# Clinical Trial Protocol

**Doc. No.: c02191106-09**

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| **EudraCT No.:** | 2014-002161-30 |
| **BI Trial No.:** | 1302.5 INVICTAN®-2 |
| **BI Investigational Product(s):** | BI 695502 |
| **Title:** | A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer |
| **Clinical Phase:** | III |
| **Trial Clinical Monitor:** | Phone:<br>Fax: |
| **Co-ordinating Investigator:** | Office:<br>Fax: |
| **Status:** | Final Protocol (Revised Protocol based on global amendment 07) |
| **Version and Date** | **Version: 8.0** **Date: 17 January 2018** |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

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| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br>NA | | | |
| **Name of active ingredient:**<br>BI 695502 | | | |
| **Protocol date:**<br>08 October 2014 | **Trial number:**<br>1302.5 | | **Revision date:**<br>17 January 2018 |
| **Title of trial:** | A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer | | |
| **Co-ordinating Investigator:** | | | |
| **Trial sites:** | Multicenter trial conducted in approximately 250 clinical sites. | | |
| **Clinical phase:** | III | | |
| **Objectives:** | Primary objective:<br>• The primary objective of this trial is to establish statistical equivalence in terms of efficacy (best overall response rate [ORR], proportion of patients with complete response [CR] plus partial response [PR]) until 18 weeks of first-line treatment with BI 695502 plus chemotherapy versus United States (US)-licensed Avastin® plus chemotherapy followed by maintenance monotherapy with either BI 695502 or US-licensed Avastin®.<br>Secondary objectives:<br>• The secondary objectives of the trial are to evaluate further efficacy parameters (progression-free survival [PFS], overall survival [OS], duration of response) and the safety and tolerability of BI 695502 versus US-licensed Avastin®. | | |

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| **Methodology:** | This is a Phase III, randomized, double-blind, multicenter, active comparator, parallel two-arm trial to compare BI 695502 plus paclitaxel and carboplatin (Arm B) versus US-licensed Avastin® plus paclitaxel and carboplatin (Arm A). After 4 to 6 induction cycles are given, all patients who do not have disease progression (i.e., patients with CR, PR or stable disease) will receive maintenance with BI 695502 or US-licensed Avastin® alone, per the original randomization.<br>The fully blinded, pooled ORR will be closely monitored to verify the sample size assumptions. After approximately 200 patients (100 patients per arm) have had tumor response assessments performed until Week 18, an independent blinded statistician will perform a blinded evaluation to confirm the initially calculated sample size.<br>The trial will investigate the equivalence of efficacy, safety data in patients with previously untreated nonsquamous (ns) non-small cell lung cancer (NSCLC), randomized in a 1:1 ratio to Arm B and Arm A.<br>The main efficacy analysis will be based upon the evaluation of tumor response as determined by central imaging (independent blinded confirmation of tumor response) according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).<br>Starting as of 21 Dec 2017, the Sponsor recommends that patients should be switched from BI 695502 to the reference product bevacizumab (IMP or commercially available Avastin®, both hereafter referred to as Avastin®) as soon as it is available at the respective clinical site. If Avastin® is not immediately available, the Investigators may temporarily allow continuation on BI 695502. The blind will be kept intact and all patients will continue the study with no additional visits in the scheduled visit cycle as per protocol. |
| **No. of patients:** | |
| **total entered:** | Approximately 660 patients will be randomized. |
| **each treatment:** | Approximately 330 patients randomized to each Arm B and A in a 1:1 ratio:<br>• BI 695502/concentrate for solution for intravenous (i.v.) infusion (+ paclitaxel and carboplatin during induction cycles) (Arm B).<br>• US-licensed Avastin®/concentrate for solution for i.v. infusion (+ paclitaxel and carboplatin during induction cycles) (Arm A). |
| **Pharmacokinetic sampling:** | Plasma concentrations of BI 695502 or Avastin® measured throughout the treatment period. |

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| **Diagnosis:** | Males and females with recurrent or metastatic disease (Stage IV), histologically or cytologically confirmed advanced nsNSCLC. |
| **Main criteria for inclusion:** | Aged ≥18 years (for Japan only: Age ≥20 years at Screening)<br>No prior systemic therapy for metastatic disease. Prior systemic therapy and/or radiotherapy for locally advanced disease permitted if completed >12 months prior to Screening.<br>Patients harboring tumors without activating EGFR or ALK mutation. Patients with unknown or activating EGFR or ALK mutation may be included provided chemotherapy is the site standard of care.<br>Patients must have at least one measurable lesion according to RECIST 1.1 (based on independent central review), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.<br>Patients must have no known sensitivity to any of the trial drugs or their excipients and must have adequate hepatic, renal, and bone marrow function. |
| **Test product(s):** | BI 695502/concentrate for solution for i.v. infusion |
| **dose:** | 15 mg/kg every 3 weeks (21 days) |
| **mode of admin.:** | Intravenous infusion administered over 90 minutes for the first infusion; if well tolerated, administered over 60 minutes for the second infusion and subsequently administered over 30 minutes. |
| **Comparator products:** | US-licensed Avastin®/concentrate for solution for i.v. infusion |
| **dose:** | 15 mg/kg every 3 weeks (21 days) |
| **mode of admin.:** | Intravenous infusion administered over 90 minutes for the first infusion; if well tolerated, administered over 60 minutes for the second infusion and subsequently administered over 30 minutes. |
| **Additional protocol medication:** | Starting as of 21 Dec 2017, the Sponsor recommends that patients should be switched from BI 695502 to Avastin®, following the same dose and administration procedure as per the Avastin® label, with the exception of the use of filters which must continue to be used. |
| **Associated products:** | Paclitaxel/carboplatin regimen:<br>Paclitaxel 200 mg/m$^2$ (i.v. infusion, administered according to regular institutional practice) followed by carboplatin target area under the curve (AUC) 6 mg/mL·minute (30- to 60-minute i.v. infusion) every 3 weeks (21 days) for up to 6 cycles with adequate pre- and concomitant medication. |

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| **Duration of treatment:** | Treatment with BI 695502 or US-licensed Avastin®, plus chemotherapy (up to 6 induction cycles) every 3 weeks (21 days, 1 cycle) followed by continued use of BI 695502 or Avastin® as a single agent for responding or stabilized patients (maintenance cycles) every 3 weeks (21 days, 1 cycle) until disease progression, death, withdrawal of consent, or unacceptable toxicity, whichever occurs earlier. | | |
| **Criteria for efficacy:** | Primary efficacy endpoint:<br>• Best ORR based on unconfirmed response assessment as assessed by central imaging review until 18 weeks after the start of treatment.<br>Secondary efficacy endpoints:<br>• Progression-free survival defined as the time from randomization until disease progression as per investigator assessment or death.<br>• Overall survival defined as the time from randomization until death from any cause.<br>• Duration of response defined as the time from first documented CR or PR until time of progression as per investigator assessment.<br>Other efficacy endpoints:<br>• Best ORR based on unconfirmed response assessments as per investigator assessment until 18 weeks after start of treatment.<br>• Best ORR based on unconfirmed response assessments as per investigator assessment until progression or death. | | |

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| **Criteria for safety:** | • The proportion of patients with the following selected adverse events (AEs) for comparability assessment of BI 695502 and US-licensed Avastin® (secondary endpoint): anaphylactic reactions/hypersensitivity reactions/infusion-related reactions; arterial and venous thromboembolic events; febrile neutropenia; gastrointestinal perforations; hypertension; proteinuria; pulmonary hemorrhage; other hemorrhages; wound-healing complications/abscess/fistulas.<br>• The proportion of patients with AEs.<br>• The proportion of patients with AEs related to trial treatment.<br>• The proportion of patients with Grade 3 or 4 AEs according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.<br>• The proportion of patients with Grade 3 or 4 AEs according to NCI-CTCAE version 4.0 related to trial treatment.<br>• The proportion of patients with protocol-specified adverse events of special interest.<br>• The proportion of patients with AEs potentially related to immunogenicity will also be evaluated.<br>• Physical examination, vital signs, weight, 12-lead electrocardiogram, laboratory findings. |
| **Statistical methods:** | The primary endpoint will be best ORR, based on unconfirmed response assessment, as assessed by central imaging review until 18 weeks after the start of treatment.<br>Stratification of patient randomization will be based on sex (male versus female), smoking status (never smoked versus current/past smoker), NSCLC stage at screening (recurrent disease versus Stage IV) and ethnicity (East Asian origin versus non East Asian).<br>Primary efficacy analysis:<br>Equivalence of BI 695502 to US-licensed Avastin® will be measured based on the ratio in best ORR (employing a log binomial regression model with subsequent transformation to ratio of proportions) and a margin of (0.736, 1.359) on the ORR ratio scale. The null hypothesis will be rejected in favor of equivalence if the 90% confidence interval (CI) for the ratio in best ORR between the treatments falls completely within the range defined by the equivalence margin; i.e., the comparison will be based on two one-sided tests with a 5% type I error rate. The primary analysis will be based on the full analysis set according to the intention-to-treat principle.<br>The equivalence margin (0.736, 1.359) for ORR ratio is based on a meta-analysis that included the following three studies: Sandler et al 2006 (R07-1161), Niho et al 2012 (R14_0473), and Johnson et al 2004 (R04-4661). |

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**Statistical methods (contd.):**

Secondary analyses:

Progression-free survival, OS, and duration of response will be assessed by a Cox-proportional hazards model using the same adjustment factors as for best ORR.

Safety analysis

All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No statistical testing will be performed for AEs. For all AE and serious AE tables, patients will be counted at most once for each preferred term and each system organ class. Adverse events will be summarized by the number and percentage of patients experiencing events by system organ class, preferred term and severity.

The analysis of the primary efficacy endpoint is not impacted by the switch from BI 695502 to Avastin® as all patients had already completed the Week 18 assessments at the time of the transition.

The main analyses will cover the period up until patients were switched from BI 695502 to Avastin® in the BI 695502 group and data will be analyzed to the extent available. Appropriate censoring methods will be applied at the time of switching and will be defined in the TSAP. Adverse events will be presented by underlying treatment and taking the corresponding exposure into account.

Additionally, after the transition from BI 695502 to Avastin® in the BI 695502 group, the impact of switching will be assessed based on the occurrence of relevant adverse events after the transition, i.e. anaphylactic reactions/hypersensitivity reactions/infusion-related reactions and the occurrence of anti-drug antibodies by comparing switched patients and patients receiving continuous treatment with Avastin®.

# FLOW CHART 1.1 – CYCLE 1 UP TO CYCLE 6

| **Trial Period** | **Screening** | **Treatment** | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Induction** | | | | **Induction/Maintenance** | |
| **Visit** | **0** | **1** | **2** | **3** | **4** | **5** | **6** |
| **Cycle** | **NA** | **1** | **2** | **3** | **4** | **5** | **6** |
| Informed consent | X | | | | | | |
| Assessment of eligibility (including EGFR and ALK mutation status[2]) | X | X | | | | | |
| Demographics | X | | | | | | |
| Medical and surgical history including surgery for lung cancer | X | | | | | | |
| Smoking status | X | | | | | | |
| Infection screen (hepatitis B, hepatitis C, TB), optional HIV test[3] | X | | | | | | |
| **LABORATORY/SAFETY ASSESSMENTS[4]** | | | | | | | |
| Serum pregnancy test[5] | X | | | | | | |
| Urine pregnancy test[6] | | X | | X | | X | |
| Physical examination (including height at Screening only) and weight | X | X | X | X | X | X | X |
| Vital signs[7] | X | X | X | X | X | X | X |
| Laboratory tests (serum chemistry, hematology, urinalysis, coagulation)[8] | X | X | X | X | X | X | X |
| 12-lead ECG[9] | X | | | X | | X | |
| Previous and concomitant therapy/medication | X | X | X | X | X | X | X |
| Adverse events[10] | X | X | X | X | X | X | X |
| **DISEASE ASSESSMENTS** | | | | | | | |
| Tumor assessment (CT[11] MRI scan ± PET scan[12]) | X[13] | | | X[14] | | X[14] | |
| ECOG PS | X | X | | X | | X | |
| Survival | | X----------X | | | | | |
| **OTHER ASSESSMENTS** | | | | | | | |

# FLOW CHART 1.1 – CYCLE 1 UP TO CYCLE 6 (continued)

| Trial Period | Screening | Treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | Induction | | | | Induction/Maintenance | |
| **Visit** | **0** | **1** | **2** | **3** | **4** | **5** | **6** |
| **Cycle** | **NA** | **1** | **2** | **3** | **4** | **5** | **6** |
| **TRIAL MEDICATION** | | | | | | | |
| Contact IXRS®[17] | X | X | X | X | X | X | X |
| Randomization | | X | | | | | |
| Trial medication infusion[18] | | X[19] | X | X | X | X | X |
| Paclitaxel premedication | | X | X | X | X[20] | X[20] | X[20] |
| Paclitaxel/carboplatin administration | | X | X | X | X[20] | (X)[20] | (X)[20] |

ALK = anaplastic lymphoma receptor tyrosine kinase; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HIV = human immunodeficiency virus; IXRS® = Interactive Telephone and Web Response System; MRI = magnetic resonance imaging; NA = not applicable; PET = positron emission tomography; PS = performance status; TB = tuberculosis.

1. Clinical assessments will be performed within 3 days before trial medication infusion.
2. EGFR and ALK mutation status will be evaluated at Screening according to local practice.
3. Hepatitis B and C testing to be performed at Screening unless obtained within 6 months prior to Screening. Screening for HIV and TB (purified protein derivative or QuantiFERON) to be performed according to local practice and local regulatory guidance.
4. Laboratory samples must be drawn prior to infusions of premedication and trial medication.
5. Only for females of childbearing potential (for definition, see Section 3.3.2, inclusion criterion #11). Serum pregnancy test will be performed at Screening and at subsequent visits if a urine pregnancy test is positive.
6. Only for females of childbearing potential. Urine pregnancy test will be performed every 6 weeks. Serum pregnancy test will be performed if a urine pregnancy test is positive.
7. Sitting blood pressure (5 minutes rest before start of measurement), respiratory rate, pulse, and body temperature. Two or more blood pressure readings should be taken at 2 minute intervals and averaged. If the first 2 diastolic readings differ by more than 5 mmHg, then an additional reading should be obtained, and averaged.
8. All trial-required laboratory tests will be analyzed by the central laboratory, unless specified in the protocol. For laboratory results that are required for decisions on chemotherapy administration, laboratory testing should be performed per standard-of-care, based on the site's regular practice. Blood samples may be analyzed locally, but will not be collected.
9. Patients should rest for at least 5 minutes in a supine position before ECG evaluations. Two consecutive recordings may be made at Screening, and before starting Cycle 3 and Cycle 5. The first of the consecutive ECGs is mandatory. The second of the consecutive ECGs is optional, at the discretion of the Investigator in case of clinical significance. Additional ECGs will be performed if clinically indicated.

10. All adverse events, regardless of relatedness, will be collected from the time of informed consent until up to 18 weeks after the last administration of trial medication. Adverse events continuing at the Safety Follow-up (SFU) visit must be followed until recovery or in case of persistency, sufficient characterization has been achieved and the investigator and medical monitor agree to not pursue them further.
11. CT scan with i.v. contrast of chest and abdomen, including adrenal glands and the entire liver, if applicable. In case of an iodine i.v.-contrast contraindication (renal insufficiency, allergy, hyperthyroidism etc), an abdomen MRI with contrast (gadolinium) will be performed with a non-contrast chest CT scan. Tumor assessment will be performed every 6 weeks (±3 days) during therapy.
12. A PET scan can be performed in addition to the CT scan, at Screening and at the End of Treatment visit. Combined PET-CT scans may be used only if performed with contrast and if resolution is sufficient to allow accurate and consistent comparison of lesion measurements with subsequent CT scans.
13. The screening tumor assessment should be performed within 21 days prior to randomization. Patients should have at least one measurable lesion according to RECIST 1.1 based on independent central review, to be confirmed prior to randomization (see Section 3.3.2).
14. The tumor assessment should be performed prior to trial medication administration. During the induction phase, tumor assessments should be performed before treatment administration of Cycles 3 and 5. If an induction therapy cycle is delayed, the tumor assessment will also be delayed.

17. IXRS® will be used for randomization, and at each visit to assign the correct vial for the allocated treatment group and the medication identification.
18. Administration of BI 695502/US-licensed Avastin® will occur on Day 1 of each cycle (every 21 days) prior to administration of paclitaxel and carboplatin.
19. Cycle 1 treatment to be administered within 4 days after randomization.
20. If the patient cannot tolerate more than 3 cycles of chemotherapy treatment, maintenance treatment with US-licensed Avastin®/BI 695502 monotherapy can be started.

# FLOW CHART 1.2 – CYCLE 7 ONWARDS

| | Treatment - Maintenance | | | | EOT[16] | Switch Visit prior to Avastin® administration[21] | Non-treatment period[17, 20] | SFU[18] | Survival[19] |
|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **7** | **8** | **9** | **10** | | | | | |
| **Cycle** | **7** | **8** | **9** | **10 and onwards** | | | | | |
| **LABORATORY/SAFETY ASSESSMENTS[2]** | | | | | | | | | |
| Serum pregnancy test[3] | | | | | X | X | | | |
| Urine pregnancy test[3] | X | | X | X[4] | | X | | | |
| Physical examination (including weight) | X | X | X | X | X | X | X | | |
| Vital signs[5] | X | X | X | X | X | X | X | X | |
| Laboratory tests (serum chemistry, hematology, urinalysis, coagulation) | X | X | X | X | X | X | X | | |
| 12-lead ECG[6] | X | | | X[7] | X | X | X | | |
| Concomitant therapy/medication | X | X | X | X | X | X | X | X | |
| Adverse events[8] | X | X | X | X | X | X | X | X | |
| Date of initiation of second-line therapy (if applicable). | | | | | | | | X | |
| **DISEASE ASSESSMENTS** | | | | | | | | | |
| Tumor assessment (CT[9]/MRI scan ± PET scan[10]) | X[11] | | | X[7] | X | X[22] | X | | |
| ECOG PS | X | | | X[7] | X | X | X | | |
| Survival | X---------- | | | | | | | | ----------X |
| **TRIAL MEDICATION** | | | | | | | | | |

| | Treatment - Maintenance | | | | EOT[16] | Switch Visit prior to Avastin® administration[21] | Non-treatment period[17, 20] | SFU[18] | Survival[19] |
|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **7** | **8** | **9** | **10** | | | | | |
| **Cycle** | **7** | **8** | **9** | **10 and onwards** | | | | | |
| Contact IXRS®[14] | X | X | X | X | | X | | | |
| Trial medication infusion[15, 23] | X | X | X | X | | X | | | |

CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; IXRS® = Interactive Telephone and Web Response System; MRI = magnetic resonance imaging; PET = positron emission tomography; PS = performance status; SFU = Safety Follow-up.

1. Clinical assessments will be performed within 3 days before trial medication infusion.
2. Laboratory samples must be drawn prior to infusions of premedication and trial medication.
3. Only for females of childbearing potential. Urine pregnancy test will be performed every 6 weeks. A serum pregnancy test should be performed if urine pregnancy test is positive.
4. Urine pregnancy test will be performed every 6 weeks from Cycle 11 onwards.
5. Sitting blood pressure (5 minutes rest before start of measurement), respiratory rate, pulse, and body temperature. Two or more blood pressure readings should be taken at 2 minute intervals and averaged. If the first 2 diastolic readings differ by more than 5 mmHg, then an additional reading should be obtained, and averaged.
6. Patients should rest for at least 5 minutes in a supine position prior to 12-lead ECG evaluations. Two consecutive recordings may be made. The first of the consecutive ECGs is mandatory. The second of the consecutive ECGs is optional, at the discretion of the Investigator in case of clinical significance. Additional ECGs will be performed if clinically indicated.
7. From Cycle 10 onwards, the following assessments should be performed every 3 cycles (approximately 9 weeks): 12-lead ECGs, tumor assessments (at least every 3 cycles or per investigator discretion), ECOG PS.
8. All adverse events (AEs), regardless of relatedness, will be collected from the time of informed consent until up to 18 weeks after the last administration of trial medication or discontinuation of Avastin®, whichever occurs later. Adverse events continuing at the SFU visit must be followed until recovery or in case of persistency, sufficient characterization has been achieved and the investigator and medical monitor agree to not pursue them further.
9. CT scan with i.v. contrast of chest and abdomen, including adrenal glands and the entire liver, if applicable. In case of an iodine i.v.-contrast contraindication (renal insufficiency, allergy, hyperthyroidism etc), an abdomen MRI with contrast (gadolinium) will be performed with a non-contrast chest CT scan. After Week 18, for patients receiving maintenance therapy and/or during the non-treatment period tumor assessment will be performed per the investigator's discretion, or a minimum of every 9 weeks (±3 days), and at the EOT visit. If a maintenance therapy cycle is delayed, the tumor assessment will also be delayed.
10. A PET scan can be performed in addition to the CT scan, at the EOT visit. Combined PET-CT scans may be used only if performed with contrast and if resolution is sufficient to allow accurate and consistent comparison of lesion measurements with subsequent CT scans.

11. The tumor assessment should be performed prior to trial medication administration. In case of a treatment cycle delay (i.e. due to toxicity), imaging assessment (e.g. CT, MRI) for the primary endpoint will be performed at Week 18 ±14 days (fixed time point), regardless of the number of cycles administered to date.

14. IXRS® will be used at each visit to assign the correct vial for the allocated treatment group and the medication identification.
15. Administration of BI 695502/Avastin® will occur on Day 1 of each cycle (every 21 days).
16. For all patients who receive at least one infusion of BI 695502 or Avastin® the EOT visit will be performed within 21 days after the last administration of trial medication.
17. For all patients who discontinue BI 695502/Avastin® for reasons other than disease progression and do not withdraw consent, visits will occur every 3 weeks after the End of Treatment visit until initiation of new treatment, disease progression, or death.
18. All patients who received at least one infusion of BI 695502 or US-licensed Avastin® will attend a SFU visit 18 weeks after the last administration of trial medication prior to the switch visit. If the patient continues to receive treatment with Avastin® beyond 18 weeks post last IMP dose, then no SFU visit will be performed.
19. After the SFU visit or discontinuation of Avastin®, whichever occurs later, all patients will be monitored for survival every 3 months via telephone call until death, see Section 6.2.3.
20. If a patient remains in the non-treatment period beyond 18 weeks post last dose of trial medication, he/she will be treated according to standard of care, and assessed for tumor progression every 6 to 9 weeks according to clinical judgment. Tumor assessments and all AEs, regardless of relatedness, will be collected at these visits. The date of initiation of second-line therapy should be recorded (if applicable).
21. During the Switch Visit (the next scheduled cycle visit per protocol following 21 Dec 2017), assessments not already scheduled should be performed prior to Avastin® administration.
22. To be performed only if a tumor assessment was not performed within the previous 4 weeks.
23. Starting as of 21 Dec 2017, the Sponsor recommends that patients should be switched from BI 695502 to Avastin®; therefore, from this date onward, patients should receive Avastin® at the Cycle Visits, as soon as Avastin® is available at the clinical site. If Avastin® is not immediately available, the Investigators may temporarily allow continuation on BI 695502.

# TABLE OF CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALK | Anaplastic lymphoma kinase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| CA | Competent authority |
| CI | Confidence interval |
| CL | Clearance |
| CR | Complete response |
| CRA | Clinical Research Associate |
| CRF | Case report form |
| CRO | Contract research organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CT | Computed tomography |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DILI | Drug Induced Liver Injury |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EDTA | Ethylenediaminetetraacetic acid |
| EGFR | Epidermal growth factor receptor |
| ELISA | Enzyme-linked immunosorbent assay |
| EOT | End of Treatment |
| FAS | Full analysis set |
| FDG | fludeoxyglucose |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| GFR | Glomerular filtration rate |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IMP | Investigational medicinal product |
| INVICTAN®-2 | Trial name of the study |
| IRB | Institutional Review Board |

| | |
|---|---|
| ISF | Investigator Site File |
| i.v. | intravenous |
| IXRS® | Interactive Telephone and Web Response System |
| LFT | Liver function test |
| MRI | Magnetic resonance imaging |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| nsNSCLC | Nonsquamous non-small cell lung cancer |
| NSAIDs | Nonsteroidal anti-inflammatory drugs |
| NSCLC | Non-small cell lung cancer |
| NTL | Non-target lesion |
| ORR | Overall response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PET | Positron emission tomography |
| PFS | Progression-free survival |
| PH | Proportional hazards |
| PPD | Purified protein derivative |
| PPS | Per-protocol set |
| PR | Partial response |
| PS | Performance status |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| REP | Residual effect period |
| RPLS | Reversible posterior leukoencephalopathy syndrome |
| SAE | Serious adverse event |
| SD | Stable disease |
| SFU | Safety follow-up |
| SPC | Summary of Product Characteristics |
| SOP | Standard operating procedure |
| TB | Tuberculosis |
| TL | Target lesion |
| TOST | Two one-sided tests |
| TNM | Tumor, node, metastasis |
| TSAP | Trial Statistical Analysis Plan |
| ULN | Upper limit of normal |
| US | United States |
| Vc | Volume of distribution |
| VEGF | Vascular endothelial growth factor |

# 1. INTRODUCTION

## 1.1 MEDICAL BACKGROUND

Worldwide, lung cancer is the most common cause of cancer-related death in men and women, and is responsible for almost 1.4 million deaths annually (R13_1113). Approximately 85% of these patients have non–small cell lung cancer (NSCLC). Only 15.9% of all lung cancer patients are alive 5 years or more after diagnosis.

The stage of disease is often advanced at the time of diagnosis with 30% to 40% of NSCLC cases being classified as Stage IV (P14-01224). The prognosis of patients with advanced stage disease is poor. Patients with clinical Stage IV disease have an historical median survival of 6 months (R11-0052) with best supportive care; in patients fit enough to receive chemotherapy recent combination regimens have improved survival to about 8 to 10 months. The addition of bevacizumab has further prolonged survival in nonsquamous NSCLC (nsNSCLC) to about 12 months.

A tissue diagnosis is frequently performed and may guide therapy when a target agent is available, because recent advances have shown that optimal therapy depends on the histology of NSCLC (squamous versus nonsquamous histology) and whether there are certain mutations in the tumor. Patients with mutations in the epidermal growth factor receptor (EGFR) and the anaplastic lymphoma kinase (ALK) gene can benefit from a variety of oral tyrosine kinase inhibitors (R09-0256, R12-1015, R13-1390). Of note, tumors with these mutations typically have nonsquamous histology. Additionally, the presence of the EGFR mutation appears to vary by ethnic origin of the patient; approximately 15% of patients in the United States (US) and European Union (EU) have an EGFR mutation while the rate is roughly double that in East Asia (R07-1194).

Patients with no known mutations or with a mutation but no access to the targeted agent are generally treated with cytotoxic chemotherapy as their first-line treatment. Contemporary first-line chemotherapy usually, but not exclusively, combines a platinum agent (cisplatin or carboplatin) with another cytotoxic agent (R09-5804). Platinum agents may be combined with compounds such as pemetrexed, gemcitabine, taxanes or vinorelbine (R08-4164). Nonplatinum-based regimens such as gemcitabine and vinorelbine or gemcitabine and docetaxel are also accepted options (R13-5402).

The Eastern Cooperative Oncology Group (ECOG) conducted a randomized clinical trial comparing four platinum-based, two-drug chemotherapy regimens in more than 1100 patients. The regimens included in this trial were cisplatin and paclitaxel, cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel. The median survival was 8 months, with no significant differences in overall survival (OS) among the groups (R04-1314).

The platinum-doublet regimens have slightly different toxicities, convenience and costs, and this can direct the choice of the physician in selecting the preferred therapy for their patients. Thus, the standard of care in 2014 for patients without a known mutation or with a mutation but no access to the targeted agent is initially a two-drug combination usually using a

platinum agent for 4 to 6 cycles. This is referred to as initial systemic chemotherapy or occasionally as "induction" therapy. For those patients with nonsquamous histology, and no risk of major bleeding, the addition of bevacizumab showed a benefit in survival and has become standard of care.

Regarding the optimal number of 'induction' cycles of chemotherapy, in trials comparing 4 or 6 cycles of chemotherapy, no survival benefit was shown with the administration of more than 4 cycles (R13-5426). In the last session of 2011, the American Society of Clinical Oncology panel of experts recommended not to administer more than 4 cycles in nonresponding patients. Finally, in two recently published trials, all patients were given a maximum of 4 cycles of chemotherapy followed by maintenance treatment. In Patel's trial, in the arm using 4 cycles of chemotherapy/bevacizumab followed by maintenance with bevacizumab alone, OS was 13 months i.e., similar to that reported in Sandler's trial in which patients received an average of 5 induction cycles (R13-5425). In the ATLAS trial, in which all responding and stabilized patients received maintenance treatment, OS was 13.6 months in the arm receiving bevacizumab alone (R13-5424).

Specific targeted therapies have been developed for the treatment of advanced NSCLC (R05-1052). Bevacizumab, a recombinant monoclonal antibody that targets the vascular endothelial growth factor (VEGF), was approved in 2006 by the US Food and Drug Administration (FDA) for patients with unresectable, locally advanced, recurrent, or metastatic nsNSCLC.

The ECOG recommends treatment with bevacizumab in combination with paclitaxel and carboplatin for selected patients with advanced nsNSCLC based on the results of the Phase III ECOG 4599 trial (R07-1161). In this study, the addition of bevacizumab significantly increased the response rate (35% versus 15%, $p<0.001$), median progression-free survival (PFS) (6.2 versus 4.5 months, $p<0.001$) and median survival (12.3 versus 10.3 months, $p=0.003$).

Selection criteria for the use of bevacizumab included, besides nonsquamous histology, no recent history of hemoptysis, and ECOG performance status (PS) 0 to 1. Bevacizumab should be used with caution in case of high risk of thrombocytopenia, and potential possible bleeding.

Accordingly, carboplatin and paclitaxel with bevacizumab represents one of the frequently used first-line regimens suitable for nonmutated EGFR and ALK nsNSCLC.

## 1.2 DRUG PROFILE

BI 695502, a monoclonal antibody, is being developed as a proposed biosimilar product to the bevacizumab product Avastin® approved in the EU and in the US (R15 -1223, R18-0043). BI 695502 is a genetically engineered humanized monoclonal antibody directed against human VEGF that selectively binds with high affinity to VEGF and neutralizes VEGF's biologic activity through a steric blockade of the binding of VEGF to its receptors on the surface of endothelial cells.

BI 695502 is produced in Chinese hamster ovary cells. It is manufactured using standard mammalian cell culture techniques, followed by a series of protein purification steps, including several chromatography steps as well as steps for removal and inactivation of potential viruses. Bevacizumab has shown antitumor activity and clinical benefit in combination with chemotherapy and Avastin® is approved for use in metastatic colorectal cancer (US, EU), advanced NSCLC (US, EU), metastatic renal cell cancer (US, EU), metastatic breast cancer (EU only), advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (EU, US), metastatic cervical cancer (US, EU), and as a single agent for glioblastoma (US only) (R15-1223, R18-0043). The local approval status for Avastin® can differ in countries outside of the US and the EU.

# 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

## 2.1 RATIONALE FOR PERFORMING THE TRIAL

BI 695502 is being developed as a proposed biosimilar to Avastin® (bevacizumab), which is planned to meet the need for alternatives to high-priced biologic agents in oncology treatments. The planned clinical development follows the currently understood concepts from published guidance documents and statements from regulatory authorities for biosimilar monoclonal antibody development. The general approach is to demonstrate in a homogenous population a high degree of similarity (i.e., statistical similarity) between the biosimilar and originator compound, at first in pharmacokinetic (PK)/pharmacodynamic and secondly in clinical efficacy, using a suitable endpoint, while also demonstrating a high degree of similarity (but not necessarily statistical similarity) for safety and immunogenicity.

The addition of bevacizumab to chemotherapy has been shown to be effective in nsNSCLC in terms of benefit in overall response rate (ORR), PFS and OS. The planned trial design follows that of three randomized trials using the same class of cytotoxic drugs, and dose of bevacizumab in patients with tumors of the same histology (Sandler et al 2006 [R07-1161], Niho et al 2012 [R14-0473], Johnson et al 2013 [R13-5424]). The weighted ORR, based on a total N of 1005 patients (bevacizumab: 530, chemotherapy alone: 475) is 43.3% for the bevacizumab 15 mg/kg plus chemotherapy group versus 20.0% for the chemotherapy alone group, resulting in a ORR ratio for bevacizumab versus chemotherapy alone of 2.220 with a 90% confidence interval (CI) of (1.847, 2.668). Such observation and feasibility considerations are the basis of the statistical rationale for the proposed clinical trial (see Section 7.2). A Phase I trial in healthy volunteers has already established pair-wise PK similarity between BI 695502, US-licensed Avastin®, and EU-approved Avastin® following one intravenous (i.v.) infusion (Trial 1302.1).

In this pivotal Phase III trial, patients with nsNSCLC will be randomly assigned to receive either BI 695502 or US-licensed Avastin®, plus chemotherapy according to standard of care (see Section 3.1 for details).

Since the introduction of bevacizumab in the therapeutic armamentarium, other targeted agents have become standard of care for patients with tumor-expressing activating mutations in EGFR and ALK receptor. Patients harboring tumors with unknown or activating EGFR and/or ALK mutation may be included provided chemotherapy is the site standard of care.

The trial will be conducted in compliance with the Clinical Trial Protocol (CTP), the International Conference on Harmonisation (ICH) guidelines, Good Clinical Practice (GCP) and with all applicable and current regulatory requirements.

## 2.2 TRIAL OBJECTIVES

### 2.2.1 Primary objective

The primary objective of this trial is to establish statistical equivalence in terms of efficacy (best ORR, proportion of patients with complete response [CR] plus partial response [PR], not required to be confirmed by a subsequent assessment) until 18 weeks of first-line treatment with BI 695502 plus chemotherapy versus US-licensed Avastin® plus chemotherapy followed by maintenance monotherapy with either BI 695502 or US-licensed Avastin®.

### 2.2.2 Secondary objectives

The secondary objectives of the trial are to evaluate further efficacy parameters (progression-free survival [PFS], overall survival [OS], duration of response) and the safety and tolerability of BI 695502 versus US-licensed Avastin®.

## 2.3 BENEFIT - RISK ASSESSMENT

Patients enrolled into this equivalence trial are expected to derive similar benefit and risk from the trial treatment across both arms. This is based on the similarity observed during pre-clinical, analytical, functional and toxicological testing between the investigational medicinal product and the comparator.

Patient risk will be minimized by implementing conservative eligibility criteria, regular and long-term safety monitoring, including immunogenicity testing.

Although rare, the potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.

There is an increased risk of gastrointestinal (GI) perforation in patients treated with Avastin®. The incidence of GI perforation ranged from 0.3% to 2.4% across clinical studies (R15-1223, R18-0043). Typical symptoms may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of Avastin®. The investigator is required to monitor the patients at regular intervals throughout the trial for any new or worsening symptoms or signs that may be suggestive of GI perforation.

Animal studies have shown that Avastin® impairs wound healing and an increased risk of wound healing complications has been observed in patients with metastatic colorectal cancer

who underwent surgery during the course of Avastin®. Therefore no major surgery is permitted within 28 days prior to the first dose of BI 695502/US-licensed Avastin®. If elective surgery is required during the course of the trial, then the trial medication should be discontinued at least 28 days prior to the procedure. Patients who undergo elective surgery during the trial or patients with anticipated elective surgery will be excluded from the trial.

Treatment with Avastin® has been shown to be associated with an increased risk of hemorrhage (including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding) and arterial thromboembolic events (including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina). Patients who have had a thrombotic or hemorrhagic event within 6 months prior to Screening will not be permitted to enter the trial. No anticoagulation therapy is allowed within 10 days of the first dose of trial medication or during the trial except for venous access or daily aspirin up to 325 mg.

The use of Avastin® has been shown to be associated with an increased risk of reversible posterior leukoencephalopathy syndrome (RPLS). The investigator is required to monitor the patients at regular intervals throughout the trial for any new or worsening neurological symptoms or signs that may be suggestive of RPLS (typical symptoms are diverse and include headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances). If a patient develops new or worsening neurological signs or symptoms, he/she will be evaluated for RPLS. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of RPLS. Any patient who is suspected of developing RPLS will be discontinued from the trial and the adverse event (AE) will be followed closely (see Section 5.2.2.2). Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae.

The incidence of severe hypertension increases in patients receiving Avastin®. Patients with systolic/diastolic blood pressure >150/100 mmHg (in the presence or absence of a stable regimen of antihypertensive therapy) are excluded from this trial. Blood pressure will be monitored every 3 weeks during the trial. Patients who develop hypertension should be treated with appropriate antihypertensive therapy at the investigator's discretion and should continue to have their blood pressure regularly monitored.

Repeat dose toxicity studies in animals have shown that Avastin® may have an adverse effect on female fertility. In a Phase III trial in the adjuvant treatment of patients with colon cancer, a substudy with premenopausal women has shown a higher incidence of new cases of ovarian failure in the Avastin® group compared to the control group. After discontinuation of Avastin® treatment, ovarian function recovered in the majority (R15-1223, R18-0043). The investigator should discuss fertility preservation strategies with the patient prior to starting treatment in this trial, as appropriate.

Due consideration has been given to previous experience with Avastin® in NSCLC patients and toxicity management advice (e.g., for hypersensitivity reactions) is provided in this CTP. A Data Safety Monitoring Board (DSMB) was established to review the safety and efficacy data of BI 695502 compared with data for the active comparator and to review accumulating

safety data at regular intervals throughout the trial (see Section 7.3.5 for further details). For details of blinding, please refer to Section 4.1.5.1.

Trial 1302.1 was a Phase 1 randomized, single-blind, single-dose, two-stage, parallel-arm, active comparator trial. In total, 91 healthy, male subjects were treated: 30 subjects were administered 1 mg/kg BI 695502, 31 subjects were administered 1 mg/kg EU-approved Avastin®, and 30 subjects were administered 1 mg/kg US-licensed Avastin®. Based on the PK results obtained from this trial, similarity could be demonstrated for all comparisons of the trial medications. No serious adverse events (SAEs), severe AEs, or other significant AEs were reported and no subject discontinued trial medication due to an AE. A total of 73 (80.2%) subjects reported at least one AE. Fewer subjects reported AEs for US-licensed Avastin® (70.0%) than for BI 695502 (86.7%) and EU-approved Avastin® (83.9%). No Grade 3, 4, or 5 AEs were reported and the majority of AEs were Grade 1 for all three trial medications. By preferred term the most frequently reported AEs were upper respiratory tract infection and headache. Overall, there was no relevant difference in the safety results for the three trial medications and no safety concerns were identified.

Based on extensive preclinical, analytical, functional and toxicological testing carried out prior to initiation of this trial, and the Phase 1 data described above, BI 695502, as a proposed biosimilar product, may be seen to provide similar efficacy, safety, immunogenicity and PK to Avastin® (US-licensed/EU-approved) in patients with advanced nsNSCLC.

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase III, randomized, double-blind, multicenter, active comparator, parallel two-arm trial.

Approximately 660 patients (330 patients per arm) with advanced nsNSCLC will be randomized in a 1:1 ratio to receive either BI 695502 (Arm B) or US-licensed Avastin® (Arm A) in combination with paclitaxel and carboplatin. Japan will randomize at least 10% of patients in the trial and this will be capped if needed.

Patients will receive treatment with 15 mg/kg of BI 695502 or US-licensed Avastin® followed by standard combination chemotherapy consisting of paclitaxel 200 mg/m$^2$ (according to regular institutional practice) followed by carboplatin target area under the curve (AUC) 6 mg/mL•min (30- to 60-minute infusion) with adequate pre- and concomitant medication every 3 weeks (each cycle) for up to 6 cycles (induction cycles).

After Cycle 4 to 6, if the patient has CR, PR or stable disease (SD), i.e., responding or stabilized patients, maintenance treatment with BI 695502/ US-licensed Avastin® monotherapy can be started per the original randomization. Patients will then receive BI 695502 or US-licensed Avastin® as a single agent until disease progression (according to Response Evaluation Criteria in Solid Tumors 1.1 [RECIST 1.1]), death, withdrawal of consent, or unacceptable toxicity, whichever occurs earlier.

A DSMB will review safety data from 40 patients (20 patients per treatment group) after 3 cycles of treatment have been completed (see Section 7.3.5.1).

The fully blinded, pooled ORR will be closely monitored to verify the sample size assumptions. After approximately 200 patients (100 patients per arm) have had tumor response assessments performed until Week 18, an independent blinded statistician will perform a blinded evaluation to confirm the initially calculated sample size.

The primary endpoint of the trial is the best ORR (CR + PR, based on unconfirmed response assessment) until the Week 18 assessment. The primary analysis will be performed after all patients in the primary analysis population have had tumor response assessments performed until Week 18. This analysis will include the primary efficacy endpoint as well as all available secondary efficacy endpoints and safety data.

Patients will undergo visits and trial procedures as shown in Flow chart 1.1 and Flow chart 1.2.

Patients may return for unscheduled visits should their medical condition warrant urgent attention at the discretion of the investigator.

Starting as of 21 Dec 2017, the Sponsor recommends that patients should be switched from BI 695502 to the reference product bevacizumab (IMP or commercially available Avastin®, both hereafter referred to as Avastin®) as soon as it is available at the respective clinical site.

If Avastin® is not immediately available, the Investigators may temporarily allow continuation on BI 695502. The blind will be kept intact and all patients will continue the study with no additional visits in the scheduled visit cycle as per protocol.

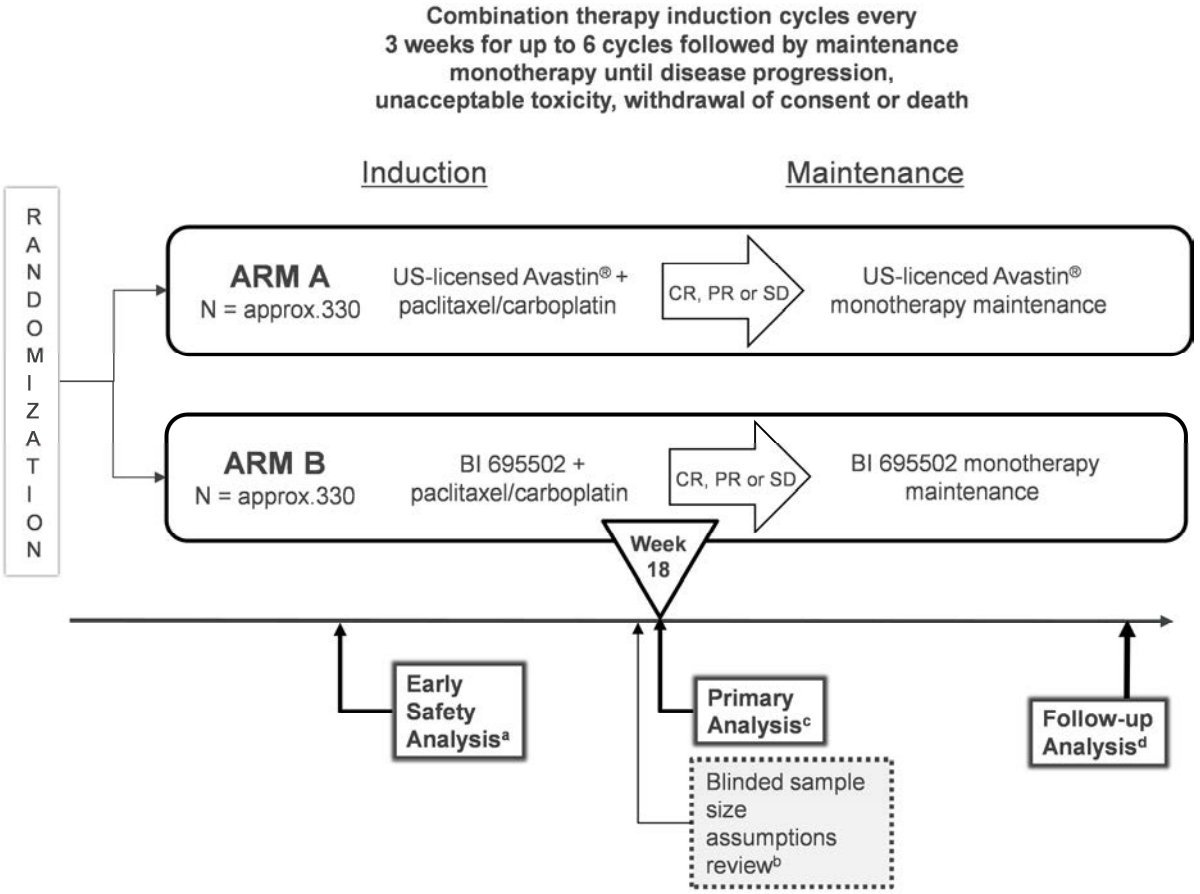
All patients who receive at least one infusion of BI 695502 or US-licensed Avastin® should return for an End of Treatment (EOT) visit within 21 days after their last administration of BI 695502 or Avastin® (see Section 3.3.4.1).

In addition, all patients should return for a Safety Follow-up (SFU) visit 18 weeks after their last administration of trial medication prior to the switch visit. If the patient continues to receive treatment with Avastin® beyond 18 weeks post last IP dose, then no SFU visit will be performed.

Patients who discontinue trial medication for reasons other than disease progression, but who do not withdraw consent will remain in the trial (non-treatment period) until initiation of a new treatment, disease progression, or death, whichever occurs earlier. Visits will be performed every 3 weeks (see Section 6.2.3) after the EOT visit. If a patient remains in the non-treatment period beyond 18 weeks post last dose of trial medication, he/she will be treated according to standard of care, and assessed for tumor progression every 6 to 9 weeks according to clinical judgment.

After the SFU visit or discontinuation of Avastin® (whichever occurs later), patients will be monitored for survival every 3 months until death or the end of the trial, whichever is earlier (see Section 6.2.3).

An overview of the trial design is shown in Figure 3.1: 1.




a An early safety analysis will be reviewed after approximately 20 patients per arm have been treated for 3 cycles (40 patients). See Section 7.3.5.1 for details.

b. Blinded sample size assumptions review to start when approximately 200 patients (100 patients per arm) have had tumor response assessments performed until Week 18 (see Section 7.3.5.2).

c. The primary analysis will be performed after all patients in the primary analysis population have had tumor response assessments performed until Week 18 (see Section 7.3.5.3).

d. A follow-up analysis will be conducted at a later time point, as required by the regulatory authorities (see Section 7.3.5.3).

Note: Starting as of 21 Dec 2017, the Sponsor recommends that patients should be switched from BI 695502 to the reference product Avastin® as soon as it is available at the respective clinical site. If Avastin® is not immediately available, the Investigators may temporarily allow continuation on BI 695502. The blind will be kept intact and all patients will continue the study with no additional visits in the scheduled visit cycle as per protocol.

Figure 3.1: 1 Overview of trial design

### 3.1.1 Administrative structure of the trial

Data will be reviewed by a DSMB (see Section 7.3.5). The DSMB will act in an advisory capacity to monitor patient safety and efficacy during the trial. The members will be selected on the basis of relevant experience and understanding of clinical research and the issues specific to the therapeutic area, as well as previous DSMB experience.

Details on the DSMB, including the analyses, the composition of the DSMB, the procedures, roles, responsibilities and their interactions will be described in the DSMB charter.

## 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

This is a Phase III, randomized, double-blind, multicenter, active comparator, parallel two-arm trial to compare the efficacy, safety and immunogenicity of BI 695502 to US-licensed Avastin® in patients with previously untreated advanced nsNSCLC.

Patients will initially be randomized in a 1:1 ratio to receive BI 695502 plus paclitaxel/carboplatin or US-licensed Avastin® plus paclitaxel/carboplatin. After approximately 200 patients (100 patients per arm) have had tumor response assessments performed until Week 18, an independent blinded statistician will perform a blinded evaluation to confirm the initially calculated sample size.

Paclitaxel + carboplatin + Avastin® is an accepted first-line chemotherapy regimen for patients with advanced nsNSCLC. This regimen conferred a significant improvement in OS, PFS, and response rate in patients with nsNSCLC and a good performance status (R07-1161).

This is a double-blind trial to minimize any bias that could be introduced by knowledge of the treatment by either the investigator or the patient.

The primary focus of this trial is to demonstrate similarity of BI 695502 with US-licensed Avastin®.

## 3.3 SELECTION OF TRIAL POPULATION

A log of all patients enrolled in the study (i.e., having given informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with investigational drug (BI 695502/US-licensed Avastin®) or not.

### 3.3.1 Main diagnosis for study entry

The main requirements for trial entry include adult patients ≥18 years of age (for Japan only: Age ≥20 years at Screening), with recurrent or metastatic disease (Stage IV), histologically or cytologically confirmed advanced nsNSCLC. For patients with recurrent disease, cytotoxic chemotherapy treatment or radiotherapy for locally advanced tumor must have been stopped for at least 12 months prior to Screening. Patients harboring tumors without activating EGFR/ALK mutation will be eligible. Patients with unknown or activating EGFR/ALK

mutation may be included provided chemotherapy is the site standard of care. Patients must have an ECOG PS of 0 or 1 and have at least one measurable lesion according to RECIST criteria 1.1. Patients must have no contraindication to Avastin® and must have adequate hepatic, renal, and bone marrow function.

### 3.3.2 Inclusion criteria

1. Males and females aged ≥18 years (for Japan only: Age ≥20 years at Screening) with histologically or cytologically confirmed nsNSCLC. Mixed tumors should be categorized according to the predominant histology.

   Note: NSCLC should be predominantly nonsquamous.
2. Recurrent or metastatic disease (Stage IV) with an indication for therapy with paclitaxel + carboplatin + Avastin® (see Appendix 10.5).
3. All patients must sign and date an Informed Consent Form consistent with ICH GCP guidelines and local legislation prior to participation in the trial (i.e., prior to any trial procedures, which include medication washout and restrictions) and be willing to follow the CTP.
4. Patients harboring tumors without activating EGFR mutation. Patients with unknown or activating EGFR mutation may be included provided chemotherapy is the site standard of care. Despite EGFR mutational status, patients may enter the trial if the site's best standard of care would be to administer such a chemotherapy regimen for that specific patient. However, if an EGFR test result is pending, and chemotherapy treatment would be switched in case of a mutational positive result, patients may not be included in this trial.
5. Patients harboring tumors without activating ALK mutation. Patients with unknown or activating ALK mutation may be included provided chemotherapy is the site standard of care. Despite ALK mutational status, patients may enter the trial if the site's best standard of care would be to administer such a chemotherapy regimen for that specific patient. However, if an ALK test result is pending, and chemotherapy treatment would be switched in case of a mutational positive result, patients may not be included in this trial.
6. At least one measurable lesion according to RECIST 1.1 based on independent central review.
7. ECOG PS 0 or 1.
8. Adequate hepatic, renal, and bone marrow function:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤2.5 x ULN. If liver metastases are present, ALT or AST ≤5 x ULN.
   b. Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in the presence of hepatic and/or bone metastases).
   c. Serum bilirubin ≤1.5 x ULN, except in the case of known Gilbert's syndrome.
   d. Serum creatinine ≤1.5 x upper limit of normal (ULN) or a creatinine clearance of ≥50 mL/min calculated by Cockroft-Gault formula.
   e. Proteinuria <2 g in 24 hours or an equivalent protein/creatinine ratio of <2000 mg/g creatinine (or <226 mg/mmol creatinine).

f. Absolute neutrophil count >1.5 x$10^9$/L.
g. Platelet count >100 x$10^9$/L.
h. Hemoglobin ≥9 g/dL (without transfusion within 2 weeks prior to randomization).

9. International normalized ratio ≤1.4 as analyzed locally. Partial thromboplastin time within normal limits according to local practice. Central laboratory analysis will be used for coagulation parameters where local analysis is not available.
10. Life expectancy >6 months based on clinical investigator's judgment.
11. For participants of reproductive potential (males and females), use of a medically acceptable method of contraception during the trial, i.e., a combination of two forms of effective contraception (defined as hormonal contraception, intrauterine device, condom with spermicide, etc). All subjects (males and females of childbearing potential) must also agree to use an acceptable method of contraception (see above) for 6 months following completion or discontinuation from the trial medication. A list of contraception methods meeting these criteria is provided in the patient information. Females will be defined as of childbearing potential if they have not undergone a permanent contraceptive operation or they are not postmenopausal. Permanent contraceptive operation is defined as: hysterectomy, hysterosalpingectomy, or bilateral oophorectomy. The status of a female should be considered as postmenopausal when she has not had a period for 12 consecutive months without an alternative medical cause.

### 3.3.3 Exclusion criteria

1. Prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including Avastin®.
2. Prior systemic therapy for metastatic disease.
3. Prior systemic anticancer therapy or radiotherapy for locally advanced nsNSCLC if completed <12 months prior to Screening.
4. Patients who have results pending for EGFR/ALK mutation status, to the investigator's knowledge.
5. Previous malignancy other than NSCLC in the last 5 years except for basal cell cancer of the skin or pre-invasive cancer of the cervix.
6. Patients with known symptomatic brain metastasis:
    a. Brain metastasis which is symptomatic at screening or randomization visits, or
    b. Patients who have previously irradiated brain metastasis that has not been shown to be stable at least 1 month after completion of the radiation therapy (either by CT scan or MRI) at screening visit.
7. Diagnosis of small cell carcinoma of the lung, squamous cell carcinoma of the lung, NSCLC NS (not specified) or NSCLC NOS (not otherwise specified).
8. Patients with tumor/metastases cavitation, or invading into large blood vessels.
9. Patients with tumor/metastases close to large blood vessels that may have an increased risk of bleeding, according to investigator's judgment.

10. Any unresolved toxicity >Common Toxicity Criteria Grade 1 (except alopecia) from previous anticancer therapy (including radiotherapy).
11. History or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding. Clinically non-significant minor bleeding is acceptable.
12. A thrombotic or hemorrhagic event ≤6 months prior to Screening (includes hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, vaginal bleeding, cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and coronary artery disease).
13. Current or recent (within 10 days of first dose of BI 695502/US-licensed Avastin®) regular use of aspirin (>325 mg/day) or other non-steroidal anti-inflammatory drugs (NSAIDs) with antiplatelet activity or treatment with dipyridamole, ticlopidine, clopidogrel or cilostazol.
14. Current treatment with oral, inhaled or topical corticosteroids; the dose must not exceed 10 mg/day prednisolone or equivalent. During the 4 weeks prior to Day 1, the dose must be stable.
15. Intravenous, intramuscular, intra-articular, or parenteral corticosteroids within 6 weeks prior to Day 1 or throughout the trial, unless used for paclitaxel infusion premedication, according to regular institutional practice.
16. Current or recent (within 10 days of first dose of BI 695502/US-licensed Avastin®) use of full-dose oral or parenteral anticoagulants or other thrombolytic agents for therapeutic (as opposed to prophylactic) purposes, clinically serious (as judged by the investigator) nonhealing wounds, or incompletely healed bone fracture.
17. Live/attenuated vaccine within 12 weeks prior to the Screening Visit.
18. History of myocardial infarction (≤6 months prior to Screening), unstable angina, New York Heart Association Grade II or greater, congestive heart failure, or serious cardiac arrhythmia requiring medication.
19. Patients with a history of poorly controlled hypertension or with resting blood pressure >150/100 mmHg in the presence or absence of a stable regimen of antihypertensive therapy (see Section 5.2.5).
20. Any surgical procedure within 28 days prior to the first dose of BI 695502/US-licensed Avastin® or anticipated elective surgery during the trial (see Table 4.2.2.1: 1 for details).
21. History of active gastroduodenal ulcer(s).
22. History of abdominal fistula as well as non-GI fistula, GI perforation or intra-abdominal abscess within 6 months prior to Screening.
23. Active or chronic hepatitis B or C, ongoing human immunodeficiency virus (HIV) infection, or tuberculosis (TB) (see Section 5.2.3). Screening for HIV and TB (purified protein derivative [PPD] or QuantiFERON) to be performed according to local practice and local regulatory guidance. There should be no radiographic or clinical evidence of active TB.
24. Treatment within a clinical trial within 4 weeks prior to initiation of trial treatment. Patients who have received treatment with a drug that has not received regulatory

approval for any indication within 4 weeks or a minimum of 5 half-lives, whichever is longer, of the initial dose of trial medication.

25. Patient considered unsuitable for inclusion by the investigator (e.g., inability to understand and/or comply with study requirements or presence of any condition which, in the opinion of the investigator, would not allow safe participation in the trial).
26. Pregnant or lactating women.
27. Known hypersensitivity to any of the trial drugs or their excipients.

### 3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

Patients may have already been pre-randomized to a treatment group at Screening (see Section 4.1.2 for details). Patients who do not meet all of the inclusion criteria or meet at least one of the exclusion criteria will not be randomized, and will be considered screen failures. The primary reason for the screen failure will be recorded on the electronic case report form (eCRF). Re-screening will be allowed on a case by case basis based on discussion with the medical monitor. Patients may be re-screened once in order to fulfil all the inclusion criteria, provided the patient would receive the bevacizumab + paclitaxel/carboplatin regimen in regular practice at the Investigator's discretion.

Patients have the right to withdraw from this trial at any time for any reason. The investigator has the right to withdraw patients from the trial if further participation in the trial may not be in the best interest of the patient.

Patients will be discontinued from trial treatment for the following reasons:

- Investigator decision due to an intolerable AE or laboratory value including but not limited to:
  - Patients who cannot tolerate at least 3 cycles of chemotherapy, or are given another backbone chemotherapy at any time.
  - Progressive disease.
  - Life-threatening reaction, including anaphylaxis, hypersensitivity reaction, renal failure, severe cardiopulmonary event and severe muco-cutaneous reaction.
  - GI perforations (including fistula formation in the GI tract, intra-abdominal abscess).
  - Fistula formation involving an internal organ.
  - Wound dehiscence and wound healing complications requiring medical intervention.
- Serious hemorrhage (i.e., requiring medical intervention).
- Severe arterial thromboembolic events.
- Hypertensive crisis or hypertensive encephalopathy.
- RPLS.
- Nephrotic syndrome.
- Congestive heart failure, any degree.

- Severe hypertension, moderate to severe proteinuria, or severe infusion reactions if the event cannot be adequately controlled within 14 days.
- Repeated protocol violation after documented discussion with the medical monitor.
- Pregnancy in a female participant.
  - The sponsor or sponsor designee is to be notified immediately (see Section 5.2.2.2)
- Any concomitant illness that prevents compliance.

Patients will be withdrawn from the trial for the following reasons:
- The patient is unwilling to continue in the trial.
- The investigator or the sponsor, for any reason, stops the trial.
- Patient lost to follow-up despite reasonable efforts to make contact with the patient. The investigator/designee must make two telephone calls, after which a registered letter must be sent. The dates of the telephone calls and the registered letter will be documented in the source documents.

Patients discontinued from trial treatment or withdrawn from the trial will not be replaced, regardless of the reason for discontinuation/withdrawal.

It is understood by all concerned that an excessive rate of withdrawals can render the trial uninterpretable; therefore, unnecessary withdrawal of patients from the trial should be avoided.

Should a patient decide to discontinue trial medication, all efforts must be made by the investigator to encourage patients to keep returning for trial visits to follow up for safety, but at a minimum to complete and report the observations as thoroughly as possible, and to complete the EOT visit within 21 days after the last trial medication administration. If applicable, the investigative staff will contact the patient (or a responsible relative or designee) to determine the reason for withdrawal from the trial. The primary reason for the withdrawal from the trial will be recorded on the appropriate pages of the eCRF.

All patients who receive at least one infusion of BI 695502 or US-licensed Avastin® should return for a Safety Follow-up (SFU) visit 18 weeks after their last administration of trial medication prior to the switch visit. If the patient continues to receive treatment with Avastin® beyond 18 weeks post last IP dose, then no SFU visit will be performed.

#### 3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time including but not restricted to the following reasons:

- Failure to meet expected enrolment goals overall or at a particular trial site.
- Emergence of any efficacy/safety information that could significantly affect continuation of the trial, or any other administrative reasons.
- Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

The investigator/the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in the case of the third reason).

# 4. TREATMENTS

## 4.1 TREATMENTS TO BE ADMINISTERED

### 4.1.1 Identity of Boehringer Ingelheim investigational product and comparator product

Details of the trial medications are provided in Table 4.1.1: 1.

Table 4.1.1: 1 Trial medication

| Trial Medication | Dosage Form[a] (Concentration) | Manufacturer |
|---|---|---|
| BI 695502, in solution consisting of: BI 695502, disodium phosphate dihydrate, sodium dihydrogenphosphate dihydrate, trehalose dihydrate, polysorbate 20 and water for injection. | Concentrate for solution for infusion (25 mg/mL) 100 mg/4 mL or 400 mg/16 mL solution in a single use vial | Boehringer Ingelheim Pharma GmbH & Co KG, Germany |
| US-licensed Avastin®, in solution consisting of: Bevacizumab, trehalose dihydrate, disodium phosphate anhydrous, sodium dihydrogenphosphate monohydrate, polysorbate 20, water for injection. | Concentrate for solution for infusion (25 mg/mL) 100 mg/4 mL or 400 mg/16 mL solution in a single use vial | Genentech, Inc., US |

a. The US label for Avastin® states "Solution for Infusion", however as per the European official terminology of pharmaceutical dosage forms, "Concentrate for solution for infusion" is stated above.

Note: Starting as of 21 Dec 2017, the Sponsor recommends that patients should be switched from BI 695502 to Avastin® as soon as it is available at the respective clinical site. If Avastin® is not immediately available, the Investigators may temporarily allow continuation on BI 695502. The blind will be kept intact and all patients will continue the study with no additional visits in the scheduled visit cycle as per protocol.

The packaging for BI 695502 and US-licensed Avastin® are different so to ensure the investigator and patient stay blinded, the infusion solutions will be prepared by an unblinded pharmacist or suitably qualified designee at each trial site (see Section 4.1.5.1).

Details on BI 695502/US-licensed Avastin® preparation and administration are provided in Appendix 10.2.

For further details, see the product information for Avastin® (R15-1223, R18-0043) and/or the Pharmacy Manual.

### 4.1.2 Method of assigning patients to treatment groups

Patients may be pre-randomized to a treatment group based on their screening transaction via the Interactive Telephone and Web Response System (IXRS®).

The Day 1 randomization or pre-randomization will depend on the trial site procedure. The process for randomization will be different depending on the country and respective trial medication shipping timelines. In countries where trial medication needs to be sent to sites in advance due to long shipping timelines (e.g., cross border shipments), or other reasons that

require trial medication provision to the sites prior to screening**,** trial medication will be provided to the sites in advance and patients will be randomized on Day 1. For countries where trial medication can be provided on short notice (short shipping times) pre-randomization will be performed at screening and trial medication will be shipped after pre-randomization only.

Eligible patients who meet all the inclusion criteria and do not meet any of the exclusion criteria will then be randomized to double-blind treatment with a 1:1 ratio according to the pre-randomization, if applicable. Patients who do not meet all of the inclusion criteria or meet at least one of the exclusion criteria will not be randomized, and will be considered screen failures. Day 1 of Cycle 1 is the first day of trial treatment and can occur up to 4 days after randomization. Patients will be randomly assigned in a blinded fashion to BI 695502 (Arm B) or US-licensed Avastin® (Arm A).

Patients will receive treatment with 15 mg/kg of BI 695502 or US-licensed Avastin®. The randomization will be performed by IXRS®. Patients will be randomized sequentially (to the lowest sequentially available randomization number).

Each vial of trial medication will be labeled with a unique medication identification number. This will be programmed into the IXRS®. At each applicable visit, the IXRS® will assign the correct vial for the allocated treatment group and visit and the medication identification will be linked to an individual patient. The medication identification assigned by the IXRS® will then be linked to the patient number and trial site.

Access to the randomization code will be controlled and documented. All persons directly involved in the conduct and analysis of the trial will have no access to the treatment allocation prior to database lock. The data of the primary analysis population will be unblinded at the time point of the primary analysis only for the team members involved in the analysis (including the sponsor and contract research organization [CRO]). For details on unblinding procedures, see Section 4.1.5.

### 4.1.3 Selection of doses in the trial

In the EU, US, and many other countries, Avastin® has received health authority approval for the treatment of nsNSCLC, in combination with carboplatin and paclitaxel, for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease.

The dose of BI 695502 selected for this trial is based on the clinically effective dose of the currently available dosage form of Avastin®.

The primary focus of this trial is to demonstrate equivalence of BI 695502 (proposed biosimilar to Avastin®) with US-licensed Avastin®. The recommended dose of Avastin®, administered as an i.v. infusion, is 15 mg/kg of body weight given once every 3 weeks. The dose should be recalculated prior to each infusion. Therefore, in this study, patients randomized to receive BI 695502 or US-licensed Avastin® will receive 15 mg/kg once every 3 weeks (R15-1223, R18-0043). The same applies to Avastin® administration after the switch from BI 695502.

Patients will receive the combined treatment (induction cycles) every 3 weeks for up to 6 cycles. After evaluation of the last induction cycle, if the patient has CR, PR or SD, i.e., responding or stabilized patients, maintenance treatment with BI 695502/US-licensed Avastin® monotherapy can be started. Patients will then receive BI 695502 or Avastin® as a single agent every 3 weeks until disease progression (according to RECIST 1.1), death, withdrawal of consent, or unacceptable toxicity, whichever occurs earlier.

### 4.1.4 Drug assignment and administration of doses for each patient

BI 695502 and Avastin® will be provided by the sponsor and the chemotherapy will be provided by the site.

Each patient will be randomized before Day 1 of Cycle 1 to receive one of two possible treatments: BI 695502 plus chemotherapy or US-licensed Avastin® plus chemotherapy.

BI 695502/US-licensed Avastin® infusion will be administered first, i.e., prior to administration of paclitaxel/carboplatin. The prepared infusion solution (see Section 4.1.1) will be administered as an i.v. infusion through a dedicated line. It must NOT be administered as an i.v. push or bolus. Drug infusions will take place under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available. At the end of each infusion, the i.v. line must remain in place for at least 1 hour to allow administration of i.v. drugs, if necessary.

Patients may be hospitalized for observation at the discretion of the investigator (such instances of hospitalization will not be recorded as a serious adverse event [SAE]).

The recommended initial dose for the first BI 695502/US-licensed Avastin® infusion should be delivered over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Drug administration start/stop and dosing amounts will be recorded in the eCRF.

For the first infusion after the switch visit, the same challenge should be done. The first infusion should be delivered over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

BI 695502/US-licensed Avastin® dose modification is NOT permitted during this trial. Any deviation to the dose will be recorded in the eCRF. Slight variations in BI 695502/US-licensed Avastin® dose may occur due to a change in a patient's body weight; dose deviations with a margin of <5% will NOT be considered protocol deviations. Dose modifications for chemotherapy are shown in Table 4.1.4.1: 1

In the event of a life-threatening reaction, including anaphylaxis, hypersensitivity reaction, renal failure, severe cardiopulmonary event and severe muco-cutaneous reaction, BI 695502 or Avastin® will be discontinued and no additional BI 695502 or Avastin® will be administered. Patients who experience any of these reactions will be discontinued from trial medication.

If extravasation occurs during infusion of the trial medication, the infusion must be stopped. Restart the remainder of the infusion either in the area of the same arm which is proximal to the body or in the other arm.

Patients who miss the allocated day for trial medication infusion will be contacted and another visit arranged as soon as practically possible in order to administer trial medication.

Refer to Appendix 10.3 for more information regarding chemotherapy regimens.

The treatment regimen for BI 695502/US-licensed Avastin® plus chemotherapy is provided in Table 4.1.4: 1.

Table 4.1.4: 1 BI 695502/US-licensed Avastin® plus paclitaxel and carboplatin

| **Immunochemotherapy regimen** | **Dose** | **Mode** | **Day 1** |
|---|---|---|---|
| BI 695502/ US-licensed Avastin® | 15 mg/kg | i.v. | X* |
| Paclitaxel | 200 mg/m$^2$ (administered according to regular institutional practice) | i.v. | X |
| Carboplatin | target AUC 6 mg/mL·min (30- to 60-minute infusion) | i.v. | X |

AUC = area under the curve; i.v. = intravenous
* US-licensed Avastin®/BI 695502 infusion should be administered prior to paclitaxel and carboplatin.

BI 695502/US-licensed Avastin® dose and schedule will remain unchanged during the maintenance period when given as single agent. The same drug (BI 695502 or US-licensed Avastin®) will be continued during maintenance therapy based on the allocation at the time of randomization.

Starting as of 21 Dec 2017, the Sponsor recommends that patients should be switched from BI 695502 to the reference product Avastin® as soon as it is available at the respective clinical site. If Avastin® is not immediately available, the Investigators may temporarily allow continuation on BI 695502. The blind will be kept intact and all patients will continue the study with no additional visits in the scheduled visit cycle as per protocol.

#### 4.1.4.1 Chemotherapy

Administration of backbone chemotherapy will be according to the standard preparation and infusion procedures of each investigational site. Patients should receive paclitaxel prior to carboplatin.

All patients will be treated with standard combination chemotherapy consisting of paclitaxel 200 mg/m$^2$ followed by carboplatin target AUC 6 mg/mL•min (30- to 60-minute infusion) every 3 weeks for up to 6 cycles with adequate pre- and concomitant medication. The initial dose of paclitaxel (Day 1, cycle 1) must be fixed to 200 mg/m² for all study patients, as well

as a dose of carboplatin to AUC: 6 mg/mL/min. In case of toxicity after this initial dose, the dose can be reduced according to the protocol guideline Table 4.1.4.1:1 and 10.3.1.

After 3 cycles, patients who cannot tolerate chemotherapy but are not progressing can start maintenance treatment with BI 695502/US-licensed Avastin® monotherapy. However, if another backbone chemotherapy is initiated at any time or if the patient cannot tolerate at least 3 cycles of chemotherapy, then the patient will be discontinued from trial treatment.

The carboplatin dose will be calculated using the Calvert formula, taking into account the glomerular filtration rate (GFR) and given in dose of AUC:

Carboplatin-dosage in mg = (target AUC) x (GFR + 25) on Day 1 of each 3-week cycle

Glomerular filtration rate is to be based on the Cockroft-Gault formula for creatinine clearance:

$$\text{GFR (mL/min)} = \frac{C \times (140 - \text{age [years]}) \times (\text{weight [kg]})}{72 \times \text{serum creatinine (mg/dL)}}$$

where C = 0.85 for female patients and C = 1.00 for male patients.

The Cockcroft–Gault formula will be used to calculate the creatinine clearance/glomerular filtration rate (GFR) (required for the Calvert´s formula). As clinically recommended, GFR will be capped at 125 mL/min (even if the result obtained is higher) so as to avoid potential overdosing. Accordingly, the maximum total dose of carboplatin would be 900 mg per cycle.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone, diphenhydramine (or its equivalent), and cimetidine/ranitidine (see Appendix 10.3).

Doses of paclitaxel and carboplatin will be reduced for hematological and non-hematological toxicity effects (see Table 4.1.4.1: 1) for a maximum of two dose reductions. When a dose reduction is required, no dose re-escalation will be permitted. Chemotherapy dose reductions can be cumulative from cycle to cycle as required based on toxicity. Patients who do not tolerate the chemotherapy dose level -2 must discontinue treatment with chemotherapy.

Table 4.1.4.1: 1 Dose modifications of paclitaxel and carboplatin

| | **0 (starting dose)** | **-1** | **-2** | **-3** |
|---|---|---|---|---|
| Paclitaxel (mg/m$^2$) | 200 | 150 | 100 | Off-treatment |
| Carboplatin (target AUC) | 6 | 4.5 | 3 | Off-treatment |

Further details on the chemotherapy regimens and dose modifications are provided in Appendix 10.3.

Drug toxicity will be assessed using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (R10-4848).

### 4.1.5 Blinding and procedures for unblinding

#### 4.1.5.1 Blinding

This is a double-blind trial. Patients, investigators, and trial personnel, except the unblinded pharmacist or designated person, will remain blinded with regard to the randomized treatment assignments until after final database lock. The data of the primary analysis population for biosimilarity will be unblinded at the time point of the primary analysis only for the team members involved in the analysis (including the sponsor and relevant CROs). In order to provide an additional fully blinded assessment of response a central evaluation process has been established.

The IXRS® will be used to manage randomization to treatment groups in a blinded manner. To randomize a patient, the investigator will contact the IXRS®.

Access to the randomization code will be controlled and documented. All persons directly involved in the conduct and analysis of the trial will have no access to the treatment allocation prior to database lock for the primary analysis (see Section 4.1.2).

The data review will be performed by the DSMB with the support of an unblinded statistician. No unblinded data will be shared with trial personnel or sponsor personnel involved in data management.

No unblinding of sites or patients will be performed at the time of switching from BI 695502 to Avastin® to ensure continued unbiased assessments. Moreover, knowledge about the initial treatment received would not impact the further treatment of patients, since after the introduction of the switch, all patients will receive Avastin®.

#### 4.1.5.2 Procedures for emergency unblinding

In the event of an emergency, each trial site will be able to unblind patient treatment allocation via IXRS® (either the principal investigator or a designated medical sub-investigator at the trial site). In the case of an AE, this may only occur in emergency situations when the identity of the trial medication must be known to the investigator in order to provide appropriate medical treatment or if required to assure the safety of trial participants. If unblinding is required in the interest of the safety of a patient and time allows, the investigator will discuss the matter with the CRO medical monitor before unblinding, whenever possible. If the code is broken for a patient (via the IXRS®) the sponsor's trial clinical monitor must be informed immediately. The reason for opening the code break must be documented on the patient's source documents and the appropriate eCRF page along with the date.

The process for breaking the blind will be handled through the IXRS®. Instructions for this will be described in the IXRS® user manual that will be provided to each site.

### 4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF. Relabeling of commercially available Avastin® for trial purposes is not required.

### 4.1.7 Storage conditions

All trial medications must be kept in a secure place under appropriate storage conditions and handled according to Good Manufacturing Practice and GCP. The medication must be stored in a refrigerator at a controlled temperature (2 to 8°C [36 to 46°F]). It should not be frozen or shaken. A temperature log with minimum/maximum readings must be maintained to make certain that the drug supplies are stored at the correct temperature. Vials will be kept in the outer carton in order to protect them from light.

After the switch visit, the sites should monitor the storage conditions in accordance with local requirements.

### 4.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor, see Section 4.1.7.

The unblinded pharmacist or the designated person will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the CTP by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Center.
- Approval/notification of the regulatory authority, e.g., competent authority (CA).
- Availability of the curriculum vitae (not older than 2 years) of the principal investigator.
- Availability of a signed and dated CTP.
- Availability of the proof of a medical licence for the principal investigator, if applicable.
- Availability of the Form 1572 for sites in US.

The unblinded pharmacist or designated person must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused products.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. Once patients are switched from BI 695502 to Avastin®, the date of administration, the batch number, and expiry dates are to be recorded for Avastin®. The unblinded pharmacist or designated person will maintain records that document adequately that the patients were given the doses specified by the CTP and reconcile all investigational product(s) received from the sponsor. At the time of return to the sponsor and/or the CRO, the unblinded

pharmacist or designated person must verify that no remaining supplies are in the investigator's possession.

The following text is only applicable for Japan:

The investigator/pharmacist/investigational drug storage manager will receive the investigational drugs delivered by the sponsor representative after IRB/ethics committee approval of the study and completion of a clinical trial contract between the sponsor representative and the Head of Trial Center.

The investigator/pharmacist/investigational drug storage manager should return the unused and collected investigational drugs (including the empty boxes) to the sponsor after unblinding the trial.

In case investigational drugs are returned before unblinding of the trial, the investigator/pharmacist/investigational drug storage manager should seal the opened box (excluding empty boxes) for the patient, and before returning the unused and collected investigational drugs (including the empty boxes) to the sponsor. When returning the investigational drugs, the investigator/pharmacist/investigational drug storage manager should exercise utmost caution to assure that the sponsor representative and other relevant trial staff members remain blinded to the patient's name on the package (box or label) of the investigational drugs.

Upon completion of the trial, the investigator/pharmacist/investigational storage manager submits to the sponsor representative a copy of the investigational drug dispensing and return log. When submitting the copy, the investigator/pharmacist/investigational drug storage manager should exercise caution to assure that the sponsor representative and other relevant trial staff members remain blind to the patient's name.

## 4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

### 4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

There are no recommended dose reductions or rescue medication for BI 695502/Avastin®.

BI 695502/Avastin® should be permanently discontinued in patients with GI perforations (including fistula formation in the GI tract, intra-abdominal abscess), fistula formation involving an internal organ; wound dehiscence and wound healing complications requiring medical intervention; serious hemorrhage (i.e., requiring medical intervention); severe arterial thromboembolic events; hypertensive crisis or hypertensive encephalopathy; RPLS; nephrotic syndrome; and congestive heart failure of any grade.

Patients with severe hypertension, moderate to severe proteinuria, or severe infusion reactions will not receive further treatment with Avastin® or BI 695502 if the event cannot be adequately controlled within 14 days.

For urinalysis, when the laboratory dipstick reports "2+" or greater, urine dipstick reading should undergo further assessment with a 24-hour urine collection either at the local laboratory or central laboratory, whichever the investigator deems more convenient. Avastin®/BI 695502 administration should be suspended for ≥ 2 g of proteinuria/24 hours and should resume when proteinuria is < 2 g/24 hours. If moderate proteinuria (≥ 2 g in 24 hours) cannot be controlled within 14 days, then the patient should discontinue the use of Avastin®/BI 695502.

If chemotherapy treatment is interrupted, e.g., due to toxicity, then BI 695502/Avastin® should also be interrupted until chemotherapy treatment is resumed.

All concomitant medication/therapies will be recorded on the eCRF.

### 4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Restrictions on prior and concomitant medications during the course of the trial are described in Table 4.2.2.1: 1.

Other medication that is considered necessary for the patient's safety (e.g., as a result of an AE) may be given at the investigator's discretion. Investigators are encouraged to discuss the introduction of any of the medications listed in Table 4.2.2.1: 1 with the sponsor physician or CRO medical monitor.

Caution must be taken in the concomitant use of any medication that may markedly affect renal function. Such medications may, however, be used with caution if deemed essential for treatment of a particular infection or continued if patients are using them prior to commencing the trial with no effect on renal function demonstrable on blood or urine testing.

Any concomitant medications will be recorded in the appropriate sections of the eCRF.

Table 4.2.2.1: 1 Prior and concomitant treatments

| Treatment | Restriction |
|---|---|
| Carboplatin + Paclitaxel | Refer to Appendix 10.3 |
| Other anticancer regimens | Patients should not have received previous systemic treatment for their metastatic NSCLC. Patients who have received adjuvant chemotherapy are eligible if the last administration of the prior adjuvant regimen occurred >12 months prior to Screening. Prior systemic therapy for locally advanced nsNSCLC is permitted if completed >12 months prior to Screening. Other anticancer treatment is not permitted. |
| Radiotherapy | Palliative local radiation therapy (outside the only measurable lesion used for RECIST assessment) is acceptable, both previously and during the trial, at the Investigator´s discretion. However, any radiotherapy to the chest must have finished >12 months prior to screening.<br>Previously irradiated brain metastasis must be shown to be stable at 1 month after completion of radiation therapy (by CT or MRI) and before screening, the patient must be asymptomatic from brain metastasis, with a stable dose of oral corticosteroids ≤10 mg/day of prednisolone (or equivalent) during the last 4 weeks, no parenteral corticosteroids in the last 6 weeks prior to Day 1 (see below item in this table), and with an indication of treatment with the study regimen (inclusion criterion #2).<br>Patients must be recovered at screening from any adverse event (>grade 1, except alopecia) related to previous radiotherapy (exclusion criterion #10). |
| Intravenous, intramuscular, intra-articular, or parenteral corticosteroids | Not permitted within 6 weeks prior to Day 1 or throughout the trial, unless used for paclitaxel infusion premedication, according to regular institutional practice. |
| Oral, inhaled, or topical corticosteroids | If receiving current treatment with oral, inhaled, or topical corticosteroids (other than intra-articular or parenteral corticosteroids), the dose must not exceed 10 mg/day prednisolone or equivalent. During the 4 weeks prior to Day 1 the dose must be stable. |
| Oral or parenteral anticoagulants | Full-dose oral or parenteral anticoagulants or thrombolytic agent for therapeutic (as opposed to prophylactic) purposes (including coumadin or warfarin) are not permitted within 10 days of the first dose of BI 695502/Avastin® or throughout the trial. |
| NSAIDs | The use of aspirin (>325 mg/day) or other NSAID with antiplatelet activity or treatment with dipyridamole, ticlopidine, clopidogrel and cilostazol within 10 days of first dose of BI 695502/Avastin® or throughout the trial. Acetaminophen (paracetamol) as well as natural and synthetic opioids could be used as pain relievers. |
| Monoclonal antibodies and small molecules | Any prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including Avastin®, are not permitted. |
| Any drug/therapy that has not received regulatory approval for any indication | Treatment within a clinical trial within 4 weeks prior to initiation of trial treatment. Patients who have received treatment with a drug that has not received regulatory approval for any indication within 4 weeks or a minimum of 5 half-lives, whichever is longer, of the initial dose of trial medication. Simultaneous participation in non-interventional studies (e.g. observational studies) is allowed. |

Table 4.2.2.1: 1 Prior and concomitant treatments (continued)

| **Treatment** | **Restriction** |
|---|---|
| Surgical procedures | Invasive procedures (major surgical procedure, open biopsy or significant traumatic injury) ≥28 days prior to the first dose of BI 695502/US-licensed Avastin®.<br>Placement of a vascular access device and mediastinoscopy are not considered as major surgical procedures if performed more than 24 hours prior to BI 695502/US-licensed Avastin® administration. |
| Live/attenuated vaccine | Not permitted within 12 weeks prior to the Screening Visit. |
| **Treatment** | **Permitted** |
| Non-pharmacological treatments (e.g., physical therapy) | Permitted freely. |
| All supportive therapies (e.g., myeloid growth factors, blood transfusions) | Permitted as appropriate and according to site routine practice. Prophylactic use of growing factors is permitted according to regular institutional practice and the PI´s judgment. |
| Bisphosphonates | These are allowed, according to regular clinical institutional practice and PI´s discretion (e.g. pamidronate, zoledronate, and alendronate). Caution may be exerted as they may affect renal function. Nephrotoxicity can be avoided by stringent adherence to infusion guidelines |

nsNSCLC = nonsquamous non-small cell lung cancer; NSCLC = non-small cell lung cancer; VEGF = vascular endothelial growth factor; NSAID = non-steroidal anti-inflammatory drugs.

Any surgical procedure is not permitted within 28 days prior to the first dose of BI 695502/US-licensed Avastin® or for the duration of the trial.

For elective surgery during the trial the interval between termination of the BI 695502/Avastin® infusion and subsequent elective surgery should be at least 28 days. If emergency surgery is performed, precautions should be taken to minimize the potential risk of bleeding and thrombosis associated with this class of agents, infusion should be stopped and close monitoring for bleeding, wound healing and thromboembolic complications should be initiated. Patients with anticipated elective surgery will not be enrolled into the trial.

4.2.2.2 Restrictions on diet and life style

Patients should abstain from smoking and alcoholic beverages 48 hours prior to the first trial medication administration until Day 8. After that, smoking is permitted (<10 cigarettes or <3 cigars or <3 pipes/day). No more than two units of alcohol per day are permitted until the end of trial. One unit of alcohol is 10 mL (or 8 g) of pure alcohol. Accordingly it may be calculated by using the following formula:

Alcohol units = Strength of the beverage (Alcohol by volume in %) x volume (mL) ÷ 1,000

In addition, patients should abstain from alcoholic beverages for 24 hours prior to each subsequent trial visit.

Participation in contact sports (e.g., ice-hockey, rugby, martial arts) should be avoided during the course of the trial.

## 4.3 TREATMENT COMPLIANCE

All drug infusions will be administered by the investigator or other designated trial personnel. This should guarantee full compliance is achieved, provided the patient attends each appropriate visit for the administration of trial medication.

The prescribed dosage, timing and mode of administration of trial medication may not be changed. Any deviation from the intended regimen must be recorded in the eCRF.

Patients showing poor compliance as assessed by visit attendance for their drug infusions must be counseled on the importance of good compliance to the trial dosing regimen.

# 5. VARIABLES AND THEIR ASSESSMENT

## 5.1 EFFICACY

### 5.1.1 Endpoints of efficacy

**Primary endpoint:**

- Best ORR, based on unconfirmed response assessment, as assessed by central imaging review until 18 weeks after the start of treatment.

**Secondary endpoints:**

- PFS defined as the time from randomization until disease progression as per investigator assessment or death.
- OS defined as the time from randomization until death of any cause.
- Duration of response defined as the time from first documented CR or PR until time of progression as per investigator assessment.

**Other endpoints:**

- Best ORR, based on unconfirmed response assessment, as per investigator assessment until 18 weeks after start of treatment.
- Best ORR, based on unconfirmed response assessment, as per investigator assessment until progression or death.

### 5.1.2 Assessment of efficacy

The following assessments will be made at the time points indicated in Flow chart 1.1 and Flow chart 1.2.

#### 5.1.2.1 Response rate

The response criteria evaluation will be carried out according to RECIST 1.1 (see Appendix 10.1). Objective response comprises those patients achieving a PR or CR until 18 weeks after the start of treatment.

Each patient will be assigned to one of the following RECIST 1.1 categories based on independent central review, irrespective of protocol violations or missing data:

- CR (complete response)
- PR (partial response)
- SD (stable disease)
- PD (progressive disease)
- NE (not evaluable, insufficient data).

Complete response and PR do not need to be confirmed by a subsequent tumor assessment (detailed rules are listed in the imaging charter).

During the induction phase, the response evaluation against baseline will be performed using computed tomography (CT) or MRI scans at the time points indicated in Flow chart 1.1. During the induction phase, tumor assessments should be performed before treatment administration of Cycles 3 and 5.

Tumor assessment must be performed at Week 18 ±14 days (where Day 1 is the first day of Cycle 1) whether or not this assessment coincides with Cycle 7.

After Week 18 (maintenance cycles with monotherapy), see Flow chart 1.2, tumor assessments should be performed at the investigator's discretion, or at a minimum of every 3 cycles (approximately every 9 weeks). Tumor assessments should be performed prior to trial treatment administration. If the cycle is delayed, tumor assessment will also be delayed. Consistency of consecutive CT or MRI scans should be ensured during all assessments for each patient, with the same technique being used for evaluating lesions throughout the treatment period. During the non-treatment period, tumor assessments should be performed at the investigator's discretion, but at a minimum of every 9 weeks.

A CT scan with i.v. contrast will be performed on the chest and abdomen, including the adrenals and the entire liver, if applicable. In case of an iodine i.v.-contrast contraindication (renal insufficiency, allergy, hyperthyroidism etc), an abdomen MRI with contrast (gadolinium) should be performed with a non-contrast chest CT scan.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast CT scan. CT scans must be used to measure lesions selected for response assessment.

A central review of all patient images will be performed until Week 18. Details will be described in the imaging charter. The results of the central review imaging data (independent blinded assessments of tumor response) will be used for the primary measure of response and will be the data used for the primary response analyses. The results of the investigator assessment will be used for sensitivity analysis (see Section 7.3.1.2).

#### 5.1.2.2 Duration of response

Duration of response is the time from first documented CR or PR until time of progression as determined by investigator assessment.

#### 5.1.2.3 Progression-free survival

Progression-free survival is defined as the time from randomization until disease progression as determined by investigator assessment or death. Disease progression is assessed according to RECIST 1.1 (see Section 5.1.2.1 and Appendix 10.1).

5.1.2.4 Overall survival

Overall survival is defined as the time from randomization until death from any cause.

## 5.2 SAFETY

### 5.2.1 Endpoints of safety

The safety of BI 695502, compared to US-licensed Avastin®, will be evaluated by means of continuous AE monitoring, laboratory tests, physical examination, vital signs (blood pressure, pulse rate, respiratory rate, body temperature, and weight), 12-lead electrocardiogram (ECG) and tolerability.

Adverse events selected for comparability assessment (secondary endpoint)

- The proportion of patients with the following selected AEs will be evaluated in comparability assessment of BI 695502 and US-licensed Avastin®:
  - Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions
  - Arterial and venous thromboembolic events
  - Febrile neutropenia
  - Gastrointestinal perforations
  - Hypertension
  - Proteinuria
  - Pulmonary hemorrhage
  - Other hemorrhages
  - Wound-healing complications/abscess/fistulas.

Other Endpoints:

- The proportion of patients with AEs
- The proportion of patients with AEs related to trial treatment
- The proportion of patients with Grade 3 or 4 AEs according to NCI-CTCAE version 4.0
- The proportion of patients with Grade 3 or 4 AEs according to NCI-CTCAE version 4.0 related to trial treatment
- The proportion of patients with AEs potentially related to immunogenicity
- The proportion of patients with adverse events of special interest (AESIs).

### 5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An AE is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A SAE is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Cancers with new histology are always considered serious. Progression of cancer (underlying disease) is exempted from reporting as an (S)AE.

Japan only: An AE that possibly leads to disability will be reported as a SAE. Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Intensity of adverse event

The intensity of AEs will be classified and recorded according to the NCI-CTCAE, version 4.0 (R10-4848), in the eCRF.

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the eCRF.

Japan only: The reason for the decision on causal relationship needs to be provided in the eCRF.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

If a SAE is reported from a still-blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs and trial design.

Worsening of pre-existing conditions

Worsening of pre-existing conditions will be recorded as an (S)AE in the eCRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the eCRF, if they are judged clinically relevant by the investigator.

Protocol-specified adverse events of special interest

Protocol-specified AESIs are events of medical concern requiring monitoring and rapid communication.

The following are considered as protocol-specified AESI:

- Patients showing the following laboratory abnormalities need to be followed up according to Appendix 10.4 of this CTP and the "DILI checklist" provided in the ISF:
  - Hepatic injury defined by the following alterations of liver parameters for patients with normal liver function at baseline: an elevation of AST and/or ALT ≥3 x ULN combined with an elevation of total bilirubin ≥2 times ULN measured in the same blood draw sample.
  - Hepatic injury defined by the following alterations of liver parameters for patients with impaired liver function at baseline: an elevation of AST and/or ALT ≥5 x ULN combined with an elevation of total bilirubin ≥2 times ULN measured in the same blood draw sample.
  - Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN
- Anaphylactic reactions.
- GI perforations.
- Pulmonary hemorrhage.

Protocol-specified AESI can be classified as serious or non-serious but all AESI must be reported in an expedited manner similar to SAEs, even if they do not meet any of the seriousness criteria (i.e., non-serious AESI must also be reported on the SAE form and follow serious timelines).

5.2.2.2 Adverse event and serious adverse event reporting

All AEs, serious and non-serious, as well as all protocol-defined AESI, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the follow-up period) will be collected, documented and reported to the sponsor or sponsor designee by the investigator on the appropriate case report forms (CRFs)/eCRF/SAE reporting forms. The Residual Effect Period (REP) for BI 695502 is 112 days/16 weeks. Therefore, all events reported within 112 days/16 weeks of the last trial medication will be considered on-treatment. All AEs will be reported up until the end of the SFU visit (18 weeks after the last dose of trial medication) or until the patient discontinues Avastin®. The investigator does not need to actively monitor patients for AEs once the trial has ended. If a patient remains in the non-treatment period beyond 18 weeks post last dose of trial medication (beyond the SFU), all AEs, SAEs and AESI will be collected. However, if the investigator becomes aware of a SAE(s) occurring after the patient has completed the trial (including any protocol-required REP and/or follow-up), it should be reported by the investigator to the sponsor or sponsor designee if considered relevant by the investigator. Reporting will be done according to the specific definitions and instructions detailed in the 'AE Reporting' section of the ISF.

For each AE, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The

investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

The investigator must report the following events via telephone/fax using the SAE form immediately (within 24 hours of awareness or the next business day whichever is shorter) to the sponsor or sponsor designee: SAEs, non-serious AEs which are relevant for a reported SAE, and any AESI.

Disease progression in oncology trials is a study endpoint for analysis of efficacy and as such is exempted from reporting as a (S)AE. Progression of the subject's underlying malignancy (nsNSCLC) will be recorded on the appropriate pages of the eCRF as part of efficacy data collection only and will not be reported on the SAE Form. It will therefore not be entered into the safety database (ARISg) and hence not get expeditiously reported. Death due to disease progression is also to be recorded on the appropriate eCRF page and not on the SAE Form.

However, when there is evidence suggesting a causal relationship between the study drug(s) and the progression of the underlying malignancy, the event must be reported as a (S)AE on the on the SAE Form and on the eCRF.

Examples of exempted events of PD may be:
- Progression of underlying malignancy (Progressive disease [PD]): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)
- Clinical symptoms and/or signs of progression (without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

Exempted events are collected and tracked following a protocol-specified monitoring plan. Exempted events are monitored at appropriate intervals preferable by an independent committee such as a Data Monitoring Committee. See Section 8.4.2 for expedited reporting to health authorities and IECs/IRBs.

Except for trial endpoints, the investigator must immediately report to the sponsor all SAEs, regardless of whether the investigator believes that they are drug related.

Cancers with new histology are always considered serious and should be reported in an expedited manner by using an SAE form.

The telephone/fax numbers will be provided to each site in the ISF in a separate document to this CTP. With receipt of any further information to these events, a follow-up SAE report has to be provided. Serious AEs, nonserious AEs relevant to the SAE, and AESI must include a causal relationship assessment made by the investigator.

Boehringer Ingelheim has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always SAEs", if a

nonserious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and a SAE has to be reported in expedited fashion following the same procedure as above. The list of these AEs can be found in the ISF.

The SAE form is to be forwarded to the sponsor/sponsor designee. Specific contact details will be provided in the ISF. This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified AESI becomes available.

Japan only: This information must be also reported immediately to the head of the trial site.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female patient has been enrolled into the clinical trial, after having taken trial medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor/sponsor designee and the pregnant study participant must be excluded. In addition, if a patient's partner becomes pregnant after the patient has been enrolled, the same procedure must be followed. In case of pregnancy in a patient's partner, the partner Pregnancy Informed consent must be completed before collecting the Pregnancy Monitoring Form for Clinical Trials. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms (specific contact details will be provided in the ISF). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

### 5.2.3 Assessment of safety laboratory parameters

Blood and urine samples for determination of serum chemistry, hematology, urinalysis and coagulation will be taken at the times indicated in Flow chart 1.1 and Flow chart 1.2. Estimated blood volumes are shown in Table 6.1: 1.

The following laboratory parameters will be measured:

- Serum chemistry: creatinine, alkaline phosphatase, AST, ALT, gamma glutamyl transpeptidase, bilirubin (total and direct), glucose, total cholesterol, total protein, albumin, sodium, potassium, chloride, calcium.
- Hematology: hemoglobin, hematocrit, platelets, white blood cells, lymphocytes, neutrophils.
- Urinalysis: protein, glucose, blood.
- Coagulation: INR, PT/PTT

In addition, the following parameters will be analyzed at the visits indicated in Flow chart 1.1 and Flow chart 1.2:

- Infection screen (for hepatitis B, hepatitis C):
  - Active Hepatitis B is defined as positive hepatitis B surface antigen (HBsAg) or immunoglobulin (Ig)M hepatitis B core antibody, depending on timing. If any of these tests are positive, the result should be confirmed by a positive hepatitis B virus DNA.
  - Active hepatitis C is defined as positive antiHCV and/or a positive antibody. If any of these tests are positive, the result should be confirmed by a positive hepatitis virus RNA.
- Screening for HIV and TB (PPD or QuantiFERON) to be performed according to local practice and local regulatory guidance.
- Pregnancy testing for females of child-bearing potential only (serum human chorionic gonadotropin or urine).

The investigator must assess all laboratory results. The investigator will evaluate any change in laboratory values and all clinical laboratory tests will be reviewed for potential clinical significance at all time points throughout the trial. The investigator should endeavor to provide a reason for all out of range results deemed not clinically significant. If the investigator determines a laboratory abnormality to be clinically significant, it will be considered an AE/SAE (see Section 5.2.2), however, if the laboratory value abnormality is consistent with a current diagnosis, it will be documented accordingly.

Blood samples will be analyzed by a central laboratory, with the exception of HIV and TB, and coagulation parameters when assessed for study inclusion. Assessment of coagulation parameters for study inclusion will be performed locally unless local analysis is not available, in which case central laboratory analysis will be used instead (see Section 3.3.2). The central laboratory provider will also provide the materials for blood sampling. Instructions for the labeling, storage and shipment of the samples can be found in the Laboratory Manual. Details of all blood variable units and reference ranges can be found in the Laboratory Manual.

For laboratory results that are required for decisions on chemotherapy administration, laboratory testing should be performed per standard-of-care, based on the site's regular practice. Blood samples may be analyzed locally, but this data will not be collected.

### 5.2.4 Electrocardiogram

Two consecutive resting 12-lead ECGs should be performed prior to administration of trial medication at the visits indicated in Flow chart 1.1 and Flow chart 1.2. The first of the consecutive ECGs is mandatory. The second of the consecutive ECGs is optional, at the discretion of the Investigator in case of clinical significance. Additional ECGs will be performed if clinically indicated.

Patients should rest for at least 5 minutes in a supine position before each of the two consecutive ECG evaluations.

The original ECG traces and variables must be stored in the patients' medical records as source data. The investigator or designee will evaluate the ECG from a clinical perspective and the result (whether the ECG result is normal or abnormal) will be recorded on the appropriate section of the eCRF and on the ECG trace signed and dated by Investigator or designee.

### 5.2.5 Assessment of other safety parameters

Vital signs

Vital signs will be assessed prior to administration of trial medication at the visits indicated in Flow chart 1.1 and Flow chart 1.2.

Blood pressure, respiratory rate, and pulse rate measurements should be taken following at least 5 minutes rest while the patient is in a sitting position. The patient's body temperature will also be recorded. Two or more blood pressure readings should be taken at 2 minute intervals and the average of the readings taken. If the first two diastolic readings differ by more than 5 mmHg, an additional reading should be obtained and an average taken of the three readings.

The investigator must immediately assess all vital signs findings at each visit. If the investigator finds any clinically relevant abnormalities, these must be reported as AEs/SAEs as appropriate (see Section 5.2.2).

Physical examination

A physical examination will be performed prior to administration of trial medication at the visits indicated in Flow chart 1.1 and Flow chart 1.2.

Whenever possible, the same person should perform the physical examination throughout the trial (i.e., for all patients at each trial site). The physical examination will include a detailed abdominal examination, an assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory, and abdomen. Body weight will also be measured. Height will be measured at screening only.

Tuberculosis Assessment

Screening for TB will be performed according to local practice and local regulatory guidance. There should be no radiographic or clinical evidence of active TB.

***Purified protein derivative skin test***

A PPD skin test may be used to assess TB status at Screening.

***QuantiFERON®-TB Gold Assay***

QuantiFERON Gold assay may be used to assess TB status at Screening.

## 5.4 APPROPRIATENESS OF MEASUREMENTS

The RECIST 1.1 guideline (R09-0262) is well established and scientifically accepted and will be used for the evaluation of tumor response. The NCI-CTCAE, version 4.0 (R10-4848), a standard for assessment of safety in oncology clinical trials, will be used in the assessment of AEs in nsNSCLC patients.

# 6. INVESTIGATIONAL PLAN

For all visits, there will be a window of ±3 days unless otherwise specified.

Cycles must not be missed but delays may occur according to Tables 10.3:1 and 10.3:2. The maximum timeframe for treatment delay should be assessed based on the investigator´s clinical judgement and discussed with the trial medical monitor. However, patients with severe hypertension, moderate to severe proteinuria, or severe infusion reactions will not receive further treatment with Avastin®/BI 695502 if the event cannot be adequately controlled within 14 days.

## 6.1 VISIT SCHEDULE

A schedule of assessments is provided in Flow chart 1.1 and Flow chart 1.2.

Visits will be scheduled as close as possible to the pre-planned schedule

- Administration of BI 695502/US-licensed Avastin® will occur on Day 1 of each cycle (every 21 days).
- Administration of chemotherapy will start on Day 1 of each cycle (see Section 4.1.4.1).
- Each subsequent cycle will occur 3 weeks (±3 days) after completion of the previous cycle, including after the switch visit.
- During the switch visit prior to infusion with Avastin®, the assessments as described in Flow Chart 1.2 will be performed.
- The EOT visit will be performed within after the last BI 695502/Avastin® dose on completion of the treatment period.
- Non-treatment period: visits will be performed every until initiation of new treatment, disease progression, or death for patients who discontinue trial medication for reasons other than disease progression but who do not withdraw consent (see Section 6.2.3). If a patient remains in the non-treatment period beyond 18 weeks post last dose of trial medication, he/she will be treated according to standard of care, and assessed for tumor progression every 6 to 9 weeks according to clinical judgment.
- A SFU visit will be performed 18 weeks after the last dose of trial medication (IMP BI 695502/US-licensed Avastin®). If the patient continues to receive treatment with Avastin® beyond the 18 weeks post last IMP dose, then no SFU visit will be performed.

Clinical assessments will be performed within before trial medication infusion. Laboratory samples must be drawn prior to infusions of premedication and trial medication.

Patients who miss the allocated day for trial medication infusion will be contacted and another visit arranged as soon as practically possible in order to administer trial medication. Such cases will be considered as CTP deviations (see Section 7.3).

The total volume of blood that will be drawn from each patient during the trial will depend on the length of time the patient receives trial medication. The total estimated volume of blood

that will be drawn from each patient who receives 10 cycles of treatment during the course of the trial, plus the EOT and SFU visits is shown in Table 6.1: 1.

Table 6.1: 1 Estimated blood sample volumes per patient

| Parameter | Sample volume (mL) | Number of samples | Total volume (mL) |
|---|---|---|---|
| Laboratory tests (including serum chemistry, serum pregnancy test) | 3.5 | 13 | 45.5 |
| Hematology | 2 | 13 | 26 |
| INR/PT/PTT | 2.7 | 13 | 35.1 |
| Infection screen | 12 | 1 | 12 |
| TB | 3 | 1 | 3 |
| **Approximate total** | | | **256.6** |

INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; TB = tuberculosis.

It should also be noted that additional samples may be required if medically indicated, e.g., at unscheduled visits to follow up safety findings.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

### 6.2.1 Screening period

Screening, Visit 0 (Week -4 to -1)

Once the patient has provided informed consent (before any trial-specific procedures or assessments are performed) and the patient meets all inclusion criteria and none of the exclusion criteria (see Section 3.3), the trial site will enter the screened patient into the system using the IXRS®.

The following assessments will be performed/collected:

- EGFR and ALK mutation status.
- Demographic information (including sex, date of birth, ethnicity and race), medical and surgical history including surgery for lung cancer, and smoking status.
- Hepatitis B and hepatitis C (unless status has previously been confirmed within 6 months prior to Screening).
- HIV test should be performed only if required per local practice and regulatory guidance.
- TB test (PPD skin test or QuantiFERON TB Gold test) according to local practice and local regulatory guidance, or no radiographic or clinical evidence of active TB.
- Serum pregnancy test for women of childbearing potential.
- Physical examination, including height (cm) and weight (kg).

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.2.5).
- Laboratory testing (serum chemistry, hematology, urinalysis and coagulation; see Section 5.2.3).
- 12-lead ECG (see Section 5.2.4).
- Previous and concomitant therapy/medications (see Section 4.2).
- Assessment of AEs (see Section 5.2.2).
- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and the involved area, if applicable). A PET scan can be performed in addition to the tumor assessment CT scan (see Section 5.1.2.1). To be performed within 21 days of randomization.
- ECOG PS.
- Contact IXRS® (see Section 4.1.2)

Subjects are only allowed to be re-screened once and he/she must be re-consented before re-screening occurs.

### 6.2.2 Treatment period

Cycle 1

Eligible patients will be randomized and allocated to treatment as per the IXRS® within 4 days of Day 1 of Cycle 1 (baseline). The following will also be performed/collected:

- Assessment of eligibility.
- Urine pregnancy test for women of childbearing potential (serum pregnancy test to be performed in case of positive urine pregnancy test).
- Physical examination, including weight (kg) (see Section 5.2.5).
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.2.5).
- Laboratory testing (serum chemistry, hematology, urinalysis and coagulation; see Section 5.2.3).
- Previous and concomitant medications (see Section 4.2).
- Assessment of AEs (see Section 5.2.2).
- ECOG PS.
- Survival.

- Contact IXRS® (see Section 4.1.2)
- Administration of premedication (see Section 4.1.4.1).
- Trial medication infusion (see Section 4.1.4).
- Administration of chemotherapy (see Section 4.1.4.1).

Cycles 2, 3, 4, 5, 6

The following will be performed/collected:

- Urine pregnancy test for women of childbearing potential to be performed every 6 weeks starting at Cycle 3 (serum pregnancy test to be performed in case of positive urine pregnancy test).
- Physical examination, including weight (kg) (see Section 5.2.5).
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.2.5).
- Laboratory testing (serum chemistry, hematology, urinalysis and coagulation; see Section 5.2.3).
- 12-lead ECG (to be performed at Cycle 3 and 5 only) see Section 5.2.4).
- Previous and concomitant medications (see Section 4.2).
- Assessment of AEs (see Section 5.2.2).
- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and involved area, if applicable). A PET scan can be performed in addition to the tumor assessment CT scan (see Section 5.1.2.1) (to be performed at Cycle 3 and 5 only). Tumor assessment must be available before administration of trial medication at Cycles 3 and 5. During the induction phase, the tumor evaluations must be performed every 2 cycles. Therefore, if a cycle is delayed, the next tumor evaluation will also be delayed.
- ECOG PS (to be performed at Cycle 3 and 5 only).
- Survival.

- Contact IXRS® (see Section 4.1.2)
- Administration of premedication (see Section 4.1.4.1).
- Trial medication infusion (see Section 4.1.4).
- Administration of chemotherapy (see Section 4.1.4.1). Paclitaxel/carboplatin chemotherapy will be administered every 3 weeks.

Cycle 7 to Cycle 10 and onwards

The following will be performed/collected:

- Urine pregnancy test for women of childbearing potential (to be performed every 6 weeks starting at Cycle 7). Serum pregnancy test to be performed in case of positive urine pregnancy test.
- Physical examination, including weight (kg) (see Section 5.2.5).
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.2.5).
- Laboratory testing (serum chemistry, hematology, urinalysis and coagulation; see Section 5.2.3).

- 12-lead ECG (to be performed at Cycles 7, 10, and every 3 cycles thereafter, see Section 5.2.4).
- Concomitant medications (see Section 4.2).
- Assessment of AEs (see Section 5.2.2).
- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and involved area, if applicable). A PET scan can be performed in addition to the tumor assessment CT scan (see Section 5.1.2.1) (to be performed at Cycles 7, 10, and every 3 cycles thereafter). In case of a treatment cycle delay (i.e. due to toxicity), imaging assessment (e.g. CT, MRI) for the primary endpoint will be performed at Week 18 ±14 days (fixed time point), regardless of the number of cycles administered to date and whether or not this assessment coincides with Cycle 7. After Week 18, if a cycle is delayed, tumor assessment will also be delayed.
- ECOG PS (to be performed at Cycles 7, 10, and every 3 cycles thereafter).
- Survival

- Contact IXRS® (see Section 4.1.2)
- Trial medication infusion (see Section 4.1.4).

Switch Visit, prior to Avastin® administration:

Prior to Avastin® administration, all patients on active treatment must undergo the following assessments:

- Serum pregnancy test.
- Physical examination, including weight (kg) (see Section 5.2.5).
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.2.5).
- Laboratory testing (serum chemistry, hematology, urinalysis and coagulation; see Section 5.2.3).
- 12-lead ECG (see Section 5.2.4).
- Concomitant medications (see Section 4.2).
- Assessment of AEs (see Section 5.2.2).
- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and involved area, if applicable; to be performed only if a tumor assessment was not performed within the previous 4 weeks). A PET scan can be performed in addition to the tumor assessment CT scan (see Section 5.1.2.1).
- ECOG PS.
- Survival.

- Contact IXRS® (see Section 4.1.2)

- Trial medication infusion (see Section 4.1.4).

### 6.2.3 End of trial and follow-up period

End of Treatment Visit

All patients who receive at least one infusion of BI 695502 or US-licensed Avastin® and who discontinue the trial at any time after Day 1 (but do not withdraw their consent) will be required to have all of the evaluations for the EOT visit as soon as possible and in any case within 21 days after the last administration of BI 695502 or Avastin®.

The following will be performed/collected:

- Serum pregnancy test.
- Physical examination, including weight (kg) (see Section 5.2.5).
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.2.5).
- Laboratory testing (serum chemistry, hematology, urinalysis and coagulation; see Section 5.2.3).
- 12-lead ECG (see Section 5.2.4).
- Concomitant medications (see Section 4.2).
- Assessment of AEs (see Section 5.2.2).
- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and involved area, if applicable). A PET scan can be performed in addition to the tumor assessment CT scan (see Section 5.1.2.1).
- ECOG PS.
- Survival.

Non-treatment period

For all patients who discontinue trial medication for reasons other than disease progression, but do not withdraw consent, the following will be performed/collected every 3 weeks after the EOT visit until death, disease progression, or initiation of a new treatment, whichever occurs earlier.

- Physical examination, including weight (kg) (see Section 5.2.5).
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.2.5).
- Laboratory testing (serum chemistry, hematology, urinalysis and coagulation; see Section 5.2.3).
- 12-lead ECG (see Section 5.2.4).
- Concomitant medications (see Section 4.2).
- Assessment of AEs (see Section 5.2.2).

- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and involved area, if applicable). A PET scan can be performed in addition to the tumor assessment CT scan (see Section 5.1.2.1) (to be performed at the investigator's discretion, or at a minimum of every 3 cycles [approximately every 9 weeks]).
- ECOG PS.
- Survival.

If a patient remains in the non-treatment period beyond 18 weeks post last dose of trial medication, he/she will be treated according to standard of care, and assessed for tumor progression every 6-9 weeks according to clinical judgment. The following will be performed/collected:

- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and involved area, if applicable). A PET scan can be performed in addition to the tumor assessment CT scan (see Section 5.1.2.1).
- Assessment of AEs (see Section 5.2.2).
- Date of disease progression (if applicable).

Safety Follow-up Visit

The SFU visit will be performed 18 weeks after the last administration of BI 695502/US-licensed Avastin® prior to the switch visit. If the patient continues to receive treatment with Avastin® beyond 18 weeks post last IP dose, then no SFU visit will be performed. The following will be performed/collected:

- Concomitant medications (see Section 4.2).
- Assessment of AEs (see Section 5.2.2).
- Date of initiation of second-line therapy (if applicable).
- Survival.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.2.5).

Survival monitoring

After the SFU visit or discontinuation of Avastin® (whichever occurs later), all patients who remain in the trial will be monitored via telephone call for survival every 3 months.

End of trial definition

The trial will be closed when all randomized and treated patients have either died, are lost to follow-up, or have withdrawn consent, or for a maximum of 20 months after the last patient randomized plus the EOT visit, whichever occurs earlier.

The sponsor may also elect to discontinue clinical investigations under this trial for any reason, at any time.

Unscheduled visit assessments

Patients may attend the trial site for unscheduled visits at any time for additional safety monitoring at the discretion of the investigator.

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN - MODEL

This is a randomized, double-blind, active-controlled multicenter trial. The primary objective is to show statistical equivalence based on the clinical efficacy endpoint. The primary endpoint will be measured as best ORR, defined as the proportion of patients with CR or PR (not required to be confirmed by a subsequent assessment) according to RECIST criteria 1.1 as assessed by central imaging review until 18 weeks after start of treatment. The ORR ratio between BI 695502 versus US-licensed Avastin® will be used for analysis of the primary endpoint.

Patients will be treated with one of the two different compounds (BI 695502 plus chemotherapy or US-licensed Avastin® plus chemotherapy).

Secondary objectives are the evaluation of additional efficacy parameters and safety and tolerability of BI 695502 versus US-licensed Avastin®.

The analysis of the primary efficacy endpoint is not impacted by the switch from BI 695502 to Avastin® as all patients had already completed the Week 18 assessment at the time of the transition. The main analyses will cover the period up until patients were switched from BI 695502 to Avastin® in the BI 695502 group and data will be analyzed to the extent available. Adverse events will be presented by underlying treatment and taking the corresponding exposure into account.

Additionally, after the transition from BI 695502 to Avastin® in the BI 695502 group, the impact of switching will be assessed based on the occurrence of relevant adverse events after the transition, i.e. anaphylactic reactions/hypersensitivity reactions/infusion-related reactions and the occurrence of anti-drug antibodies by comparing switched patients and patients staying continuously on Avastin®.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary test for equivalence will be performed with respect to BI 695502 versus US-licensed Avastin®. The primary hypothesis is based on the ratio in best ORR between the two treatments:

$H_0$: Ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) $\leq 0.736$ or $\geq 1.359$.

$H_1$: Ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) within the interval (0.736, 1.359).

The null hypothesis will be rejected in favor of equivalence if the two-sided 90% CI for the ratio in best ORR between the treatments falls completely within the range defined by the equivalence margin; i.e., the comparison will be based on two one-sided tests (TOST) with a

5% type I error rate. The TOST procedure controls the overall type I error rate at alpha=5% (R14-3718).

The equivalence margin (0.736, 1.359) for ORR ratio is based on a meta-analysis that included the following three studies: Sandler et al 2006 (R07-1161), Niho et al 2012 (R14-0473), and Johnson et al 2004 (R04-4661). The rationale to include these studies was to meet the following criteria:

- Studies being representative for efficacy effect of Avastin® and BI 695502 in the intended 1302.5 trial population as measured by comparing the ratio of best ORR.
- All data used were taken from studies with a backbone chemotherapy control arm.
- Only studies using the identical backbone therapy as planned in trial 1302.5 (paclitaxel 200 mg/m$^2$ followed by carboplatin target AUC 6) were considered to ensure homogeneity and representativeness of the reference data to the planned trial 1302.5. All data used were taken from studies or study arms excluding squamous cell type.
- All data used were taken from studies or study arms with a dosing regimen of 15 mg/kg Avastin®.

Table 7.2: 1 summarizes the estimation results of the treatment effect of Avastin® over control using a fixed effects meta-analysis of the three reference studies based on the ORR ratio between Avastin® plus chemotherapy and carboplatin-paclitaxel chemotherapy alone.

Table 7.2: 1 Meta-analysis of ORR ratio

| | Avastin® | | | Control | | | | |
|---|---|---|---|---|---|---|---|---|
| **Source** | **Events** | **Total N** | **ORR** | **Events** | **Total N** | **ORR** | **Weight** | **ORR ratio** |
| Sandler (2006) | 133 | 381 | 34.9% | 59 | 392 | 15.1% | 64.4% | 2.319 |
| Niho (2012) | 71 | 117 | 60.7% | 18 | 58 | 31.0% | 28.6% | 1.955 |
| Johnson (2013) | 16 | 32 | 50.0% | 5 | 25 | 20.0% | 6.5% | 2.500 |
| Total (weighted) | | | 43.3% | | | 20.0% | | 2.220 |

ORR = overall response rate
Calculations based on Metacalc v3.0

The calculated ORR of Avastin® combined with paclitaxel and carboplatin in nsNSCLC is 43.3% and the ORR ratio for Avastin® versus chemotherapy alone is 2.220 with a 90% CI of (1.847, 2.668) across all studies included in the meta-analysis (Table 7.2: 1).

The non-inferiority margin is chosen in a conservative way to preserve 50% of the lower 90% CI bound on the log-ratio scale. This corresponds to an equivalence margin of (0.736, 1.359) on the ORR ratio scale.

In this equivalence trial, the test of the primary hypothesis and the corresponding equivalence margin are designed in order to provide evidence of clinical similarity; i.e., absence of a clinically meaningful difference between BI 695502 versus US-licensed Avastin® with

respect to the primary endpoint best ORR. If, for example, best ORR of BI 695502 is estimated at 37.6% and the best ORR of US-licensed Avastin® at 43.3% then the ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) would equal 0.867 with a 90% CI of (0.741,1.013), and then the primary null hypothesis could be rejected. This corresponds to a difference between the treatments that is clinically not meaningful. Thus the choice of the equivalence margin is justified on both clinical and statistical grounds.

For details of the margin calculation and justification refer to Appendix 10.6.

## 7.3 PLANNED ANALYSES

The primary analysis set will be the full analysis set (FAS) according to the intention-to-treat principle. The FAS will consist of all randomized patients who receive at least one dose of trial medication and have a baseline tumor assessment. Patients will be assigned to the treatment to which they were randomized.

Additionally a per-protocol set (PPS) of patients following the CTP in all essential criteria will be created for sensitivity analyses. Patients included in the FAS who have important CTP violations will be excluded from the PPS. A CTP violation will be considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint. Important CTP violations include but are not limited to:

- Randomized trial medication not administered or incorrect trial medication administered.
- Major violation of treatment compliance.
- Major violation of inclusion criteria.

All patients treated with at least one dose of trial medication (treated set) will be included in the safety evaluation.

For the handling of missing values refer to Section 7.4.

The main analyses will cover the period up until patients were switched from BI 695502 to Avastin® in the BI 695502 group and data will be analyzed to the extent available; the above described definitions for the analysis populations will be applied. Appropriate censoring methods will be applied at the time of switching and will be defined in the TSAP.

Exploratory analyses will be performed based on all available data beyond the timepoint of switching with side-by-side displays of the BI 695502/Avastin® and Avastin® treatment groups. No additional analysis populations will be defined.

### 7.3.1 Primary analyses

7.3.1.1 Primary ORR ratio analyses

The primary endpoint of the study is the best ORR, defined as the proportion of patients with CR or PR (not required to be confirmed by a subsequent assessment according to RECIST 1.1, R09-0262) as assessed by central imaging review until 18 weeks after the start of treatment. The best ORR ratio between BI 695502 versus US-licensed Avastin® will be used for analysis of the primary endpoint.

The primary analysis will be based on the FAS and will be performed after centrally reviewed tumor response assessments have been provided for all patients of the primary analysis population for the biosimilarity hypothesis testing. Overall response rate will be evaluated from date of randomization until either progression, treatment stop for unacceptable toxicity, death or up to 18 weeks, whichever happens earlier. The data of the primary analysis population for biosimilarity will be unblinded at the time point of the primary analysis only for the team members involved in the analysis (including the sponsor and the CRO). For details on unblinding procedures see Section 4.1.5.1.

The primary analysis is based on a log binomial regression model (R14-3815) with subsequent transformation of the estimated parameters to the ratio in best ORR including the respective CI.

The statistical model will be:

log (E{ORR}) = treatment + sex + smoking status + NSCLC stage + ethnicity

The difference in log(best ORR) between BI 695502 and US-licensed Avastin® will be estimated, with 90% CI, adjusted for sex, smoking status, NSCLC stage, and ethnicity. The estimate and CI will be exponentiated to return to the ratio scale.

This model includes the following explanatory variables: treatment, sex (male versus female), smoking status (never smoked versus current/past smoker), NSCLC stage (recurrent versus Stage IV) and ethnicity (East Asian origin versus non East Asian). In case of sparse data in one (or more) strata which affects the convergence of the model the respective factors may be omitted in the model.

For the handling of missing primary efficacy assessment scores see Section 7.4.1. For the assessment of the primary efficacy endpoint best ORR at Week 18 a time window of ±14 days will be applied.

Equivalence will be declared if the two-sided 90% CI for the ORR ratio between BI 695502 and US-licensed Avastin® falls completely between the lower margin bound of 0.736 and the upper margin bound of 1.359.

For details on the statistical model and the equivalence test refer to Appendix 10.6.2.

7.3.1.2 Sensitivity analyses for the primary endpoint best ORR

To assess the robustness of the results, the primary analysis will be repeated using the PPS population. The same model will be employed as for the primary analysis. A further sensitivity analysis will be based on investigator overall response assessment employing the same methods and statistical model as used in the primary analysis.

To further assess the robustness of the results, the primary analysis will be repeated for an additional way of calculating the equivalence margin and corresponding hypothesis test.

An equivalence margin (0.727, 1.376) for the ORR ratio preserves 3/5 of the point estimate of the historical treatment effect of Avastin® based on the same meta-analysis that was used for the primary hypothesis on the log-ratio scale. If the two-sided 95% CI for the ORR ratio falls completely within the range defined by the equivalence margin (0.727, 1.376), equivalence would be shown with the TOST procedure following a more strict alpha=2.5% type I error rate.

### 7.3.2 Secondary analyses

Secondary analyses include:

- PFS: A Cox-proportional hazards (PH) model using the same adjustment factors as for best ORR ratio will be used to assess PFS. Progression-free survival is defined as the time from randomization until disease progression or death. Disease progression is assessed according to the RECIST 1.1 response criteria for NSCLC.
- OS: A Cox-PH model using the same adjustment factors as for best ORR ratio will be used to assess OS. Overall survival is defined as the time from randomization until death from any cause. Overall survival data will be collected every 3 months.
- Duration of response: A Cox-PH model using the same adjustment factors as for best ORR ratio will be used to assess Duration of response. Duration of response is defined as the time from first documented CR or PR until time of progression as per investigator assessment.

### 7.3.3 Other analyses

Other analyses will explore the influence of different number of cycles on the primary endpoints. For this purpose, number of cycles will be added as an independent, fixed effect factor to the primary analysis models, if sufficient data for both groups are available.

In addition, other analyses will explore the influence of country/region on the primary endpoint. For this purpose the primary analysis model will additionally include country/region as a fixed effect; small countries/regions may be combined.

A further analysis will assess the best ORR until progression or death (instead of until 18 weeks) based on investigator assessment employing descriptive statistical methods.

### 7.3.4 Safety analyses

All safety data, including secondary safety parameters, will be displayed and analyzed using descriptive statistical methods. No formal inferential analysis is planned for safety comparisons. For AEs selected for comparability assessment, separate tables will be displayed including descriptive CIs comparing the proportion of patients with AEs selected for comparability assessment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be assigned to the screening phase, as appropriate. All AEs with an onset after the first dose of trial medication up to a period of 16 weeks after the last dose of the trial medication will be assigned to the treatment phase for evaluation and will be considered as treatment-emergent AEs. Severity of AEs will be reported using the NCI-CTCAE version 4.0 criteria (see Section 5.2.2). Frequencies of AEs will be derived and compared for the treatment groups BI 695502 and US-licensed Avastin®. Adverse events potentially related to immunogenicity will also be evaluated.

Laboratory values taken after the first dose of trial medication up to a period of 16 weeks after the last dose of the trial medication will be assigned to the treatment phase for evaluation. Laboratory values will be graded according to the NCI-CTCAE version 4.0 and reported by frequency for each treatment group. Non-graded laboratory parameters will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range.

Changes in blood pressure, pulse rate and ECG parameters will be summarized by treatment group.

### 7.3.5 Interim analyses

No interim analysis will be performed in this trial.

#### 7.3.5.1 DSMB analyses

The DSMB analyses will be performed as specified in the DSMB charter.

An early safety analysis will be reviewed after approximately 20 patients per arm have been treated for 3 cycles (40 evaluable patients). To keep the trial blinded, the safety analysis will be reviewed by the DSMB using descriptive statistics of AEs. If no unexpected changes in the known safety profile for Avastin® are observed for BI 695502, the DSMB will recommend continuing the trial. An indirect comparison with historical safety data for Avastin® might also be considered by the DSMB.

The DSMB will review patient safety on an ongoing basis. For the DSMB analyses, no interim reports will be provided to the sponsor. Since May 2016, there have been 5 regularly spaced DSMB meetings, all of which recommended continuation of the trial without modification.

#### 7.3.5.2 Blinded review of sample size assumption

The fully blinded, pooled ORR will be closely monitored to verify the sample size assumptions. After approximately 200 patients (100 patients per arm) have had tumor response assessments performed until Week 18, an independent blinded statistician will perform a blinded evaluation to confirm the initially calculated sample size.

The blinded sample size assumption review will take into consideration whether blinded results observed so far allow for sufficient precision and power of the primary analysis. In case that the pooled ORR is substantially below 40%, the sample size and the primary analysis model will be revisited.

No formal statistical testing for efficacy will be performed.

#### 7.3.5.3 Primary analysis time point and follow-up analysis time point

As described in Section 7.3.1 the primary analysis will take place when all primary efficacy endpoint data are available, i.e., after all patients have had tumor response assessments performed after Week 18, or earlier if no more patients are expected to complete the Week 18 visit. At this point all data including safety data will be evaluated. The data will be unblinded at the time point of the primary analysis for the team members involved in the analysis (including the sponsor and its designees). All other team members will remain blinded until the final unblinding. The results will be summarized in a CTR (primary analysis of efficacy and safety).

A follow-up analysis will be conducted at a later time point, as required by the regulatory authorities. In this follow-up analysis, all analyses performed at the primary analysis time point will be repeated with the (partially) updated data, in particular with respect to safety and the endpoints collected. The results of this analysis will be summarized in a follow-up CTR. For details on unblinding procedures, see Section 4.1.5.1.

## 7.4 HANDLING OF MISSING DATA

### 7.4.1 Efficacy endpoints

The central imaging unit will work with the clinical sites towards a standard implementation of the RECIST 1.1 criteria. An imaging charter will detail all procedures, including quality control and the criteria needed to handle missing assessments.

For response assessment, drop out due to disease progression or death will be classified to "disease progression" response category. For the primary endpoint, in order to preserve any observed difference between treatment groups, best ORR will be assumed to be missing at random. Robustness of the primary conclusion to the missing at random assumption will be evaluated by sensitivity analyses that will take account of the reason for discontinuation.

### 7.4.3 Safety and other endpoints

For safety and other endpoints rules for handling of missing data will be specified in the TSAP.

## 7.5 RANDOMIZATION

Patients may be pre-randomized in a blinded fashion to either BI 695502 or US-licensed Avastin® at screening (see Section 4.1.2 for details). At Day 1 patients will be randomized to double-blind treatment according to their pre-randomization, if applicable. Patients who do

not meet all the inclusion criteria or meet one or more of the exclusion criteria will not be randomized and will be considered screen failures.

For biosimilarity evaluation, patients in the trial will be randomly assigned in a blinded fashion to either BI 695502 or US-licensed Avastin® with a 1:1 allocation ratio. The randomization will be stratified by the following variables:

- Sex (male versus female)
- Smoking status (never smoked versus current/past smoker)
- NSCLC stage (recurrent versus Stage IV).
- Ethnicity (East Asian origin versus non East Asian)

Randomization will be performed by IXRS®. Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Trial Support Group or a CRO appointed by the sponsor will provide the randomization list using a validated randomization number generating system. Access to the randomization code will be controlled and documented. Boehringer Ingelheim/Quintiles will not have access to the randomization assignments generated by the IXRS®. All persons directly involved in the conduct and analysis of the trial will have no access to the treatment allocation prior to final database lock. The data of the primary analysis population for biosimilarity evaluation will be unblinded at the time point of the primary analysis only for the team members involved in the analysis (including the sponsor and CRO) (see Section 4.1.2 and Section 4.1.5). On an individual patient basis, the drug administered may be revealed during pharmacovigilance activities. The block size(s) of the randomization will be documented in the CTR.

## 7.6 DETERMINATION OF SAMPLE SIZE

The sample size is approximately N = 660 patients (n = 330 per treatment arm) based on an ORR ratio of 1.000, an equivalence margin of (0.736, 1.359) on the ORR ratio scale and a power of 92%. The equivalence margin is based on meta-analysis (see Section 7.2).

Using the above equivalence margin, the total sample size (N = 660) is robust with respect to the assumed ORR effect size in both arms and the assumed ORR ratio. A high power is ensured even if the observed ORR effect size is slightly lower than calculated from the trials included in the meta-analysis (Table 7.6: 1).

Table 7.6: 1 Robustness of trial design with respect to power (primary hypothesis)

| **ORR** | 36% | 38% | 40% | 43.3% |
|---|---|---|---|---|
| **Power** | 80% | 84% | 88% | 92% |

ORR = overall response rate
Calculations based on Addplan v6.0.4

Based on this sample size of N = 660, if the sensitivity analysis margin (0.727, 1.376) for the ORR ratio would be tested with the TOST procedure following a more strict alpha=2.5% type I error rate, a similarly high power would be achieved (Table 7.6: 2).

Table 7.6: 2 Robustness of trial design with respect to power (sensitivity analysis)

| **ORR** | 36% | 38% | 40% | 43.3% |
|---|---|---|---|---|
| **Power** | 72% | 78% | 82% | 88% |

ORR = overall response rate
Calculations based on Addplan v6.0.4

For details of the sample size calculation refer to Appendix 10.6.3.

# 8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for GCP and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

The rights of the investigator (trial site – Japan only) and of the sponsor with regard to publication of the results of this trial are described in the investigator contract (trial site's contract – Japan only). As a general rule, no trial results should be published prior to finalisation of the CTR.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF.

## 8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/IEC and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorized monitors (Local Clinical Monitor/Clinical Research Associate [CRA]) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Starting as of 21 Dec 2017, all patients will be informed verbally by the investigator about the switch from BI 695502 to Avastin®. Once the updated ICF is available, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country.

Japan only: The investigator must give a full explanation to trial patients by using the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

The following items need to be included:

1. That the clinical trial is aimed at testing.

2. Objectives of the trial.

3. The name, title, and address of the investigator to contact.

4. Trial procedures.

5. Anticipated benefits of the investigational products and anticipated disadvantages to the patient.

6. Matters concerning other therapeutic measures.

7. Duration of participation in the clinical trial.

8. That the patient may withdraw from the trial at any time.

9. That patient's refusal of or withdrawal from participation in the trial does not cause any disadvantage to him or her.

10. That the monitors, the auditors, and the IRB are given access to the relevant source documents on condition that confidentiality of the patient is fully secured.

11. That privacy of the patient is kept.

12. The office of the medical institution to contact in the event of trial-related injury.

13. That necessary treatment is available to the patient in the event of trial-related injury.

14. Matters concerning compensation in the event of any trial-related injury.

15. The type of the IRB which is used for the reviews and deliberations on the matters such as appropriateness of conducting the clinical trial, the matters to be reviewed and deliberated by each IRB, and other matters concerning the IRBs involved in the clinical trial.

16. Other necessary matters concerning the clinical trial.

In case of partner's pregnancy, written consent for pregnancy follow-up will be requested. Follow-up on the pregnancy and its outcome will be performed to evaluate whether there are risks to the pregnant woman or the unborn fetus.

## 8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

## 8.3 RECORDS

Case report forms for individual patients will be provided by the sponsor, either on paper or via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

### 8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

### 8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. All CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g., FDA). The CRA/on-site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

### 8.3.3 Storage of records

Japan only:

Storage period of records

Trial sites: The trial sites must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and the sponsor's SOP.

Sponsor: The sponsor must retain the essential documents according to the sponsor's SOPs.

When it is no longer necessary for the trial site to retain the source documents and essential documents, the sponsor must notify the head of trial site.

## 8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

### 8.4.1 Listedness

To fulfill the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular AE is "listed", i.e., is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For BI 695502 this is the current version of the Investigator's Brochure. The current version of this reference document is to be provided in the ISF. Expected AEs are listed in the most current version of the EU Summary of Product Characteristics (SPC) and the US Prescribing Information for Avastin® (R15-1223, R18-0043). For the non-investigational medicinal products, the reference document for paclitaxel is the UK SPC and for carboplatin the UK SPC. The current versions of these reference documents are to be provided in the ISF.

### 8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of SAEs, e.g., suspected unexpected serious adverse reactions (known as SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Progression of underlying disease and death due to progression of underlying disease are considered as outcome events and are not to be reported as SAEs. Further details regarding this reporting procedure are provided in the ISF.

## 8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

## 8.6 COMPLETION OF TRIAL

Additional information for EU member states:

The ethics committee/CA in each participating EU member state needs to be notified about the end of the trial (last patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

Japan only:

When the trial is completed, the investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

## 8.7 PROTOCOL VIOLATIONS

Japan only:

The investigator or sub-investigator should record all CTP violations regardless of their reasons. Only when the protocol is not followed in order to avoid an immediate hazard to trial patients or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

## 8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

Japan only:

In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.

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## 9.2 UNPUBLISHED REFERENCES

Not applicable.

# 10. APPENDICES

## 10.1 GUIDELINES FOR EVALUATION OF OBJECTIVE TUMOR RESPONSE USING RECIST 1.1 CRITERIA (RESPONSE EVALUATION CRITERIA IN SOLID TUMORS)

### INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Guidelines (R09-0262) for the 1302.5 trial with regards to Investigator assessment of tumor burden including protocol-specific requirements for this trial.

### DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been irradiated within 12 weeks prior to the date of randomization.

Measurable:

- For tumor lesions: the longest diameter in the plane of measurement has to be recorded with a minimum size of 10 mm by computed tomography (CT) scan when CT scan slice thickness is no greater than 5 mm or by magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

- For nodal lesions: at baseline and in the follow-up, only the short axis of lymph node will be measured and followed. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed at baseline.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline). Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTL).

- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.

- Measurable previously irradiated lesions where other measurable lesions are available for assessment as target lesions and lesions irradiated within 12 weeks of randomization.

- Skin lesions assessed by clinical examination,

Special Cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

**METHODS OF ASSESSMENT**

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the 1302.5 trial, CT or MRI examinations of the chest and abdomen, including adrenals, will be used to assess tumor burden at baseline and follow-up visits. CT examination with i.v. contrast media administration is the preferred method. MRI with contrast (Gadolinium) should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

Clinical examination

In the 1302.5 trial, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

X-ray

*Chest X-ray*

In the 1302.5 trial, chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

*Plain X-ray*

In the 1302.5 trial, plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound

In the 1302.5 trial, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In the 1302.5 trial, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers

In the 1302.5 trial, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

Cytology and histology

In the 1302.5 trial, histology will not be used as part of the tumor response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (PD) (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of

clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the 1302.5 trial, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

Fludeoxyglucose-Positron emission tomography scan

In the 1302.5 trial, fludeoxyglucose (FDG)-positron emission tomography (PET) scans may be used as a method for identifying new lesions if a baseline FDG-PET scan is done, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

**TUMOR RESPONSE EVALUATION**

Schedule of evaluation

Baseline assessments should encompass the chest and abdomen, including adrenals, and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 21 days (see Flow chart 1.1 and Flow chart 1.2) before the start of study treatment. Follow-up assessments will be performed every 6 weeks (± 3 days) after randomization until Week 18, then every 9 weeks (± 3 days) (see Flow chart 1.1 and Flow chart 1.2) until objective disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Target lesions (TL)

*Documentation of target lesions*

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then the sum of the diameters of those parts should be recorded.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, an estimate of the size of the lesion should be provided.
- When a TL has had any intervention e.g., radiotherapy, embolization, surgery etc., during the study, the size of the TL should still be provided where possible.

*Evaluation of target lesions*

This section provides the definitions of the criteria used to determine objective tumor visit response for TL.

**Complete Response (CR)** Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10 mm.

**Partial Response (PR)** At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.

**Stable Disease (SD)** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

**Progressive Disease (PD)** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

**Not Evaluable (NE)** Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.

Non-Target lesions

*Evaluation of non-target lesions*

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

**Complete Response (CR)** Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).

**Non CR/Non PD** Persistence of one or more NTL.

**Progression (PD)** Unequivocal progression of existing NTL. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.

**Not Evaluable (NE)** Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 10.1: 1.

Table 10.1: 1 Overall visit response

| **Target lesions** | **Non-target lesions** | **New lesions** | **Overall response** |
|---|---|---|---|
| CR | CR | No | CR |
| CR | NA | No | CR |
| NA | CR | No | CR |
| CR | Non CR/Non PD | No | PR |
| CR | NE | No | PR |
| PR | Non PD or NE | No | PR |
| SD | Non PD or NE | No | SD |
| NA | Non CR/Non PD | No | SD (Non CR/Non PD) |
| NE | Non PD or NE | No | NE |
| NA | NE | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; NA = not applicable (only relevant if there were no target lesions/non-target lesions at baseline).

## CENTRAL REVIEW

Radiological examinations performed in the conduct of this study for RECIST response assessments must be retained at the trial site as source data and a copy anonymized for personal identifiers e.g., name, initials, be available for collection by the sponsor for centralized review if required.

## 10.2 GUIDELINES FOR BI 695502/ AVASTIN® PREPARATION AND ADMINISTRATION

### Supply

BI 695502 will be provided as a concentrate for solution for infusion in 4 mL vials (containing 100 mg of BI 695502 per 4 mL) and in 16 mL vials (containing 400 mg of BI 695502 per 16 mL) at a concentration of 25 mg/mL.

Avastin® will be provided as a concentrate for solution for infusion in 4 mL vials (containing 100 mg of bevacizumab per 4 mL) and 16 mL vials (containing 400 mg of bevacizumab per 16 mL) at a concentration of 25 mg/mL.

### Stability and Storage

No preservative is used in BI 695502/US-licensed Avastin®; therefore, the vials are intended for single use only. BI 695502/US-licensed Avastin® is biologically and chemically stable at 2 to 8°C (36 to 46°F). Once reconstituted into i.v. bags, the solution is chemically stable for up to 8 hours at 2 to 8°C (36 to 46°F). However, since no preservative is included, diluted solutions must be stored refrigerated (2 to 8°C). As no incompatibilities between polyvinylchloride or polyolefin bags/lines have been observed for BI 695502/US-licensed Avastin®, only bags/lines made of these materials are to be used for US-licensed Avastin® and BI 695502 infusion administration in this trial. The following special infusion sets ***must*** be used:

| **Infusion sets** | **BI 695502** |
|---|---|
| PVC bag | X |
| PE bag, as a polymer of polyolefin | X |
| PP bag | X |
| DEHP free bag and PVC-free bag | X |
| PVC tubing | X |
| PE tubing | X |
| PUR tubing | X |
| BR | X |
| Filters tested: for B.Braun Spaceline standard tubing, an additional infusion filter (PALL 0.2 µm Posidyne ELD-Filter) was used, all other tested tubings include a 0.2 µm infusion filter | |

BR = Polybutadiene; PVC = Polyvinyl chloride; PP = Polypropylene; PE = Polyethylene; DEHP = di-(2-ethylhexyl)phthalate; PUR = Polyurethane; X = tested and passed.

Do not use beyond the expiration date stamped on the vial.

Once switched from BI 695502 to Avastin®, the use of bags and lines should be as per Avastin® label. The use of filters as for BI 695502 administration will also be mandatory for Avastin® administration.

**Preparation of BI 695502/US-licensed Avastin® for Intravenous Administration**

The recommended dose is 15 mg/kg every 3 weeks when used in combination with carboplatin/paclitaxel chemotherapy. The dose of BI 695502/Avastin® should be recalculated prior to each infusion.

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. It is recommended that the necessary amount of BI 695502/US-licensed Avastin® will be withdrawn and diluted in 0.9% sodium chloride. The mandatory concentration is 16.5 mg/mL. The volume to be administered for each patient will be calculated based on the patient's weight. Discard any unused portion left in the vial, as the product contains no preservatives. If appropriate infusion materials are not available, a smaller investigational product concentration of 1.4 mg/mL up to 16.5 mg/mL can be temporarily used until the required materials are available.

The packaging for BI 695502 and US-licensed Avastin® are different, so to ensure the investigator and patient stay blinded, the infusion solutions will be prepared by an unblinded pharmacist or suitably qualified designee at each trial site.

After the switch from BI 695502 to Avastin®, the recommended concentration for Avastin® is from 1.4 mg/mL to 16.5 mg/mL.

## 10.3 CHEMOTHERAPY REGIMENS AND RECOMMENDATIONS FOR DOSE MODIFICATIONS IN CASES OF TOXICITY

Patients will receive carboplatin/paclitaxel as outlined in earlier sections of the protocol.

Cycles of carboplatin/paclitaxel plus BI 695502/US-licensed Avastin® should be repeated every 3 weeks for up to 6 cycles.

Cycles are not skipped but delay may occur according to the Clinical Trial Protocol, Tables 10.3:1 and 10.3:2. Maximum timeframe treatment delay should be assessed based on the investigator´s clinical judgment and should be discussed with the study Medical Monitor. However, patients with severe hypertension, moderate to severe proteinuria, or severe infusion reactions will not receive further treatment with Avastin®/BI 695502 if the event cannot be adequately controlled within 14 days.

During the induction phase, any chemotherapy delay mandates a bevacizumab/BI 695502 infusion delay. All three drugs of this regimen (paclitaxel + carboplatin + bevacizumab/ BI 695502) should always be administered together during the induction phase, if the patients fulfills the criteria for receiving the next treatment cycle.

Administration of carboplatin/paclitaxel will be according to the standard preparation and infusion procedures of each investigational site. The doses should be administered as shown below. For the purpose of this Clinical Trial Protocol (CTP), Day 1 is the day when the cycle of carboplatin/paclitaxel is initiated. All patients should receive premedication prior to carboplatin/paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 16 mg orally administered approximately 12 and 6 hours before paclitaxel diphenhydramine (or its equivalent) 50 mg intravenously (i.v.) (infusion should be completed 30 to 60 minutes prior to paclitaxel), cimetidine (300 mg) or ranitidine (50 mg) i.v. (infusion should be completed 30 to 60 minutes before paclitaxel) (see Section 4.1.4.1).

Paclitaxel will be administered first, followed by carboplatin. All patients will be treated with standard combination chemotherapy consisting of paclitaxel 200 mg/m$^2$ followed by carboplatin target area under the curve (AUC) 6 mg/mL/min (30- to 60-minute infusion) every 3 weeks for up to 6 cycles with adequate pre- and concomitant medication. The initial dose of paclitaxel (day 1, cycle 1) must be fixed to 200 mg/m² for all study patients, as well as a dose of carboplatin to AUC: 6 mg/mL/min. In case of toxicity after this initial dose, the dose can be reduced in the event of toxicity according to the protocol guideline Table 4.1.4.1:1 and 10.3.1.

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare paclitaxel solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Aluminum reacts with carboplatin causing precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

**Preparation of carboplatin intravenous solutions**

Carboplatin Injection is supplied either as a ready-to-use solution or as lyophilized powder.

In the first case, 10 mg/mL is supplied as a Ready To Use (RTU) sterile solution in 5 mL, 15 mL, 45 mL or 60 mL vials. Total content of carboplatin per vial is described in following table:

| Vial Strength | Diluent Volume |
|---|---|
| 50 mg | 5 mL |
| 150 mg | 15 mL |
| 450 mg | 45 mL |
| 600 mg | 60 mL |

If supplied as a lyophilized powder, immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP, 5% Dextrose in Water (D5W), or 0.9% Sodium Chloride Injection, USP, according to the following schedule:

| Vial Strength | Diluent Volume |
|---|---|
| 50 mg | 5 mL |
| 150 mg | 15 mL |
| 450 mg | 45 mL |

These dilutions all produce a carboplatin concentration of 10 mg/mL.

Carboplatin for injection can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP.
When prepared as directed, Carboplatin for injection solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that Carboplatin solutions be discarded 8 hours after dilution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

**Storage**

Unopened vials of Carboplatin for injection are stable for the life indicated on the package when stored at 25°C (77°F) [excursions permitted to 15°- 30°C (59°- 86°F) [see USP Controlled Room Temperature] and protected from light. Carboplatin injection multidose vials maintain microbial, chemical, and physical stability for up to 15 days at 25°C following multiple needle entries.

**Recommended dose modifications:**

**Please refer to the Prescribing Information for paclitaxel and carboplatin for details.**

Table 10.3: 1 Dose Modifications for Hematologic Toxicities (Regardless of Causality)

| **Toxicity** | | **Paclitaxel/Carboplatin** |
|---|---|---|
| **Grade 3 Neutropenia of any duration or Grade 4 < 7 days** | 1st event | Interrupt until recovery to ≥1500/mm$^3$<br>Preferably reinitiate at original dose, unless investigator deems dose reduction by one level is necessary based on individual patient status. Discuss with Medical Monitor Sponsor |
| | 2nd event | Interrupt until recovery to ≥1500/mm$^3$<br>Consider dose reduction by one level at investigators discretion, discuss with Medical Monitor Sponsor |
| | 3rd event despite dose reduction | Interrupt until recovery to ≥1500/mm$^3$<br>Consider dose reduction by one level at investigators discretion, discuss with Medical Monitor Sponsor |
| | 4th event despite dose reduction | Off Treatment |
| **Grade 4 Neutropenia ≥ 7 days** | 1st event | Interrupt until recovery to ≥1500/mm$^3$<br>Reinitiate at next lower dose level. |
| | 2nd event despite dose reduction | Interrupt until recovery to ≥1500/mm$^3$<br>Reinitiate at previous lower dose level. |
| | 3rd event despite dose reduction | Off Treatment |
| **Febrile Neutropenia with Absolute Neutrophil Count (ANC) <3 1000/mm** | 1st event | Hold dose until ANC ≥1500/mm$^3$ and T ≤38ºC<br>Reinitiate at next lower dose level |
| | 2nd event despite dose reduction | Hold dose until ANC ≥1500/mm$^3$ and T ≤38ºC<br>Reinitiate at next lower dose level |
| | 3rd event despite dose reduction | Off Treatment |
| **Thrombocytopenia ≥ 50,000 to <100,000/mm$^3$**, all events | | Hold dose until recovery to ≥100,000/mm$^3$<br>No change in dose |

Table 10.3: 1 Dose Modifications for Hematologic Toxicities (Regardless of Causality) (continued)

| **Toxicity** | | **Paclitaxel/Carboplatin** |
|---|---|---|
| **Grade ≥3 Thrombocytopenia** | ≥25,000/mm$^3$ to <50,000/mm$^3$, 1st event | Hold dose until recovery to >100,000/mm$^3$<br>Reinitiate at original dose level |
| | ≥25,000/mm$^3$ to <50,000/mm$^3$, 2nd event | Hold dose until recovery to >100,000/mm$^3$<br>Reinitiate at next lower dose level |
| | <50,000/mm$^3$, despite previous dose reduction | Off Treatment |
| **Grade 4 Thrombocytopenia Or Grade 3 with Bleeding Requiring Platelet Transfusion** | <25,000/mm$^3$, 1st event | Hold dose until recovery to >100,000/mm$^3$<br>Reinitiate at next lower dose level |
| | <25,000/mm$^3$ despite previous dose reduction | Off Treatment |
| **Any Grade Non-hemolytic Anemia** | | Manage by transfusions<br>No change in dose. |

If protocol treatment is held for >1 week for granulocyte recovery, then prophylactic filgrastim (Neupogen®) or pegfilgrastim (Neulasta®) will be administered (according to the package insert) with all subsequent cycles. If a febrile neutropenic episode (≥ 38.5ºC) occurs at any time during therapy accompanied by a granulocyte count of <1000/mm$^3$, prophylactic granulocyte-colony stimulating factor (G-CSF) will be used for all subsequent cycles. Other additional uses of G-CSF are allowed, according to regular institutional practice and the PI´s judgment.

Criteria for dose reductions and discontinuation of therapy for some specific non-hematologic toxicities are summarized in Table 10.3: 2:

Table 10.3: 2 Dose Modifications for Selected Non-Hematologic Toxicity (Regardless of Causality)

| **Toxicity** | **Paclitaxel/Carboplatin** |
|---|---|
| **Metabolic** | |
| **Hyperglycemia** | No Change |
| **Hypoglycemia** | No Change |
| **Gastrointestinal-related** | |
| **≥ Grade 3 Nausea/Vomiting (1st Event)** | No change |
| **≥ Grade 3 Nausea/Vomiting (2nd Event)** | Decrease both by one dose level |

Table 10.3: 2 Dose Modifications for Selected Non-Hematologic Toxicity (Regardless of Causality) (continued)

| Toxicity | Paclitaxel/Carboplatin |
|---|---|
| **Grade 1 - 2 Diarrhea** | No change |
| **≥ Grade 3 Diarrhea lasting >24 hours despite maximum anti-diarrheal management (1st event)** | Hold study drug treatment until decreased to ≤ Grade 1 or to baseline<br>Reinitiate at original dose level |
| **≥ Grade 3 Diarrhea lasting >24 hours despite maximum anti-diarrheal management (2nd Event)** | Hold study drug treatment until decreased to ≤ Grade 1 or to baseline<br>Reinitiate at original dose level |
| **Grade 1 - 2 Mucositis** | Hold study drug treatment until decreased to ≤ Grade 1 or to baseline<br>Reinitiate at original dose level |
| **≥ Grade 3 Mucositis (1st event)** | Hold study drug treatment until decreased to ≤ Grade 1 or to baseline<br>Reinitiate at original dose level |
| **≥ Grade 3 Mucositis (2nd Event)** | Hold study drug treatment until decreased to ≤ Grade 1 or to baseline<br>Decrease current dose by one dose level |
| **Hepatobiliary** | |
| **≥ Grade 2 Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) and ≤ Grade 1 Total Bilirubin** | Hold until liver function tests (LFTs) ≤ Grade 1. Restart paclitaxel at same dose when bilirubin is within normal limit. Lower paclitaxel one dose level when bilirubin = Grade 1<br>No dose adjustment for carboplatin |
| **≥ Grade 3 AST or ALT or ≥ Grade 2 Total Bilirubin** | Hold until LFTs ≤ Grade 1. Restart paclitaxel at same dose when bilirubin is within normal limit. Lower paclitaxel one dose level when bilirubin = Grade 1<br>No dose adjustment for carboplatin |
| **Allergic/Hypersensitivity to Paclitaxel** | |
| **≥ Grade 3 allergic/ hypersensitivity despite adequate premedications** | Off treatment |
| **Neuropathy** | |
| **Neuropathy Grade 2** | Hold study drug treatment until decreased to ≤ Grade 1 or to baseline<br>Decrease paclitaxel by one dose level. No dose adjustment for carboplatin |
| **Neuropathy ≥ Grade 3** | Hold study drug treatment until decreased to ≤ Grade 1 or to baseline<br>Decrease paclitaxel by two dose levels. No dose adjustment for carboplatin |

Since there are no commonly accepted recommendations for dose modifications it is suggested to follow the hospital standards and carefully capture any modification in the respective electronic case report form page.

## 10.4 CLINICAL EVALUATION OF LIVER INJURY

### 10.4.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Protocol-Specified adverse events of special interest [AESI]), are to be further evaluated using the following procedures:

### 10.4.2 Procedures

Repeat the following laboratory tests according to the following criteria:

Patients with liver function test (LFT) value(s) within normal limits at baseline: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin (total and direct) within 48 to 72 hours. If ALT and/or AST ≥ 3 times upper limit of normal (ULN) combined with an elevation of total bilirubin ≥ 2 times ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to Boehringer Ingelheim as soon as possible.

Patients with elevated LFT value(s) at baseline: Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) within 48 to 72 hours. If ALT and/or AST ≥ 5 times ULN combined with an elevation of total bilirubin ≥ 2 times ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to Boehringer Ingelheim as soon as possible.

Patients with elevated total bilirubin at baseline: The threshold to qualify for repeat laboratory tests is defined as elevation of hepatic enzymes based on the above criteria, combined with concurrent elevation of total bilirubin above baseline.

In addition:

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the “Drug Induced Liver Injury (DILI) checklist” provided in the ISF;
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the “DILI checklist” provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the “DILI checklist” provided in the Investigator Site File (ISF);

and report these via the electronic case report form. A copy of the DILI checklist should also be provided along with the SAE form.

The investigator is to follow the laboratory testing and assessments as noted in the DILI checklist in the ISF. These assessments include but are not limited to:

*Clinical chemistry including coagulation*

- alkaline phosphatase, albumin, prothrombin time or International Normalized Ratio, creatine kinase, creatine kinase muscle-brain, coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, triglycerides, cholinesterase.

*Serology*

- Hepatitis A (Anti-immunoglobulin [Ig]M, total Anti-Ig), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, total Anti-Ig), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Antinuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Antimitochondrial antibody, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)

*Hormones, tumor marker*

- Thyroid stimulating hormone.

*Hematology*

- Complete blood count (including differential counts)

Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g., bile duct stones or neoplasm.

Initiate close observation of patients by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g., by reflex testing will be followed up based on medical judgement and Good Clinical Practice (GCP).

## 10.5 TUMOR, NODE, METASTASIS (TNM) STAGING


### Definitions

#### Primary Tumor (T)

**TX** Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

**T0** No evidence of primary tumor

**Tis** Carcinoma in situ

**T1** Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (for example, not in the main bronchus)[1]

**T1a** Tumor 2 cm or less in greatest dimension

**T1b** Tumor more than 2 cm but 3 cm or less in greatest dimension

**T2** Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

**T2a** Tumor more than 3 cm but 5 cm or less in greatest dimension

**T2b** Tumor more than 5 cm but 7 cm or less in greatest dimension

**T3** Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina[1] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe

**T4** Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

#### Distant Metastasis (M)

**M0** No distant metastasis

**M1** Distant metastasis

**M1a** Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion[2]

**M1b** Distant metastasis (in extrathoracic organs)

#### Notes

[1] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

[2] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

| ANATOMIC STAGE/PROGNOSTIC GROUPS | | | |
|---|---|---|---|
| Occult Carcinoma | TX | N0 | M0 |
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1a | N0 | M0 |
| | T1b | N0 | M0 |
| Stage IB | T2a | N0 | M0 |
| Stage IIA | T2b | N0 | M0 |
| | T1a | N1 | M0 |
| | T1b | N1 | M0 |
| | T2a | N1 | M0 |
| Stage IIB | T2b | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T1a | N2 | M0 |
| | T1b | N2 | M0 |
| | T2a | N2 | M0 |
| | T2b | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| Stage IIIB | T1a | N3 | M0 |
| | T1b | N3 | M0 |
| | T2a | N3 | M0 |
| | T2b | N3 | M0 |
| | T3 | N3 | M0 |
| | T4 | N2 | M0 |
| | T4 | N3 | M0 |
| Stage IV | Any T | Any N | M1a |
| | Any T | Any N | M1b |



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# Lung Cancer Staging

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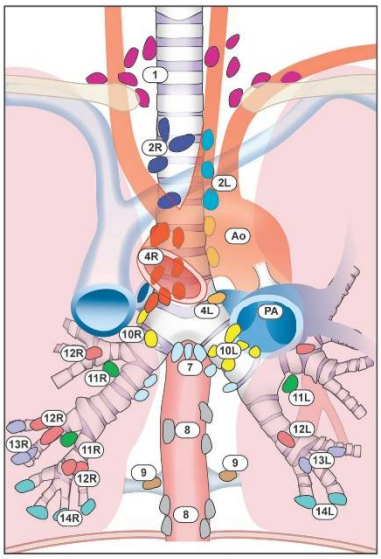



*Supraclavicular zone*

- **1** Low cervical, supraclavicular, and sternal notch nodes

**Superior Mediastinal Nodes**

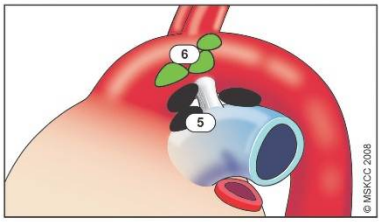
*Upper zone*

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

**Aortic Nodes**

*AP zone*

- **5** Subaortic
- **6** Para-aortic (ascending aorta or phrenic)



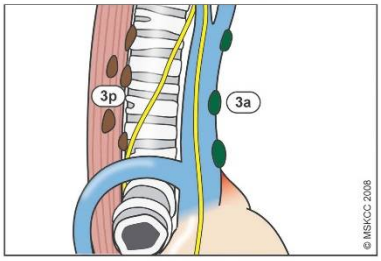

**Inferior Mediastinal Nodes**

*Subcarinal zone*

- **7** Subcarinal

*Lower zone*

- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament




**$N_1$ Nodes**

*Hilar/Interlobar zone*

- **10** Hilar
- **11** Interlobar

*Peripheral zone*

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

**Regional Lymph Nodes (N)**

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastases
- **N1** Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
- **N2** Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
- **N3** Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

ILLUSTRATION

The IASLC lymph node map shown with the proposed amalgamation of lymph into zones.

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Website://cancerstaging.org/references-tools/quickreferences/documents/lungmedium.pdf (accessed on 24 Mar 2015)

## 10.6 DETAILS OF THE STATISTICAL CONCEPT FOR CLINICAL SIMILARITY ASSESSMENT

### 10.6.1 Equivalence Margin

The historical treatment effect of Avastin® is estimated based on a meta-analysis of studies being representative for the treatment effect of Avastin® and BI 695502 in the intended 1302.5 trial population:

- All data used were taken from studies with a backbone chemotherapy control arm.
- All data used were taken from studies or study arms excluding squamous cell type lung cancer.
- All data used were taken from studies or study arms with a dosing regimen of 15 mg/kg bevacizumab.
- Only studies using the identical backbone therapy as planned in trial 1302.5 (paclitaxel 200 mg/m$^2$ followed by carboplatin target area under the curve (AUC) 6 mg/mL•minute) were considered to ensure homogeneity and representativeness of the reference data to the planned trial 1302.5.

Thus in the meta-analysis the following three studies, which are part of the Soria 2013 (R14-0472) review, were included: Sandler et al 2006 (R07-1161), Niho et al 2012 (R14-0473), and the non-squamous cell histology subgroup (15 mg/kg bevacizumab versus control) of Johnson et al 2004 (R04-4661).

While the treatment effect of Avastin® by meta-analysis was not significantly heterogeneous on the overall response rate (ORR) difference scale (Table 10.6.1: 1), the treatment effect of Avastin was even more homogenous on the ORR ratio scale (Table 10.6.1: 2). Therefore the best ORR ratio is chosen as the primary measure for treatment differences in this trial.

Table 10.6.1: 1 Fixed-effects meta-analysis of ORR difference

| | Avastin® | | Control | | | | |
|---|---|---|---|---|---|---|---|
| **Source** | **Events** | **Total N** | **Events** | **Total N** | **Weight** | **ORR difference** | **(90% CI)** |
| Sandler (2006) | 133 | 381 | 59 | 392 | 81.6% | 19.9% | (14.9%, 24.9%) |
| Niho (2012) | 71 | 117 | 18 | 58 | 13.1% | 29.6% | (17.2%, 42.1%) |
| Johnson (2004) | 16 | 32 | 5 | 25 | 5.3% | 30.0% | (10.4%, 49.6%) |
| Total (weighted) | | | | | | 21.7% | (17.2%, 26.2%) |

Test for heterogeneity: p=0.3761.
CI = confidence interval; ORR = overall response rate
Calculations based on Metacalc v3.0

Table 10.6.1: 2 Fixed-effects meta-analysis of ORR ratio

| | Avastin® | | Control | | | | |
|---|---|---|---|---|---|---|---|
| **Source** | **Events** | **Total N** | **Events** | **Total N** | **Weight** | **ORR ratio** | **(90% CI)** |
| Sandler (2006) | 133 | 381 | 59 | 392 | 64.4% | 2.319 | (1.846, 2.914) |
| Niho (2012) | 71 | 117 | 18 | 58 | 28.6% | 1.955 | (1.386, 2.759) |
| Johnson (2004) | 16 | 32 | 5 | 25 | 6.5% | 2.500 | (1.218, 5.132) |
| Total (weighted) | | | | | | 2.220 | (1.847, 2.668) |

Test for heterogeneity: p=0.7632.
CI = confidence interval; ORR = overall response rate
Calculations based on Metacalc v3.0

To account for variability in the treatment effect estimate, a conservative estimate of the historical ORR ratio between Avastin® plus chemotherapy and chemotherapy alone is given by the lower limit of the 90% confidence interval (CI) of the ORR ratio, $M_1 = 1.847$. The non-inferiority margin $M_2$ that preserves ½ (50%) of $M_1$ is calculated on the log ORR ratio scale for symmetry reasons. It follows that $M_2 = \exp(\log(M_1)/_2) = 1.359$ and therefore the equivalence margin for best ORR ratio is given by the interval (1/1.359, 1.359) = (0.736, 1.359). This margin will be used for the test of the primary hypothesis.

An alternative method to obtain assay-sensitivity with respect to the control therapy of carboplatin and paclitaxel alone is to base the margin calculation on preserving more than half of the point estimate of the historical treatment effect of Avastin®. The non-inferiority margin $M_2 = 1.376$ preserves 3/5 (60%) of the point estimate of the treatment effect measured on the log ORR ratio scale, i.e., it preserves 82.4 percentage points or more than 2/3 of the 122 percentage points relative increase in ORR. The corresponding equivalence margin for best ORR ratio is given by the interval (1/1.376, 1.376) = (0.727, 1.376). This margin will be used in a sensitivity analysis to the primary analysis to assess the robustness of the results with respect to the margin calculation.

### 10.6.2 Statistical model and equivalence test

The primary analysis is based on a log binomial regression model with subsequent transformation of the estimated parameters to the ratio in best ORR including the respective CI. The log binomial regression model is a generalized linear model for the binomial distribution with log link. It is suited for estimating relative risks (Spiegelman and Hertzmark 2005; R14-3815). The ratio of best ORR is a relative risk.

The statistical model will be:

log (E{ORR}) = treatment + sex + smoking status + NSCLC stage + ethnicity

The difference in log(best ORR) between BI 695502 and US-licensed Avastin® will be estimated, with 90% CI, adjusted for sex, smoking status, nonsmall cell lung cancer (NSCLC) stage, and ethnicity. The estimate and CI will be exponentiated to return to the ratio scale.

This model includes the following explanatory variables: treatment, sex (male versus female), smoking status (never smoked versus current/past smoker), NSCLC stage (recurrent versus Stage IV) and ethnicity (East Asian origin versus non East Asian). In case of sparse data in one (or more) strata which affects the convergence of the model the respective factors may be omitted in the model.

The primary test for equivalence will be performed with respect to BI 695502 versus US-licensed Avastin®. The primary hypothesis is based on the ratio in best ORR between the two treatments:

$H_0$: Ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) $\leq$0.736 or $\geq$1.359.

$H_1$: Ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) within the interval (0.736, 1.359).

The primary hypothesis will be tested using a union-intersection test based on two one-sided tests (TOST) with a 5% type I error rate. This test, also called equivalence test or similarity test preserves the overall type I error rate at alpha = 5% (R14-3718).

To implement this, a decision rule based on the 90% two-sided confidence interval of the ORR ratio between BI 695502 and US-licensed Avastin® will be used. The null hypothesis will be rejected in favor of the alternative hypothesis of clinical equivalence if the 90% CI for the ORR ratio falls completely between the lower bound of 0.736 and the upper bound of 1.359 of the similarity margin.

The test of the primary hypothesis is designed in a way to provide evidence of no clinically meaningful difference between BI 695502 versus US-licensed Avastin® with respect to the primary endpoint best ORR.

If, for example, the best ORR of BI 695502 would be estimated at 37.3% and the best ORR of US-licensed Avastin® at 43.3% and the ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) would equal 0.860, with a 90% CI of (0.735, 1.005), then the primary null hypothesis could not be rejected.

However, if best ORR of BI 695502 would be estimated at 37.6% and the best ORR of US-licensed Avastin® still at 43.3% and the ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) would equal 0.867 with a 90% CI of (0.741,1.013), then in this case the primary null hypothesis could be rejected. The difference between the treatments would not be clinically meaningful. Thus the choice of the equality margin is justified on both clinical and statistical grounds.

If BI 695502 and US-licensed Avastin® are clinically equal, a high power is obtained (Appendix 10.6.3).

### 10.6.3 Sample Size

The sample size is approximately N = 660 patients (n = 330 per treatment arm). It is based on an ORR ratio of 1.000, an equivalence margin of (0.736, 1.359) on the ORR ratio scale and a power of 92% in the test of the primary hypothesis for an ORR of 43.3% in both treatment arms.

The ORR of 43.3% is the weighted average of the ORR of Avastin® in the meta-analysis for ORR ratio, using the weights resulting from this meta-analysis. Since the meta-analysis is based on the ORR ratio and not designed to provide an estimate of ORR, other ways of computing the ORR for Avastin® are possible and would lead to similar results.

The total sample size (N = 660) is chosen to be robust with respect to the assumed ORR effect size in the BI 695502 and US-licensed Avastin® treatment arms. A high power for the test of the primary hypothesis is ensured even if the observed ORR effect size is slightly lower than calculated from the trials included in the meta-analysis (Table 7.6: 1).

For an ORR >30%, the power for the test based on the ratio of best ORR is also higher than the power of a test based on the best ORR difference scale. For example a margin of (-8.6%, 8.6%) preserving 50% of the lower bound of the 90% CI for the treatment difference on the ORR difference scale tested using a 90% CI results in a power of only 44% (assuming an ORR of 43.3%). This further justifies the use of the best ORR ratio as compared to the best ORR difference in the primary analysis.

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

| | | |
|---|---|---|
| **Number of global amendment** | | 1 |
| **Date of CTP revision** | | 01 April 2015 |
| **EudraCT number** | | 2014-002161-30 |
| **BI Trial number** | | 1302.5 |
| **BI Investigational Product(s)** | | BI 695502 |
| **Title of protocol** | | A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer |
| | | |
| **To be implemented only after approval of the IRB/IEC/Competent Authorities** | | ☒ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only** | | ☐ |
| | | |
| **Section to be changed** | | Throughout protocol |
| **Description of change** | | 1. US-sourced Avastin® has been updated to US-licensed Avastin®.<br>2. EU-sourced Avastin® has been updated to EU-approved Avastin®.<br>3. References to Avastin® or bevacizumab have been updated to US-licensed Avastin®, as applicable. |
| **Rationale for change** | | As a result of FDA feedback the use of the term US-licensed Avastin® has been specified, as applicable, to indicate clearly which product will be used in the trial. Since the source of Avastin® is not specified in originator publications, the general term “Avastin®” has been used when referencing such documents. For general mode- |

| | | |
|---|---|---|
| | | of-action description of the molecule, the term "bevacizumab" has been used. |
| | | |
| **Section to be changed** | | Synopsis, Main Criteria for Inclusion |
| **Description of change** | | The statement "Patients must have no contraindication to Avastin®" has been revised to state patients must have no known sensitivity to any of the trial drugs or their excipients. |
| **Rationale for change** | | To ensure consistency with Section 3.3.3, Exclusion Criterion 27. |
| | | |
| **Section to be changed** | | 1.2 |
| **Description of change** | | 1. In the first sentence, "reference bevacizumab product" has been revised to "bevacizumab product".<br>2. In the last paragraph, text has been revised to state that bevacizumab is approved for primary peritoneal cancer in the US as well as in the EU.<br>3. In the last paragraph (and throughout the protocol), references to R14-3588 and R14-3589 have been updated to R15-1223 and R15-1222 |
| **Rationale for change** | | To improve clarity and update references |
| | | |
| **Section to be changed** | | 3.1 |
| **Description of change** | | The description of the requirements for the SFU Visit has been clarified. |
| **Rationale for change** | | To clarify that all patients will be required to attend the SFU visit once they have completed trial therapy. |
| | | |
| **Section to be changed** | | 3.3.2 |
| **Description of change** | | Inclusion criterion 10 has been revised to specify that all patients (males and females of childbearing potential) must continue to use an acceptable form of contraception for 6 months following completion or discontinuation of trial medication, and to add text defining child-bearing potential. |
| **Rationale for change** | | To ensure the protocol and Informed Consent Form are consistent. |
| | | |
| **Section to be changed** | | 3.3.4.1 |
| **Description of change** | | The criteria for withdrawal from the trial, discontinuation from trial medication and the |

| | | |
|---|---|---|
| | | requirements for follow-up of patients who discontinue treatment have been clarified. |
| **Rationale for change** | | FDA requirement to state clearly the difference between criteria that lead to withdrawal from trial and those that lead to discontinuation from treatment. |
| | | |
| **Section to be changed** | | 4.1.4 |
| **Description of change** | | The reference to the table for chemotherapy dose modification has been corrected. |
| **Rationale for change** | | To correct an error. |
| | | |
| **Section to be changed** | | 4.1.4.1 |
| **Description of change** | | To clarify that patients who are unable to tolerate at least 3 cycles of chemotherapy or those that start a new backbone chemotherapy will not be withdrawn from the trial, but will be discontinued from trial medication. |
| **Rationale for change** | | For consistency with the changes made in Section 3.3.4.1. |
| | | |
| **Section to be changed** | | 4.2.2.1 |
| **Description of change** | | Text stating that for elective surgery during the trial the interval between termination of the BI 695502/ US-licensed Avastin® infusion and subsequent elective surgery should be at least 28 days to comply with the black box warning of the Avastin® US prescribing information has been revised to remove the reference to the US prescribing information. |
| **Rationale for change** | | Text removed as the warning is not specific to the US. |
| | | |
| **Section to be changed** | | 8.6 |
| **Description of change** | | The text “last patient/patient out” has been revised to “last patient out” |
| **Rationale for change** | | To improve clarity |
| | | |
| **Section to be changed** | | 9.1 |
| **Description of change** | | The reference for the US prescribing information and EU SPC for Avastin® have been updated and minor formatting changes have been made. |
| **Rationale for change** | | To reflect the most recent version of the labels for Avastin® and to ensure correct and consistent formatting of references. |

| | | |
|---|---|---|
| **Number of global amendment** | | 2 |
| **Date of CTP revision** | | 10 July 2015 |
| **EudraCT number** | | 2014-002161-30 |
| **BI Trial number** | | 1302.5 |
| **BI Investigational Product(s)** | | BI 695502 |
| **Title of protocol** | | A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer |
| | | |
| **To be implemented only after approval of the IRB/IEC/Competent Authorities** | | ☒ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only** | | ☐ |
| | | |
| **Section to be changed** | | 4.1.4.1 |
| **Description of change** | | Second paragraph last sentence “In case of anticipated toxicity, the investigator may start paclitaxel at a dose of 175 mg/m2 and/or carboplatin target AUC 5 mg/mL•min.” has been changed to “The dose can be reduced in the event of toxicity according to the protocol guideline Table 4.1.4.1:1 and 10.3.1.” |
| **Rationale for change** | | As a result of FDA feedback to ensure consistency with prior clinical trials, all patients should start treatment at the proposed dose of paclitaxel 200 mg/m2 and/or carboplatin AUC 6 mg/mL/min; the dose can be reduced in the event of toxicity following the protocol guideline. |
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| **Section to be changed** | | 4.2.1 |
| **Description of change** | | Second paragraph “Administration of BI 695502/US-licensed Avastin® should be |

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| | | temporarily suspended for at least 28 days following severe hypertension not controlled with medical management; moderate to severe proteinuria pending further evaluation; or severe infusion reactions. " was deleted and replaced by "Patients with severe hypertension, moderate to severe proteinuria, or severe infusion reactions will not receive further treatment with US-licensed Avastin® or BI695502 if the event cannot be adequately controlled within 14 days." |
| **Rationale for change** | | As a result of FDA feedback that a patient who experienced an event of such severity that required a 28 day treatment interruption for recovery would not benefit from further treatment with bevacizumab or BI695502. |
| | | |
| **Section to be changed** | | Appendix 10.3 |
| **Description of change** | | Paragraph 4 last sentence: "In case of anticipated toxicity, the investigator may start paclitaxel at a dose of 175 mg/m2 and/or carboplatin target AUC 5 mg/mL min." was cancelled and replaced by "The dose can be reduced in the event of toxicity according to the protocol guideline Table 4.1.4.1:1 and 10.3.1." |
| **Rationale for change** | | As a result of FDA feedback to ensure consistency with prior clinical trials, all patients should start treatment at the proposed dose of paclitaxel 200 mg/m2 and/or carboplatin AUC 6 mg/mL/min; the dose can be reduced in the event of toxicity following the protocol guideline. |

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| **Number of global amendment** | | 3 |
| **Date of CTP revision** | | 19 February 2016 |
| **EudraCT number** | | 2014-002161-30 |
| **BI Trial number** | | 1302.5 |
| **BI Investigational Product(s)** | | BI 695502 |
| **Title of protocol** | | A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer |
| | | |
| **To be implemented only after approval of the IRB/IEC/Competent Authorities** | | ☒ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only** | | ☐ |
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| **Section to be changed** | | Throughout protocol |
| **Description of change** | | Minor editorial modifications |
| **Rationale for change** | | To improve understanding, correct spelling and update study personnel qualifications. |
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| **Section to be changed** | | Synopsis (Main criteria for inclusion) |
| **Description of change** | | The Japan age requirement was changed from "Age ≥20 years at Visit 1" to Age ≥20 years at Screening" |
| **Rationale for change** | | To clarify the requirement that patients from Japan be ≥20 years when informed consent is taken. |

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| **Section to be changed** | | Throughout protocol |
| **Description of change** | | Throughout the protocol text has been added to specify that coagulation parameters will be assessed more frequently, updated so that coagulation assessments follow the same schedule as laboratory tests. This includes update to Flow Charts 1.1 and 1.2. |
| **Rationale for change** | | To provide further clarity on when coagulation parameters should be assessed. |
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| **Section to be changed** | | Flow chart 1.1 – cycle 1 up to cycle 6 |
| **Description of change** | | The second sentence of the third footnote "Screening for HIV and TB will be performed according to local practice and local regulatory guidance." Has been revised to "Screening for HIV and TB (purified protein derivative or QuantiFERON) to be performed according to local practice and local regulatory guidance." |
| **Rationale for change** | | To further clarify the methods for HIV and TB screening. |
| | | |
| **Section to be changed** | | Flow chart 1.1 – cycle 1 up to cycle 6 |
| **Description of change** | | Footnote 9, after first sentence "Two consecutive recordings will be made" was added and "ECGs will be performed" deleted so that Footnote 9 reads "Patients should rest for at least 5 minutes in a supine position before ECG evaluations. Two consecutive recordings will be made at Screening, and before starting Cycle 3 and Cycle 5. Additional ECGs will be performed if clinically indicated." |
| **Rationale for change** | | To clarify ECG procedures and ensure consistency with Flow Chart 1.2. |
| | | |
| **Section to be changed** | | Flow chart 1.1 – cycle 1 up to cycle 6 |
| **Description of change** | | Footnote 11. Text was added to specify that abdominal MRIs will be performed with contrast using gadolinium. |
| **Rationale for change** | | To be aligned with the Investigator Site Image Manual from Parexel |
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| **Section to be changed** | | Flow chart 1.1 – cycle 1 up to cycle 6 |

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| **Description of change** | | Footnote 14. The following text was added to the end of the footnote: "During the induction phase, tumor assessments should be performed before treatment administration of Cycles 3 and 5. If an induction therapy cycle is delayed, the tumor assessment will also be delayed." |
| **Rationale for change** | | To further clarify the timing of tumor assessments. |
| | | |
| **Section to be changed** | | Flow chart 1.2 |
| **Description of change** | | An assessment of vital signs was added to the safety follow-up visit. |
| **Rationale for change** | | To clarify that vital signs should be assessed at safety follow-up. |
| | | |
| **Section to be changed** | | Flow chart 1.2 – cycle 7 onwards |
| **Description of change** | | Footnote 9. Text was added to specify that abdominal MRIs will be performed with contrast using gadolinium, and to specify that a delay in a maintenance therapy cycle will result in a delay in tumor assessment. |
| **Rationale for change** | | To be aligned with the Investigator Site Image Manual from Parexel, and to align with induction phase procedures. |
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| **Section to be changed** | | Flow chart 1.2 – cycle 7 onwards |
| **Description of change** | | Footnote 11. The following text was added to the end of the footnote: "In case of a treatment cycle delay (i.e. due to toxicity), imaging assessment (e.g. CT, MRI) for the primary endpoint will be performed at Week 18 ±14 days (fixed time point), regardless of the number of cycles administered to date." |
| **Rationale for change** | | To further clarify the procedure for tumor assessments where a treatment cycle delay occurs. |
| | | |
| **Section to be changed** | | 1.2 |
| **Description of change** | | The list of indications and territories in which Avastin® is approved for use was updated to reflect the approval of Avastin® for metastatic cervical cancer in the European Union as well as the US. |
| **Rationale for change** | | To update the current status of Avastin® licensing. |

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| **Section to be changed** | | 3.3.1 |
| **Description of change** | | The Japan age requirement was changed from "Age ≥20 years at Visit 1" to Age ≥20 years at Screening". It was also specified that for patients with recurrent disease, radiotherapy for locally advanced tumor must have been stopped for at least 12 months prior to Screening |
| **Rationale for change** | | To clarify the requirement that patients from Japan be ≥20 years when informed consent is taken, and to ensure consistency with exclusion criterion 3 |
| | | |
| **Section to be changed** | | 3.3.1 |
| **Description of change** | | Second sentence: the following text was added: "or radiotherapy for locally advanced tumor" to add treatment of locally advanced tumors by radiotherapy to the list of treatments not permitted within 12 months prior to screening. |
| **Rationale for change** | | To ensure consistency with exclusion criterion 3. |
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| **Section to be changed** | | 3.3.2 |
| **Description of change** | | Criterion 1. The Japan age requirement was changed from "Age ≥20 years at Visit 1" to Age ≥20 years at Screening" |
| **Rationale for change** | | To clarify the requirement that patients from Japan be ≥20 years when informed consent is taken. |
| | | |
| **Section to be changed** | | 3.3.2 |
| **Description of change** | | Criterion 4. The following text was added to the end of the criterion: "Despite EGFR mutational status, patients may enter the trial if the site's best standard of care would be to administer such a chemotherapy regimen for that specific patient. However, if an EGFR test result is pending, and |

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| | | chemotherapy treatment would be switched in case of a mutational positive result, patients may not be included in this trial." |
| **Rationale for change** | | The text was added to anticipate investigator's questions regarding the eligibility criterion. |
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| **Section to be changed** | | 3.3.2 |
| **Description of change** | | Criterion 5. The following text was added to the end of the criterion: "Despite ALK mutational status, patients may enter the trial if the site's best standard of care would be to administer such a chemotherapy regimen for that specific patient. However, if an ALK test result is pending, and chemotherapy treatment would be switched in case of a mutational positive result, patients may not be included in this trial" |
| **Rationale for change** | | The text was added to anticipate investigator's questions regarding the eligibility criterion. |
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| **Section to be changed** | | 3.3.2 |
| **Description of change** | | Criterion 8. Bullets a to i were reordered. Additionally, bullet h (international normalized ratio) was deleted and added as criterion 9. The mg/mmol protein/creatinine ratio was updated from 226 to 22.6 mg/mmol. |
| **Rationale for change** | | To remove the International normalized ratio criterion from this list, to reorder the bullet points to a more logical order, and to correct an error in the mg/mmol protein/creatinine ratio. |
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| **Section to be changed** | | 3.3.2 |
| **Description of change** | | A new criterion 9 was inserted as follows: "International normalized ratio ≤1.4 as analyzed locally. Partial thromboplastin time within normal limits according to local practice. Central laboratory analysis will be used for coagulation parameters where local analysis is not available." Subsequent inclusion criteria were renumbered to account for new criterion 9. |
| **Rationale for change** | | To clarify the order of the inclusion criteria and align the study population with that in the original approval dossier for Avastin, and to permit coagulation parameters for inclusion criteria to be assessed locally where possible. Coagulation is a test which is susceptible to |

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| | | sample deterioration artefacts. Therefore the shipping process and time to a central laboratory for analysis can impact the result obtained. values. |
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| **Section to be changed** | | 3.3.2 |
| **Description of change** | | Criterion 11 (previously 10). Text was added to highlight that a list of acceptable contraception methods is provided in patient information. |
| **Rationale for change** | | To clarify where information on acceptable methods of contraception can be found. |
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| **Section to be changed** | | 3.3.3 |
| **Description of change** | | Criterion 6 was deleted and replaced with "6. Patients with known symptomatic brain metastasis:<br>a. Brain metastasis which is symptomatic at screening or randomization visits, or<br>b. Patients who have previously irradiated brain metastasis that has not been shown to be stable at least 1 month after completion of the radiation therapy (either by CT scan or MRI) at screening visit. |
| **Rationale for change** | | To further clarify the exclusion of patients with brain metastasis |
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| **Section to be changed** | | 3.3.3 |
| **Description of change** | | Criterion 23. The following text was added to the end of the criterion: "There should be no radiographic or clinical evidence of active TB." Additionally the HIV and TB screening methods QuantiFERON and purified protein derivative were added as appropriate tests. |
| **Rationale for change** | | To provide further clarity regarding testing for HIV and TB. |
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| **Section to be changed** | | 3.3.4.1 |
| **Description of change** | | The following text was added to the end of the first paragraph: "Patients may be re-screened once in order to fulfill all the inclusion criteria, provided the patient would receive the bevacizumab + paclitaxel/carboplatin regimen in regular practice at the Investigator's discretion." |
| **Rationale for change** | | To provide further clarification on re-screening process. |
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| **Section to be changed** | | 3.3.4.1 |
| **Description of change** | | The following items were added to the list of reasons patients can be discontinued from trial treatment:<br>• Progressive disease<br>• GI perforations (including fistula formation in the GI tract, intra-abdominal abscess)<br>• Fistula formation involving an internal organ<br>• Wound dehiscence and wound healing complications requiring medical intervention<br>• Serious hemorrhage (i.e., requiring medical intervention)<br>• Severe arterial thromboembolic events<br>• Hypertensive crisis or hypertensive encephalopathy<br>• RPLS<br>• Nephrotic syndrome.<br>• Severe hypertension, moderate to severe proteinuria, or severe infusion reactions if the event cannot be adequately controlled within 14 days.<br>The list was also reordered to a more logical order. |
| **Rationale for change** | | To ensure consistency with the discontinuation reasons listed in Section 4.1.4, and to clarify that progressive disease requires discontinuation. |
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| **Section to be changed** | | 3.3.4.1 |
| **Description of change** | | Prior to the paragraph “It is understood by all concerned that an excessive rate of withdrawals can render the trial uninterpretable; therefore, unnecessary withdrawal of patients from the trial should be avoided.” the following text was added: “Patients discontinued from trial treatment or withdrawn from the trial will not be replaced, regardless of the reason for discontinuation/withdrawal.” |
| **Rationale for change** | | To clarify whether discontinued/withdrawn patients will be replaced. |
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| **Section to be changed** | | 3.3.4.2 |
| **Description of change** | | Text was added in the first sentence to specify that the trial may be discontinued overall or at a particular trial site for reasons including but not |

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| | | restricted to those listed in Section 3.3.4.2 |
| **Rationale for change** | | To clarify that circumstances outside those listed in Section 3.3.4.2 may result in trial discontinuation locally or overall. |
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| **Section to be changed** | | 4.1.3 |
| **Description of change** | | Text was added to state that the dose of Avastin/ BI 695502 should be recalculated prior to each infusion. |
| **Rationale for change** | | To clarify that the correct dose needs to be calculated at each infusion. |
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| **Section to be changed** | | 4.1.4.1 |
| **Description of change** | | In the second paragraph. "(according to regular institutional practice)" was deleted, as was the final sentence. The following text was added to the end of the paragraph: "The initial dose of paclitaxel (day 1, cycle 1) must be fixed to 200 mg/m² for all study patients, as well as a dose of carboplatin to AUC: 6 mg/mL/min. In case of toxicity after this initial dose, the dose can be reduced according to the protocol guideline Table 4.1.4.1:1 and 10.3.1." |
| **Rationale for change** | | This change was made at the request of the regulatory authority, and to obtain a more homogeneous trial treatment population. The change was also made in anticipation of requests for initial dose at 175 mg. |
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| **Section to be changed** | | 4.1.4.1 |
| **Description of change** | | The following text was added after the description of the Cockroft-Gault formula equation: "The Cockcroft–Gault formula will be used to calculate the creatinine clearance/glomerular filtration rate (GFR) (required for the Calvert´s formula). As clinically recommended, GFR will be capped at 125 mL/min (even if the result obtained is higher) so as to avoid potential overdosing. Accordingly, the maximum total dose of carboplatin would be 900 mg per cycle." |
| **Rationale for change** | | To further clarify the dosing calculation. |
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| **Section to be changed** | | 4.1.8 |
| **Description of change** | | Text indicating that investigational drugs can be received by a site if signing of the CTP is |

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| | | imminent was deleted. |
| **Rationale for change** | | To clarify that a signed and dated CTP is required prior to sites receiving investigational drugs. |
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| **Section to be changed** | | Table 4.2.2.1: 1 Prior and concomitant treatments |
| **Description of change** | | The radiotherapy restriction text "Patients should not have received radiotherapy for locally advanced nsNSCLC within 12 months prior to screening. Palliative radiotherapy is permitted during treatment for local/non-target lesions, but this must not include radiotherapy to the chest." was deleted and replaced with "Palliative local radiation therapy (outside the only measurable lesion used for RECIST assessment) is acceptable, both previously and during the trial, at the Investigator´s discretion. However, any radiotherapy to the chest must have finished >12 months prior to screening. Previously irradiated brain metastasis must be shown to be stable at 1 month after completion of radiation therapy (by CT or MRI) and before screening, the patient must be asymptomatic from brain metastasis, with a stable dose of oral corticosteroids ≤10 mg/day of prednisolone (or equivalent) during the last 4 weeks, no parenteral corticosteroids in the last 6 weeks prior to Day 1 (see below item in this table), and with an indication of treatment with the study regimen (inclusion criterion #2). Patients must be recovered at screening from any adverse event (>grade 1, except alopecia) related to previous radiotherapy (exclusion criterion #10)." |
| **Rationale for change** | | To ensure consistency with inclusion criterion 2 and exclusion criterion 10, and to provide greater specificity regarding radiotherapy restrictions. |
| | | |
| **Section to be changed** | | Table 4.2.2.1: 1 Prior and concomitant treatments |
| **Description of change** | | The following text was added to the restrictions on drugs/therapies that have not received regulatory approval for any indication: "Simultaneous participation in non-interventional studies (e.g. observational studies) is allowed." |
| **Rationale for change** | | To ensure consistency with new exclusion criterion 28 |
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| **Section to be changed** | | Table 4.2.2.1: 1 Prior and concomitant treatments |
| **Description of change** | | The following text was added to the end of the NSAID restrictions: "Acetaminophen (paracetamol) as well as natural and synthetic opioids could be used as pain relievers" |
| **Rationale for change** | | To provide further clarification on permitted medication form pain management |
| | | |
| **Section to be changed** | | Table 4.2.2.1: 1 Surgical procedures |
| **Description of change** | | The timeframe for permitted invasive procedures was changed from "within 28 days prior to the first dose of BI 695502/US licensed Avastin®" to "≥28 days prior to the first dose of BI 695502/US licensed Avastin®" |
| **Rationale for change** | | To clarify the timeframe in which invasive procedures are permitted. |
| | | |
| **Section to be changed** | | Table 4.2.2.1: 1 Prior and concomitant treatments |
| **Description of change** | | The following text was added to the end of the All supportive therapies restrictions: "Prophylactic use of growing factors is permitted according to regular institutional practice and the PI´s judgment." |
| **Rationale for change** | | To provide further guidance to investigators on the use of growing factors. |
| | | |
| **Section to be changed** | | Table 4.2.2.1: 1 Prior and concomitant treatments |
| **Description of change** | | New row added. For treatment column following text was added: "Bisphosphonates"; for permitted column, following text was added: "These are allowed, according to regular clinical institutional practice and PI´s discretion (e.g. pamidronate, zoledronate, and alendronate). Caution may be exerted as they may affect renal function. Nephrotoxicity can be avoided by stringent adherence to infusion guidelines" |
| **Rationale for change** | | To provide further guidance on bisphosphonates use |
| | | |
| **Section to be changed** | | 4.2.2.2 |
| **Description of change** | | The following text was added to the end of the first paragraph: "One unit of alcohol is 10 mL (or 8 g) of pure alcohol. Accordingly it may be calculated by using the following formula: |

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| | | Alcohol units = Strength of the beverage (Alcohol by volume in %) x volume (mL) ÷ 1,000” |
| **Rationale for change** | | To anticipate potential questions from investigators about alcohol unit calculation |
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| **Section to be changed** | | 5.1.2.1 |
| **Description of change** | | Text was added indicating that:<br>- In the induction phase, tumor assessments should be performed before treatment administration of Cycles 3 and 5.<br>- The Week 18 tumor assessment must be held at Week 18 ±14 days, whether or not this assessment coincides with Cycle 7<br>- In the maintenance phase tumor assessments can be delayed in cycles are delayed |
| **Rationale for change** | | To provide more clarity about tumor assessment time points in the induction phase, at Week 18 and in the maintenance phase. |
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| **Section to be changed** | | 5.1.2.1 |
| **Description of change** | | Text was added to the fifth paragraph to specify that abdominal MRIs will be performed with contrast using gadolinium. |
| **Rationale for change** | | To be aligned with the Investigator Site Image Manual from Parexel |
| | | |
| **Section to be changed** | | 5.2.2.1 |
| **Description of change** | | Text was added to specify that progression of cancer (underlying disease) is exempted from reporting as an AE. |
| **Rationale for change** | | For consistency with updated Section 5.2.2.2. |
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| **Section to be changed** | | 5.2.2.1 (Protocol-specified adverse events of special interest) |
| **Description of change** | | The elevation of AST and/or ALT required to define hepatic injury for patients with impaired liver function at baseline was changed from “≥3 x ULN” to “≥5 x ULN”<br>Additionally, “Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN” was added to the list of laboratory abnormalities requiring follow up. |
| **Rationale for change** | | To ensure consistency with Section 10.4.2. |
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| **Section to be changed** | | 5.2.2.2 |
| **Description of change** | | The guidance for reporting disease progression events was updated. A cross-reference was added to indicate that local regulations should be followed as described in Section 8.4.2. |
| **Rationale for change** | | To reflect new guidance for reporting of disease progression events. |
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| **Section to be changed** | | 5.2.2.2 (Pregnancy) |
| **Description of change** | | Text was added to clarify that pregnant participants must be excluded from the study and to provide detail on the procedure when a patient's partner becomes pregnant. |
| **Rationale for change** | | Updated to include the Partner Pregnancy reporting requirement. |
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| **Section to be changed** | | 5.2.3 |
| **Description of change** | | The definitions of active hepatitis B and active hepatitis C were updated, and text was added to indicate that HIV and TB screening assessments are not mandatory but should be done according to local practice and local regulatory guidance. |
| **Rationale for change** | | To further clarify the requirements for HIV test and TB status assessments. |
| | | |
| **Section to be changed** | | 5.2.3 |
| **Description of change** | | The sentence "International normalized ratio and partial thromboplastin time will be measured at screening only." was deleted. Additionally, text was added that permits coagulation parameters for inclusion criteria to be assessed locally where possible. |
| **Rationale for change** | | To reflect the fact that International normalized ratio and partial thromboplastin time will not be assessed to the same schedule as other laboratory tests, and to ensure consistency with newly added inclusion criterion 9. |
| | | |
| **Section to be changed** | | 5.2.4 |
| **Description of change** | | After "Patients should rest for at least 5 minutes in a supine position before ECG evaluations." the following text was added: "Two consecutive recordings must be made." |
| **Rationale for change** | | To ensure consistency with Flow Chart 1.2. |
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| **Section to be changed** | | 5.2.5 |
| **Description of change** | | Second paragraph under Physical examination heading. The requirement for rectal examination was removed. |
| **Rationale for change** | | Rectal examination is not necessary unless signs or symptoms are present, as it is not a target area to be assessed. |
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| **Section to be changed** | | 6 |
| **Description of change** | | After the first sentence the following paragraph was added “Cycles must not be missed but delays may occur according to Tables 10.3:1 and 10.3:2. The maximum timeframe for treatment delay should be assessed based on the investigator´s clinical judgement and discussed with the trial medical monitor. However, patients with severe hypertension, moderate to severe proteinuria, or severe infusion reactions will not receive further treatment with Avastin®/BI695502 if the event cannot be adequately controlled within 14 days.” |
| **Rationale for change** | | To further clarify the frequency of cycles |
| | | |
| **Section to be changed** | | 6.1 |
| **Description of change** | | The bullet point “Each subsequent cycle will occur within 3 days (±3 days) of completion of the previous cycle.” Was amended to “Each subsequent cycle will occur 3 weeks (±3 days) after completion of the previous cycle.” |
| **Rationale for change** | | To further clarify the timing of cycles |

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| **Section to be changed** | | Table 6.1: 1 |
| **Description of change** | | Blood sample volumes for INR/PT/PTT were updated. The approximate total was also increased accordingly. |
| **Rationale for change** | | To reflect the increased number of measures of coagulation parameters. |
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| **Section to be changed** | | 6.2.1 |
| **Description of change** | | The third bullet point "Hepatitis B and hepatitis C (unless status has previously been confirmed within 6 months prior to Screening) and HIV test (all tests will be performed according to local practice and local regulatory guidance)." was replaced with two bullet points as follows: "• Hepatitis B and hepatitis C (unless status has previously been confirmed within 6 months prior to Screening). • HIV test should be performed only if required per local practice and regulatory guidance." |
| **Rationale for change** | | To further clarify the requirements for HIV test and hepatitis B and hepatitis C assessments. |
| | | |
| **Section to be changed** | | 6.2.1 |
| **Description of change** | | The following text was added to the end of the section: "Subjects are only allowed to be re-screened once and he/she must be re-consented before re-screening occurs." |
| **Rationale for change** | | To clarify the procedure for re-screening. |
| | | |
| **Section to be changed** | | 6.2.2 (Cycles 2, 3, 4, 5, 6) |
| **Description of change** | | The following text was added to the end of the eighth bullet point: "During the induction phase, the tumor evaluations must be performed every 2 cycles. Therefore, if a cycle is delayed, the next tumor evaluation will also be delayed." |
| **Rationale for change** | | To further clarify the procedure for tumor assessments where a treatment cycle delay occurs. |
| | | |
| **Section to be changed** | | 6.2.2 (Cycle 7 to Cycle 10 and onwards) |
| **Description of change** | | The following text was added to the end of the eighth bullet point: "In case of a treatment cycle delay (i.e. due to toxicity), imaging assessment (e.g. CT, MRI) for the primary endpoint will be performed at Week 18 ±14 days (fixed time |

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| | | point), regardless of the number of cycles administered to date and whether or not this assessment coincides with Cycle 7. After cycle 7, if a cycle is delayed, tumor assessment will also be delayed." |
| **Rationale for change** | | To further clarify the procedure for tumor assessments where a treatment cycle delay occurs. |
| | | |
| **Section to be changed** | | 6.2.3 |
| **Description of change** | | Assessment of vital signs was added as a procedure for the safety follow-up visit. |
| **Rationale for change** | | To clarify that vital signs should be assessed at safety follow-up. |
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| **Section to be changed** | | 7.3.1.1 |
| **Description of change** | | Text specifying that a window of ±14 days will apply to the assessment of the primary efficacy endpoint at Week 18 was added |
| **Rationale for change** | | To clarify handling of assessments performed within ±14 days of the planned Week 18 assessment. |
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| **Section to be changed** | | 7.3.6 |
| **Description of change** | | Details of pharmacokinetic analyses were updated |
| **Rationale for change** | | To clarify the pharmacokinetic analyses that will be performed, and that details will be described in a separate analysis plan. |
| | | |
| **Section to be changed** | | 8.1 |
| **Description of change** | | The following text was added to the end of the section: "In case of partner's pregnancy, written Consent for Pregnancy Follow-up will be requested to the subject's partner in case of pregnancy. Follow-up on the pregnancy and its |

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| | | outcome will be done to evaluate whether there are risks to the pregnant women or the unborn fetus." |
| **Rationale for change** | | To include the partner pregnancy ICF in the study protocol. |
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| **Section to be changed** | | Appendix 10.1 |
| **Description of change** | | The short axis measurement of nodal lesions that is considered pathologically enlarged and measurable was updated from >15 mm to ≥15 mm. |
| **Rationale for change** | | To ensure consistency with RECIST guidelines. |
| | | |
| **Section to be changed** | | Appendix 10.1 (CT and MRI) |
| **Description of change** | | In the second paragraph, text was added to specify that MRIs will be performed with contrast using gadolinium. |
| **Rationale for change** | | To be aligned with the Investigator Site Image Manual from Parexel |
| | | |
| **Section to be changed** | | Appendix 10.2 |
| **Description of change** | | Text was added to state that the dose of Avastin/ BI 695502 should be recalculated prior to each infusion. Clarifying text was also added to provide further guidance on IMP preparation. |
| **Rationale for change** | | To clarify that the correct dose needs to be calculated at each infusion, and to provide further recommendations on preparation of IMP. |
| | | |
| **Section to be changed** | | Appendix 10.3 |
| **Description of change** | | The following paragraph was added "Cycles are not skipped but delay may occur according to the Clinical Trial Protocol, Tables 10.3:1 and 10.3:2. Maximum timeframe treatment delay should be assessed based on the investigator´s clinical judgment and should be discussed with the study Medical Monitor. However, patients with severe hypertension, moderate to severe proteinuria, or severe infusion reactions will not receive further treatment with Avastin®/BI 695502 if the event cannot be adequately controlled within 14 days. |
| **Rationale for change** | | To provide further information regarding delays to cycles |
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| **Section to be changed** | | Appendix 10.3 |
| **Description of change** | | The following paragraph was added: "During the |

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| | | induction phase, any chemotherapy delay mandates a bevacizumab/BI 695502 infusion delay. All three drugs of this regimen (paclitaxel + carboplatin + bevacizumab/BI 695502) should always be administered together during the induction phase, if the patients fulfills the criteria for receiving the next treatment cycle." |
| **Rationale for change** | | To clarify how delays to chemotherapy affect bevacizumab treatment during the induction phase. |
| | | |
| **Section to be changed** | | Appendix 10.3 |
| **Description of change** | | In the fourth paragraph. "(according to regular institutional practice)" and the final sentence were deleted. The following text was added to the end of the paragraph: "The initial dose of paclitaxel (day 1, cycle 1) must be fixed to 200 mg/m² for all study patients, as well as a dose of carboplatin to AUC: 6 mg/mL/min. In case of toxicity after this initial dose, the dose can be reduced in the event of toxicity according to the protocol guideline Table 4.1.4.1:1 and 10.3.1." |
| **Rationale for change** | | This change was made at the request of the regulatory authority, and to obtain a more homogeneous trial treatment population. The change was also made in anticipation of requests for initial dose at 175 mg. |
| | | |
| **Section to be changed** | | Appendix 10.3 |
| **Description of change** | | Text was added to instruct against the use of needles or intravenous sets containing aluminum parts that may come into contact with carboplatin when preparing or administering carboplatin, and to provide guidance on the preparation of carboplatin intravenous solutions. |
| **Rationale for change** | | To provide further guidance on carboplatin preparation and administration. |
| | | |
| **Section to be changed** | | Appendix 10.3 |
| **Description of change** | | The following text was added to the end of the paragraph under Table 10.3: 1: "Other additional uses of G-CSF are allowed, according to regular institutional practice and the PI´s judgment." |
| **Rationale for change** | | Updated in response to investigator questions regarding use of G-CSF |

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| **Section to be changed** | | Appendix 10.4.2 |
| **Description of change** | | The following text was added after the sentence following the third bullet point: “A copy of the DILI checklist should also be provided along with the SAE form.” to read “and report these via the electronic case report form. A copy of the DILI checklist should also be provided along with the SAE form.” |
| **Rationale for change** | | To clarify that a copy of the DILI checklist should be sent along with the paper SAE form. |

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| **Number of global amendment** | | 4 |
| **Date of CTP revision** | | 18 July 2016 |
| **EudraCT number** | | 2014-002161-30 |
| **BI Trial number** | | 1302.5 |
| **BI Investigational Product(s)** | | BI 695502 |
| **Title of protocol** | | A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer |
| | | |
| **To be implemented only after approval of the IRB/IEC/Competent Authorities** | | ☐ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only** | | ☒ |
| | | |
| **Section to be changed** | | 3.3.2 |
| **Description of change** | | In inclusion criterion 2, <22.6 mg/mmol creatinine was amended to <226 mg/mmol creatinine. |
| **Rationale for change** | | To correct a typographical error. |
| | | |
| **Section to be changed** | | 4.1.4.1 |
| **Description of change** | | The Cockroft-Gault formula was amended. |
| **Rationale for change** | | To correct a typographical error. |
| | | |
| **Section to be changed** | | Throughout the protocol |
| **Description of change** | | The trial number has been updated to 1302.5 INVICTAN®-2 |
| **Rationale for change** | | The new brand name for the trial has been secured by BI Trade Marks and therefore the protocol has been updated to reflect the new trial name. |

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| **Number of global amendment** | | 5 |
| **Date of CTP revision** | | 03 May 2017 |
| **EudraCT number** | | 2014-002161-30 |
| **BI Trial number** | | 1302.5 |
| **BI Investigational Product(s)** | | BI 695502 |
| **Title of protocol** | | A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer |
| | | |
| **To be implemented only after approval of the IRB/IEC/Competent Authorities** | | ☐ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only** | | ☒ |
| | | |
| **Section to be changed** | | Flowchart 1.2 |
| **Description of change** | | Clarification of non-treatment period visits added to footnote 17. |
| **Rationale for change** | | To clarify the non-treatment period visits in the protocol and to ensure consistency with the ICF description. |
| | | |
| **Section to be changed** | | 3.1, 6.1, 6.2.3 |
| **Description of change** | | Clarification of non-treatment period visits added |
| **Rationale for change** | | To clarify the non-treatment period visits in the protocol and to ensure consistency with the ICF description. |

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| **Number of global amendment** | | 6 |
| **Date of CTP revision** | | 26 October 2017 |
| **EudraCT number** | | 2014-002161-30 |
| **BI Trial number** | | 1302.5 |
| **BI Investigational Product(s)** | | BI 695502 |
| **Title of protocol** | | A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer |
| | | |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | ☐ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | ☒ |
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| **Section to be changed** | | Title page |
| **Description of change** | | Trial Clinical Monitor details updated to:<br><br>Phone:<br>Fax: |
| **Rationale for change** | | Administrative update. |
| | | |
| **Section to be changed** | | Flow chart 1.1, Flow chart 1.2 |
| **Description of change** | | The following text was added to the 12-lead ECG footnote:<br>The first of the consecutive ECGs is mandatory. The second of the consecutive ECGs is optional, at the discretion of the Investigator in case of clinical significance. |
| **Rationale for change** | | To clarify that the second of the consecutive |

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| | | ECGs is optional. |
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| **Section to be changed** | | 4.1.4 |
| **Description of change** | | The following text was added:<br>Slight variations in BI 695502/US-licensed Avastin® dose may occur due to a change in a patient's body weight; dose deviations with a margin of <5% will NOT be considered protocol deviations. |
| **Rationale for change** | | To clarify the criteria for dose deviations to be considered protocol deviations. |
| | | |
| **Section to be changed** | | 5.2.4 |
| **Description of change** | | The first two paragraphs in this section were updated to:<br>Two consecutive resting 12-lead ECGs may be performed prior to administration of trial medication at the visits indicated in Flow chart 1.1 and Flow chart 1.2. The first of the consecutive ECGs is mandatory. The second of the consecutive ECGs is optional, at the discretion of the Investigator in case of clinical significance. Additional ECGs will be performed if clinically indicated.<br>Patients should rest for at least 5 minutes in a supine position before each of the two consecutive ECG evaluations. |
| **Rationale for change** | | To clarify that the second of the consecutive ECGs is optional. |
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| **Section to be changed** | | 9.1 |
| **Description of change** | | Details for references R15-1222 and R15-1223 were updated. |
| **Rationale for change** | | Administrative update. |
| | | |
| **Section to be changed** | | 10.2 |
| **Description of change** | | Polyethylene bags and infusion sets made of polybutadiene were added to the table of special infusion sets that must be used for administration of BI 695502/US-licensed Avastin®. |
| **Rationale for change** | | The use of polyethylene bags for infusion of BI 695502/US-licensed Avastin® is now permitted in this trial.<br><br>The use of polybutadiene infusion sets is common in day-to-day practice. The use of infusion sets made of polybutadiene for |

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| | | administration of BI 695502 is now permitted in this trial. |
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| **Section to be changed** | | 10.2 |
| **Description of change** | | The mandatory concentration of BI 695502/US-licensed Avastin® for intravenous infusion was updated to 16.5 mg/mL. Previously, the recommended concentration was from 1.4 mg/mL to 16.5 mg/mL.<br><br>The following text was added:<br>If appropriate infusion materials are not available, a smaller investigational product concentration of 1.4 mg/mL up to 16.5 mg/mL can be temporarily used until the required materials are available. |
| **Rationale for change** | | Sponsor decision to change the administration instruction to allow only the use of 16.5 mg/mL concentration of BI 695502. In new compatibility studies, acceptance criteria were only fully met for the highest concentration tested (16.5 mg/mL) in all tested bags and infusion sets; visible and subvisible particles exceeded compendial limits for the lower concentration (1.4 mg/mL). This change of preparation of study medication does not increase the volume of investigational medicinal product preparation or the speed of infusion; therefore, there is no change in risk for the patient. The change in administration instructions also applies to US-licensed Avastin® to avoid unintentional unblinding. |

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| **Number of global amendment** | | 7 |
| **Date of CTP revision** | | 17 January 2018 |
| **EudraCT number** | | 2014-002161-30 |
| **BI Trial number** | | 1302.5 |
| **BI Investigational Product(s)** | | BI 695502 |
| **Title of protocol** | | A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer |
| | | |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | ☐ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☒ |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | ☐ |
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| **Section to be changed** | | Synopsis, Flow chart 1.2, 3.1, 4.1.1, 4.1.2 |
| **Description of change** | | Text has been added to describe the recommendation of the Sponsor to switch from BI 695502 to Avastin® starting from 21 Dec 2017. In addition, text is included to clarify that patients may continue temporarily to receive BI 695502 if Avastin® is not immediately available at the site. |
| **Rationale for change** | | As a consequence of the observation of particles for IMP batches E6719F01 and E6719F02, the Sponsor has recommended that patients be switched from IMP BI 695502 to the reference medicinal product as soon as it is available at the respective clinical site. |
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| **Section to be changed** | | Flow chart 1.2 |
| **Description of change** | | A new column has been added for the Switch Visit and assessments to be done at the new visit are included |

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| **Rationale for change** | | To provide detailed information on what assessments need to be performed at the Switch Visit |
| | | |
| **Section to be changed** | | 3.1, 3.3.4.1, 6.1, 6.2.3 |
| **Description of change** | | The End of Treatment (EOT) visit has been changed to 21 days after the last administration of trial medication (BI 695502 or Avastin®) |
| **Rationale for change** | | To bring the EOT visit in line with the study visits which occur every 3 weeks. |
| | | |
| **Section to be changed** | | 3.3.4.1, 4.2.1 |
| **Description of change** | | 'Congestive heart failure, any degree' has been added to the possible reasons for permanently discontinuing trial treatment |
| **Rationale for change** | | To clarify that the trial medication should be discontinued if the patient experiences congestive heart failure of any kind. |
| | | |
| **Section to be changed** | | 4.1.3 |
| **Description of change** | | Text added to state that the recommended dose for Avastin® remains the same after the switch from BI 695502 |
| **Rationale for change** | | To clarify the administration of Avastin® |
| | | |
| **Section to be changed** | | 4.1.4 |
| **Description of change** | | Text has been added to state that the first infusion of Avastin® for all patients after the switch visit should be delivered over 90 minutes. If well-tolerated, the second infusion should be delivered over 60 minutes, and if the 60 minute infusion is well tolerated all subsequent infusions can be administered over 30 minutes. |
| **Rationale for change** | | As this may be the first time a patient is exposed to Avastin®, the administration procedure should be according to the Avastin® label. This is for patient safety and also to maintain the blind |
| | | |
| **Section to be changed** | | 4.1.5.1 |
| **Description of change** | | Text has been added to clarify that no unblinding of patients or sites will occur as a result of switching from BI 695502 to Avastin® |
| **Rationale for change** | | To clarify that the double-blind of the trial will not be impacted by the switch from BI 695502 to Avastin® |
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| **Section to be changed** | | 4.1.6 |
| **Description of change** | | Text has been added to state that relabeling of commercially available Avastin® for trial purposes is not required |
| **Rationale for change** | | To clarify that commercially available Avastin® will not be relabeled |
| | | |
| **Section to be changed** | | 4.1.7 |
| **Description of change** | | Text has been added to state that after the switch visit, the sites should monitor the storage conditions of Avastin® in accordance with local requirements |
| **Rationale for change** | | To clarify that the sites will no longer maintain the temperature log for Avastin® |
| | | |
| **Section to be changed** | | 4.1.8 |
| **Description of change** | | Text has been added to clarify that after the patient has switched from BI 695502 to Avastin® the drug accountability details will be recorded |
| **Rationale for change** | | To clarify the process for drug accountability after the switch from BI 695502 to Avastin® |
| | | |
| **Section to be changed** | | 4.2.1 |
| **Description of change** | | Text added to provide clarification on process for evaluating proteinuria |
| **Rationale for change** | | A memo has been provided to the sites to provide clarification on proteinuria assessment. The information from the memo has been added to the protocol for completeness |
| | | |
| **Section to be changed** | | 6.1, 6.2.2 |
| **Description of change** | | Text added to describe the switch visit |
| **Rationale for change** | | Clarification on timing of switch visit and the |

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| | | assessments to be performed |
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| **Section to be changed** | | Flow chart 1.2, 3.1, 5.3.7, 6.1, 6.2.3 |
| **Description of change** | | The text has been modified to state that the 18-week SFU visit will take place 18 weeks after the last dose of trial medication prior to the switch visit.<br>Also, text has been added to state that any patient who is still receiving treatment with Avastin® at 18 weeks post the last BI 695502 dose will not have a SFU visit. |
| **Rationale for change** | | The clarify the REP is 18 weeks after the last dose of trial medication and thus this is when the SFU should be performed.<br>Patients who are still being seen at the site every 3 weeks will not need an additional SFU visit. |
| | | |
| **Section to be changed** | | 6.2.3 |
| **Description of change** | | The end of trial definition has been updated to take into account that patients may continue to receive Avastin® after the SFU visit. The definition now states: “The trial will be closed when all randomized and treated patients have either died, are lost to follow-up, or have withdrawn consent, or for a maximum of 20 months after the last patient randomized plus the EOT visit, whichever occurs earlier.” |
| **Rationale for change** | | To update the end of trial definition to accurately reflect the updated trial design |
| | | |
| **Section to be changed** | | Synopsis, 7.1, 7.3 |
| **Description of change** | | Text has been added to state that the primary analysis was not impacted by the switch.<br>Text has been added to described the period covered by the main analyses plus that appropriate censoring methods will be applied at the time of switching.<br>Text has been added to describe how the impact of switching will be assessed. |
| **Rationale for change** | | To provide clarification on the statistical methods to be used to analyze the study data as a result of switching |
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| **Section to be changed** | | 7.3.5.1 |
| **Description of change** | | Text has been added to state that 5 DSMB meetings have taken place during the study to |

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| | | date |
| **Rationale for change** | | To provide further information on the DSMB meetings that have occurred and that all meetings recommended the continuation of the trial without modification |
| | | |
| **Section to be changed** | | 8.1 |
| **Description of change** | | Text has been added to state that patients will be informed orally by the investigator about the switch from BI 695502 to Avastin®. As soon as the updated ICF is available, informed consent will be obtained from all patients in the trial. |
| **Rationale for change** | | To clarify the informed consent procedures |
| | | |
| **Section to be changed** | | 9.1 |
| **Description of change** | | Details for reference R15-1222 were updated to reflect latest version of the US Prescribing Information for Avastin® |
| **Rationale for change** | | Administrative update. |
| | | |
| **Section to be changed** | | Appendix 10.2 |
| **Description of change** | | Text has been added to clarify the administration procedures to be used for Avastin®, to state that the Sponsor highly recommends the use of the same filters as for BI 695502 administration, and to clarify the recommended concentration of Avastin® after switching |
| **Rationale for change** | | To provide clarification on administration of Avastin® |
| | | |

**APPROVAL / SIGNATURE PAGE**

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**Title:** A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Approval-Team Member Medicine | | 18 Jan 2018 10:54 CET |
| Approval-Clinical Pharmacokinetics | | 18 Jan 2018 10:55 CET |
| Author-Trial Clinical Monitor | | 18 Jan 2018 10:59 CET |
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| Approval-Therapeutic Area | | 19 Jan 2018 09:43 CET |
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