Number of subjects with at least one of Absent/Normal assessment
  - Number of subjects with at least one of Present/Stable assessment

- Number of subjects with at least one Progressed assessment
- Number of subjects not assessed

- For new lesions:
  - Number of subjects with at least one new lesion

15.2.3.2. ANALYSIS OF PROGRESSION-FREE SURVIVAL

The PFS will be analyzed descriptively using Kaplan-Meier (KM) estimates.The 1-year PFS rate and median PFS time will be estimated with 95% confidence intervals and will displayed in a summary table. The CI for 1-year PFS rates will be determined using Greenwood's variance estimate [2]. The CI for the median PFS time will be calculated according to the Brookmeyer and Crowley method [3].

In addition, the KM survival rate will be presented graphically.The number of subjects at risk, as well as the number of events, the 1-year PFS rate and median PFS time will also be provided in the same figure. This figure will also be provided by subgroup.

15.2.3.3. ANALYSIS OF DURATION OF RESPONSE, TIME TO PROGRESSION AND OVERALL SURVIVAL

The DOR, TTP and OS will be analyzed descriptively using KM estimates, in the same manner as for the PFS (see Section 15.2.3.2). The 1-year rate will not be calculated for the DOR.

Kaplan-Meier estimates of duration of follow-up will also be presented, with the 'event' defined as the point at which the subject was censored for the original survival analysis. For this analysis, subjects who died are considered to be censored at the time at which the death occurred.

15.2.4. Sensitivity Analysis of Secondary Efficacy Variables

No sensitivity analyses are planned.

16. SAFETY OUTCOMES

For the pre-switch period, all outputs for safety outcomes will be based on the TS.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section. Limited safety outcomes will be presented for the post-switch period as noted in the relevant sections below. Unless specified, safety outcomes will be presented tabulated for the pre-switch period only. All post-switch safety outcomes will be listed.For the post-switch period, a limited group of SWS safety outcomes (Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions and occurrence of anti-drug antibodies) will be analyzed.

Safety endpoints in this trial are:

Primary endpoint:

- The primary safety endpoint of the trial is subjects with any of the following selected AEs:
    1. Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions,
    2. Arterial and venous thromboembolic events
    3. GI perforations,
    4. Hypertension,
    5. Proteinuria,
    6. Pulmonary hemorrhage,
    7. All haemorrhages including pulmonary haemorrhages,
    8. Wound-healing complications including abscess and fistulas,
    9. Posterior reversible encephalopathy syndrome,
    10. Ovarian failure.

Other Endpoints:

- Subjects with other haemorrhages.
- All AEs including AEs related to trial treatment, assessed according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, with a focus on those AEs of Grade 3 or 4.
- All AEs potentially related to immunogenicity.
- All protocol-specified adverse events of special interest (AESIs).
- ADAs/nADAs at Weeks 0, 4, 8, 16, 24, 32, 40, 52 and 30-day FU and long-term SFU Visit.

16.1. Adverse Events

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 19.1 or higher if

available at the time of the data cut-off.

Non-switched subjects:

- Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of trial medication and prior to the last date of trial medication + 18 weeks inclusive (126 days) (REP).
- Post-treatment AEs are defined as AEs that started after treatment stop + 18 weeks (126 days).

Switched subjects (SWS):

For the pre-switch period,

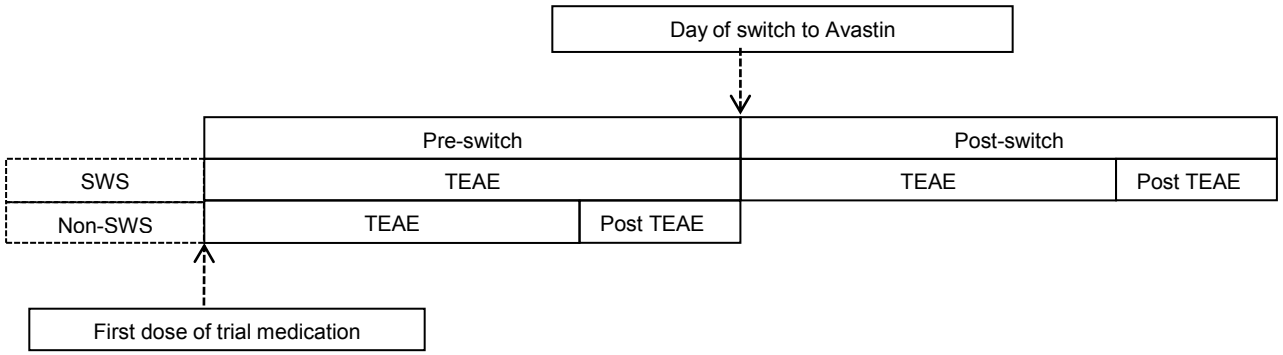
- TEAEs are defined as AEs that started or worsened in severity on or after the first dose of trial medication up to (and not including) the date of first Avastin®.

For the post-switch period,

The REP of the initial treatment needs to be re-considered. Every AE that occurred on or after the switching date and up to (and including) the 30-days follow-up visit will be analysed as "(BI 695502 to Avastin)" in order to take the initial treatment into consideration and to distinguish pre-switch and post-switch events. So for switched subjects, TEAE will be defined as all AEs that started up to the 30-days follow-up visit. Note that a 30-days follow-up visit is scheduled 30 days after last Avastin administration.

Figure below provides an overview of the relationship between pre- and post-switch and TEAE and Post TEAE for those that switched (SWS) and those that did not switch (non-SWS).

Figure – Treatment Emergent Adverse Events, Pre-Switch and Post-Switch period



Note: Post TEAEs are not tabulated for the post-switch period.

See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, then the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number and percent of subjects within each of the categories described in the sub-sections below, will be provided as specified in the PTs, the SOCs will be sorted by internationally agreed EMA SOC order (refer to APPENDIX 4), PTs will be sorted by decreasing frequencies (within SOC).

An overall summary of number and percent of subjects within relevant sub-sections below will be also presented for the post-switch period.

A combined listing will be produced of all AEs (including TEAEs and Non-TEAEs) for the pre and post-switch periods. Unless otherwise stated, other AE listings below will i) include only TEAEs and ii) be combined for the pre and post-switch periods..

16.1.1. Post-Treatment AEs

Frequency and percentage of post-treatment AEs will be presented by SOC and PT for the pre-switch period. All post treatment AEs will be listed

16.1.2. TEAEs Specific Derivation

16.1.2.1. PATIENT-YEARS INCIDENCE RATE

Patient-years incidence rate per 1000 years for AEs meeting the specific criterion for the analysis (see Sections 16.1.3 ,16.1.7,16.1.9, and 16.1.9) will be calculated as follows:

(Number of subjects with AE meeting the specific criterion) / (Patient-Years) * 1000

Where Patient-Years is the cumulative time at risk for all subject (calculated in days) in the treatment group divided by 365.25.

The time at risk (in days) per subject for the pre-switch period is derived as following:

If the subject :	Time at risk (days)
Had at least one AE with specific criterion	start date of first AE meeting the specific criterion – first trial medication date +1
Without AE with specific criterion Completed REP	(last trial medication date + 126 – first trial medication date +1
Without AE with specific criterion Ongoing, not yet completed REP	(Snapshot date) – first trial medication date +1
Without AE with specific criterion deaths	(Death date) – first trial medication date +1

For the post-switch period, the time at risk (in days) per subject will be deriving as following:

If the subject :	Time at risk (days)
Had at least one AE with specific criterion	start date of first AE meeting the specific criterion – first Avastin administration date +1
Without AE with specific criterion and attended 30-days follow-up visit	(last Avastin administration date + 30 – first Avastin administration date +1
Without AE with specific criterion Ongoing, not yet attended 30-days follow-up visit	(Snapshot date) – first Avastin administration date +1
Without AE with specific criterion deaths	(Death date) – first Avastin administration date +1

16.1.2.2. WILSON SCORE CONFIDENCE LIMITS

PROC FREQ with option BINOMIAL will be used for programming purpose, for the Wilson score CI (Wilson, 1927 [4]).

16.1.3. All TEAEs

Frequency and percentage of TEAEs will be presented by SOC and PT and also broken down further by maximum severity and relationship to trial medication. Patient-year incidence rate (as defined in Section 16.1.2.1) will also be displayed. Patient-years incidence rate will be reported only for pre-switch period. For the post-switch period, it will also be reported only for the SWS.

In addition, a summary of frequencies, percentages and number of events by SOC, PT and by NCI-CTCAE grade will be displayed.

All TEAEs will be listed separately for the pre-switch and post-switch period.

16.1.3.1. INTENSITY

TEAE intensity is classified from Grade 1 to Grade 5, according to the NCI-CTCAE v4.03 or later. If a subject reports a TEAE more than once within a SOC/ PT, then the AE with the worst case intensity will be used in the corresponding intensity summaries. Intensity categories collected in the "Adverse Event" page of the eCRF are:

- "Grade 1 – Mild Adverse Event",
- "Grade 2 – Moderate Adverse Event",
- "Grade 3 – Severe Adverse Event",
- "Grade 4 – Life threatening or disabling",
- "Grade 5 – Death".

The categories "Any grade", "Grade 1", "Grade 2", "Grade 3", "Grade 4", "Grade 5" and "Missing grade" will be displayed in the outputs.

16.1.3.2. RELATIONSHIP TO TRIAL MEDICATION

A related TEAE is defined as a TEAE with a relationship to trial medication ticked "yes" in the eCRF according to the investigator. TEAEs with a missing relationship to trial medication will be regarded as related to trial medication. If a subject reports the same AE more than once within a SOC/ PT, then the AE with the worst case relationship to trial medication will be used in the corresponding relationship tables. "Related" will be considered as the worst case relationship to trial medication compared to "Not Related".

For TEAEs with a relationship to trial medication (as defined in Section 16.1.3.2), a summary of frequencies, percentages and number of events by SOC and PT, as well as, a by subject listing will be prepared. Patient-years incidence rate (as defined in Section 16.1.2.1) will also be displayed.

In addition, a summary of frequencies, percentages and number of events by SOC, PT and by NCI-CTCAE grade will be displayed.

16.1.4. TEAEs Leading to Temporary Interruption of Trial Medication, Oxaliplatin, Leucovorin or 5FU

TEAEs leading to temporary interruption of trial medication, Oxaliplatin, Leucovorin or 5FU will be identified by using the "Drug interrupted" category on the "Adverse Events" page of the eCRF.

For TEAEs leading to temporary interruption of trial medication, Oxaliplatin, Leucovorin or 5FU, separate summaries of frequencies, percentages and number of events by SOC and PT, as well as, a by subject listing will be prepared.

In addition, the same summary table will also be prepared for TEAEs leading to temporary interruption of any of the chemotherapy components (either Oxaliplatin, Leucovorin or 5FU).

In this context 'temporary interruption' refers to any interruption during the administration of the trial medication.

16.1.5. TEAEs Leading to Discontinuation of Trial Medication, Oxaliplatin, Leucovorin or 5FU

TEAEs leading to permanent discontinuation of trial medication, Oxaliplatin, Leucovorin or 5FU will be identified by using the "Drug Withdrawn" category on the "Adverse Events" page of the eCRF.

For TEAEs leading to permanent discontinuation of trial medication, Oxaliplatin, Leucovorin or 5FU, separate summaries of frequencies, percentages and number of events by SOC and PT will be prepared.

In addition, the same summary table will also be prepared for TEAEs leading to permanent discontinuation of any of the chemotherapy components (either Oxaliplatin, Leucovorin or 5FU).

TEAEs leading to permanent discontinuation of trial medication due to progression disease will be identified by using the "Progressive disease" category on the "End of Treatment" page of the eCRF.

For TEAEs leading to permanent discontinuation of trial medication due to progression of disease a listing will be prepared.

TEAEs leading to treatment drug discontinuation will be listed, for trial medication, Oxaliplatin, Leucovorin and 5FU.

16.1.6. TEAEs Leading to Reduction of Chemotherapy

TEAEs leading to reduction of Oxaliplatin, Leucovorin or 5FU will be identified by using the "Dose reduced" category on the "Adverse Events" page of the eCRF.

For TEAEs leading to reduction of Oxaliplatin, Leucovorin or 5FU, separate summaries of frequencies, percentages and number of events by SOC and PT will be prepared.

In addition, the same summary table will also be prepared for TEAEs leading to reduction of any of the chemotherapy components (either Oxaliplatin, Leucovorin or 5FU).

TEAEs leading to Oxaliplatin reduction, as well as TEAEs leading to Leucovorin reduction and TEAEs leading to 5FU reduction, will be listed.

16.1.7. Serious TEAEs

Serious adverse events (SAEs) are those events which the investigator ticked "Yes, specify" to the item "Is this a serious adverse event?" on the "Adverse Events" page of the eCRF.

A table with the number of subjects, percentages and number of Treatment Emergent SAEs by SOC and PT will be prepared. Patient-years incidence rate (as defined in Section 16.1.2.1) will also be displayed. A comparable table regarding the post-switch period will be performed for the SWS.

In addition, separate summaries of frequencies, percentages and number of events by SOC and PT will be displayed for serious TEAEs leading to death, serious TEAEs related to trial medication and serious TEAEs related to trial medication and leading to death.

Serious TEAEs will be listed and also be presented for the post-switch period for the SWS.

16.1.8. Non-Serious TEAEs

Non-serious TEAEs are those events for which the investigator ticked “No” to the item “Is this a serious adverse event?” on the AEs page of the eCRF.

Frequency of subjects, number of events and incidence of subject with non-serious TEAEs, as well as number of events, will be presented by SOC and PT, if PT incidence is >5%.

16.1.9. TEAEs Leading to Death

TEAEs leading to Death are those events which are recorded as “Fatal” on the “Adverse Events” page of the eCRF.

For TEAEs leading to death, a summary of frequencies, percentages and number of events by SOC and PT will be prepared. Patient-years incidence rate (as defined in Section 16.1.2.1) will also be displayed.

TEAEs leading to Death will also be listed.

16.1.10. AEs Selected

16.1.10.1. AEs Selected for Primary Endpoint Assessment (Primary Endpoint)

The number and percentage of subjects with at least one AE selected for primary endpoint assessment will be summarized. Percentage will be reported with associated 95% Wilson score confidence interval (as defined in Section 16.1.2.2). The patient-years incidence rate (as defined in Section 16.1.2.1) will also be reported in the same summary. This table will be produced by AE category.

In addition, a summary of frequencies, percentages and number of events by category and by PT will be displayed. A comparable summary description regarding the post-switch period will be performed for the SWS.

The selected AEs for primary analysis are the following:

1. Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions
2. Arterial and venous thromboembolic events

3. GI perforations
4. Hypertension
5. Proteinuria
6. Pulmonary hemorrhage
7. All haemorrhages including pulmonary haemorrhages
8. Wound-healing complications including abscess and fistulas
9. Posterior reversible encephalopathy syndrome
10. Ovarian failure

Identification of these categories will be based on pre-specified MedDRA terms according to medical input – see APPENDIX 7.

AEs selected for primary endpoint assessment will be listed separately for the pre and post-switch period.

Frequency and percentage of subjects with at least one AE selected for primary endpoint assessment, overall and by AE category, will be analyzed for each of the levels of the subgroups as defined in Section 7.5. The Wilson score method will be used to determine the 95% CIs for the proportions of subjects with selected AEs. These estimates will be produced by subsetting the data to the individual levels within the subgroup.

16.1.10.2. AEs Selected for Exploratory Analysis

Other haemorrhages is selected for the exploratory analysis.

Identification of this category will be based on pre-specified MedDRA terms according to medical input – see APPENDIX 7.

The number and percentage of subjects with at least one “Other haemorrhages” AE will be summarized. Percentage will be reported with associated 95% Wilson score confidence interval (as defined in Section 16.1.2.2). The patient-years incidence rate (as defined in Section 16.1.2.1) will also be reported in the same summary.

In addition, a summary of frequencies, percentages and number of events by PT will be displayed.

16.1.11. TEAEs Of Special Interest

AESIs reported by investigators are those events recorded as “Adverse Event of Special Interest” equal to “Yes” on the “Adverse Events” page of the eCRF.

A table with the number of subjects, percentages and number of Treatment Emergent AESIs reported by investigators, by the categories described in the sub-sections below and by PT, will be provided for the Pre-Switch Period. A comparable table regarding the post-switch period will be presented for the SWS.

Treatment Emergent AESIs reported by investigator will be listed. A comparable listing regarding the post-switch period will be performed for the SWS.

16.1.11.1. HEPATIC INJURY

Hepatic injuries events are those events identified by medical advisor on the subset of AEs for subjects presenting laboratory potential Hepatic injury findings (refer to Section16.4.1.1) as follows.

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

Subjects showing the following laboratory abnormalities need to be followed up according to Section

- Hepatic injury defined by the following alterations of liver parameters for subjects with normal liver function at baseline: an elevation of AST and/or ALT ≥3 x ULN combined with an elevation of total bilirubin ≥2 x ULN measured in the same blood draw sample.
- Hepatic injury defined by the following alterations of liver parameters for subjects with impaired liver function at baseline: an elevation of AST and/or ALT ≥5 x the baseline value combined with an elevation of total bilirubin ≥2 x the baseline value measured in the same blood draw sample.
- Marked peak aminotransferase (ALT and/or AST) elevations >10 x ULN.

Hepatic injury considered to be AESIs are those events identified as both hepatic injury adverse events related to trial medication and recorded as “Adverse Event of Special Interest” equal to “Yes” on the Adverse Events page of the eCRF.

Hepatic injury TEAEs related to trial medication will also be listed. The listing will include the “Adverse Event of Special Interest” equal to “Yes” information from the “Adverse Events” page of the eCRF as a flag.

16.1.11.2. GASTROINTESTINAL PERFORATIONS

GI perforations are those events recorded as MedDRA code in the pre-defined SMQ = “Gastrointestinal perforation”.

GI perforations considered to be AESIs are those events identified as both GI perforations and recorded as “Adverse Event of Special Interest” equal to “Yes” on the “Adverse Events” page of the eCRF.

Treatment emergent GI perforations will also be listed. The listing will include the “Adverse Event of Special Interest” equal to “Yes” information from the “Adverse Events” page of the eCRF as a flag.

16.1.11.3. ANAPHYLACTIC REACTIONS

Anaphylactic reactions are those events recorded as MedDRA code in the pre-defined Standardized MedDRA Queries (SMQ) = “Anaphylactic reactions” (narrow).

Anaphylactic reactions considered to be AESIs are those events identified as both anaphylactic reactions and recorded as “Adverse Event of Special Interest” equal to “Yes” on the “Adverse Events” page of the eCRF, that occurred within 24 hours of trial medication infusion and the casualty is related to trial medication. Treatment emergent anaphylactic reactions will also be listed. The listing will include the “Adverse Event of Special Interest” equal to “Yes” information from the “Adverse Events” page of the eCRF as a flag.

16.1.11.4. PULMONARY HAEMORRHAGES

Pulmonary haemorrhages are those events recorded in BIcMQ "Pulmonary haemorrhage" (refer to APPENDIX 7).

Pulmonary haemorrhage AEs considered to be AESIs are those events identified as both Pulmonary haemorrhage and recorded as "Adverse Event of Special Interest" equal to "Yes" on the "Adverse Events" page of the eCRF.

Treatment emergent pulmonary haemorrhages will also be listed. The listing will include the "Adverse Event of Special Interest" equal to "Yes" information from the Adverse Events page of the eCRF as a flag.

16.1.11.5. OTHER AESIS

Other AESIs are those not falling into any of the above mentioned MedDRA categories and recorded as "Adverse Event of Special Interest" equal to "Yes" on the Adverse Events page of the eCRF.

Other AESIs will be listed. The listing will include the "Adverse Event of Special Interest" equal to "Yes" information from the Adverse Events page of the eCRF as a flag.

16.1.12. TEAEs Potentially Related to Immunogenicity

A table with the number of subjects, percentages and number of TEAEs potentially related to immunogenicity will be prepared by SOC and PT. A comparable table regarding the post-switch period will be performed for the SWS.

Identification of these TEAEs potentially related to immunogenicity will be based on PTs according to medical input.

16.1.13. Local Tolerability

Injection site reactions are those events which are recorded as “infusion reaction” on the Adverse Events page of the eCRF. A table with the number of subjects, percentages and number of TEAEs injection site reactions by SOC and PT will be prepared.

16.1.14. Grade 3 or 4 TEAEs

Grade 3 or 4 TEAEs are those events with a Grade 3 or a Grade 4 intensity according to NCI-CTCAE v4.03.

Note that if a subject reports a TEAE more than once within a SOC/ PT, then the worst case intensity won’t be used and in case of Grade 3 or a Grade 4 intensity at least once, the AE will be counted in the Grade 3 or 4 TEAEs summaries.

For Grade 3 or 4 TEAEs, a summary of frequencies, percentages and number of events by SOC and PT will be prepared. A similar summary will also be prepared for Grade 3 or 4 TEAEs with a relationship to trial medication.

16.2. Exempted Events of Disease Progression

Progression of disease and death due to progression are considered as disease outcome and therefore, are exempted from reporting as a (S)AE. Frequency and percentage of these will be summarized by cycle.

16.3. Deaths

If any subject dies during the trial,

will be presented in a summary table and listed.

The SWS will be noted on the associated listing, so that any deaths occurring to the SWS will be attributed to the post-switch period.

16.4. Laboratory Evaluations

All laboratory analyses will be done on the TS. All laboratory evaluations (16.4.1-16.4.2) will be assessed for the pre-switch period. Combined listings of laboratory evaluations for the pre and post-switch period will be provided.

Laboratory values taken after the first dose of trial medication up to a period of 18 weeks after the last dose of the trial medication will be assigned to the treatment phase for evaluation. Baseline and treatment phase assessments will be used in summary tables. All assessments will be presented in listings.

Results from the central laboratory will be included in the reporting of this trial for Serum Chemistry, Hematology, Urinalysis and Coagulation. A list of laboratory assessments to be included in the outputs is included in APPENDIX 3.

In general, laboratory evaluations will be summarized in SI units. Additionally, the data will be summarized in US units, if applicable. Listings will present both SI and US units in case of differences, otherwise only SI units will be presented.

Quantitative laboratory measurements reported as “< X”, i.e. below the lower limit of quantification (BLQ), or “> X”, i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries.

The handling of retests, unscheduled and early termination data are described in Section 6.3.

16.4.1. Regular Safety Laboratory Evaluations

summaries and listings will be provided for laboratory data:

16.4.1.1. LABORATORY SPECIFIC DERIVATIONS

- Potential Hy's law categories :
    - Category 1: ALT or AST >=3xULN and TBL >=2xULN within the same sample
    - Category 2: TBL >=2xULN within 30 days after transaminase peak (ALT or AST >=3 ULN)

  Potential Hy's Law subjects are defined as subjects with laboratory data in at least one Potential Hy's law category at any time point of the trial.

16.4.1.2. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

16.4.1.3. CTC GRADING FOR LABORATORY DATA

Laboratory results will be classified according to the NCI-CTCAE v.4.03 or later. Only programmable parts of definitions will be performed. The "Grade 0" will be introduced to indicate that a certain laboratory value can be seen as "normal" and does not fulfill the criteria of NCI-CTCAE grading, either within the reference range or elevated in the other direction than defined in the NCI-CTCAE document. For uncertain cases (for example when the values can be assigned to Grade 0 based on the normal range and Grade 1 or 2 based on the toxicity criteria), a medical check will be performed, to determine the correct grade.

16.4.2. Other Safety Laboratory Evaluations

16.4.2.1. INFECTION SCREEN

Descriptive table will present hepatitis B and hepatitis C results and the results will also be listed.

16.4.2.2. HUMAN IMMUNODEFICIENCY VIRUS TEST

Descriptive table will present human immunodeficiency virus (HIV) test results and the results will also be listed.

16.4.2.3. TUBERCULOSIS TEST

Descriptive table will present Tuberculosis (TB) test results and the results will also be listed.

16.4.2.4. PREGNANCY TEST

Descriptive table will present pregnancy results for females and the results will also be listed.

16.5. Hypertension

All hypertension analyses will be performed on the TS for the pre-switch period.

16.6. Brain Lesions

If any subject has a brain lesion during the trial, as recorded on the “Non Target Lesion” and “New Lesion” pages of the eCRF, the information will be listed.

16.7. ECG Evaluations

Results from ECGs will be summarized by visit and listed using the categories as recorded in the eCRF page “12-Lead-ECG” (“normal”, “abnormal, not clinically significant” and “abnormal, clinically significant”). Changes from baseline category, by visit, will be reported in a separate summary. Results from ECGs will be assessed for the pre-switch period.

16.8. Vital Signs

The following Vital Signs measurements will be reported for this trial for the pre-switch period:

- Sitting Systolic BP (mmHg)
- Sitting Diastolic BP (mmHg)
- Sitting Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{0}C)
- Weight (kg)
- BSA (m²)

The following summaries will be provided for vital signs data on the TS and for the pre-switch period:

- Actual and change from baseline by visit

A combined listing of Vital Signs for the pre and post-switch periods will be provided.

16.9. Physical Examination

Incidence of evaluation categories (normal, abnormal) at baseline and post-baseline visits will be provided and listed for physical examination data for the pre-switch period. Changes from baseline category, by visit, will be reported in a separate summary.

16.10. ECOG

ECOG performance status at baseline and post-baseline visits will be listed.

16.11. Other Safety Assessments

16.11.1. Immunogenicity Evaluation

Pre-switch period Immunogenicity data will be displayed for all treated subjects, and the post-switch period for Immunogenicity data will be displayed for only the SWS.

The following summaries tables will be provided for Immunogenicity data:

- Number and frequency of subjects with ADA / nADA sampling results by visit

17. REFERENCES

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

[2] Kalbfleisch JD and Prentice RL. The Statistical Analysis of Failure Time Data, New York: 2nd ed. Hoboken: John Wiley & Sons (2002).

[3] Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

[4] Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Statistical Science. 2001;16:101-133.

APPENDIX 3. LABORATORY ASSESSMENTS

Laboratory parameter	Gradable with NCI-CTCAE	SI unit	US unit
Serum chemistry			
Creatinine	X	umol/L	mg/dL
Alkaline phosphatase	X	IU/L	
AST	X	IU/L	
ALT	X	IU/L	
Gamma glutamyl transpeptidase (g-GT)	X	IU/L	
Bilirubin	X	umol/L	mg/dL
Glucose	X (Hypoglycemia/Hyperglycemia)	mmol/L	mg/dL
Total cholesterol	X (Cholesterol high)	mmol/L	mg/dL
Total protein		mmol/L	mg/dL
Albumin	X (Hypoalbuminemia)	g/L	g/dL
Sodium	X (Hyponatremia/Hypernatremia)	mmol/L	mEq/L
Potassium	X (Hypokalemia/Hyperkalemia)	mmol/L	mEq/L
Chloride		mmol/L	mEq/L
Calcium	X (Hypocalcemia/Hypercalcemia)	mmol/L	mg/dL
Creatinine clearance		mL/s	mL/min
Hematology			
Hemoglobin	X (Anemia/ Hemoglobin increased)	g/L	g/dL
Hematocrit		V/V	%
Platelets	X	10^9/L	10^3/uL
White blood cells	X (White blood cell decreased/Leukocytosis)	10^9/L	10^3/uL
Lymphocytes	X (Lymphocyte count decreased/Lymphocyte count increased)	10^9/L	10^3/uL
Neutrophils (abs)	X	10^9/L	10^3/uL
Neutrophils (%)		% of white blood cells	
Monocytes (abs)		10^9/L	10^3/uL
Monocytes (%)		% of white blood cells	
Eosinophils (abs)		10^9/L	10^3/uL
Eosinophils (%)		% of white blood cells	
Basophils (abs)		10^9/L	10^3/uL

Laboratory parameter	Gradable with NCI-CTCAE	SI unit	US unit
Basophils (%)		% of white blood cells	
Reticulocyte count		10^12/L	10^6/uL
Reticulocyte (%)		% of white blood cells	
Urinalysis			
Protein	Gradable proteinuria is only reported at screening which is not reported (as per section 16.4)	g/L	mg/dL
Glucose		mmol/L	mg/dL
Blood		N/A	
Coagulation			
INR (International Normalized Ratio,)		N/A	
aPTT (activated Partial Thromboplastin Time)	X	second	
PT (Prothrombin Time)		second	

APPENDIX 4. EMA SOC ORDER FOR PRESENTATION OF THE AE IN THE TABLES

Order	System Organ Class
0	Uncoded
1	Infections and infestations
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3	Blood and lymphatic system disorders
4	Immune system disorders
5	Endocrine disorders
6	Metabolism and nutrition disorders
7	Psychiatric disorders
8	Nervous system disorders
9	Eye disorders
10	Ear and labyrinth disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
14	Gastrointestinal disorders
15	Hepatobiliary disorders
16	Skin and subcutaneous tissue disorders
17	Musculoskeletal and connective tissue disorders
18	Renal and urinary disorders
19	Pregnancy, puerperium and perinatal conditions
20	Reproductive system and breast disorders
21	Congenital, familial and genetic disorders
22	General disorders and administration site conditions
23	Investigations
24	Injury, poisoning and procedural complications
25	Surgical and medical procedures
26	Social circumstances
27	Product issues

APPENDIX 5. CUT-OFF APPLICATION RULES

Cut-off rules are detailed in a separate document named “BI1302.3_SDTM_cut_off_ v3.0 04May2018”.

APPENDIX 6. IMPORTANT PROTOCOL VIOLATIONS

Important protocol violations are detailed in a separate document named “BI1302.3_Important protocol violations_v3.0_04May2018”.

APPENDIX 7. BIcMQs, SMQs AND SELECTED PTs

Each of the safety concerns listed in the table below can be difined by one or more MedDRA preferred terms defined per SMQ or BIcMQ which are part of the medical concept of the safety concern.

Safety concern	
Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions	
Arterial and venous thromboembolic events	
GI perforations	
Hypertension	
Proteinuria	
Pulmonary haemorrhage	
Other haemorrhages	
Other haemorrhages excluding Pulmonary haemorrhage	

Wound-healing complications including abscess and fistulas	MedDRA PT selection by medical reviewer and BIcMQ 'Wound-healing complications'
Posterior reversible encephalopathy syndrome	MedDRA PT selection by medical reviewer
Ovarian failure	Narrow and Broad SMQ 'Fertility disorders' (20000210)

Note: all external files are based on MedDRA version 21.0. Files will be upgraded to the higher MedDRA version available at the time of each data cut-off.