Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c08875184-06**
EudraCT No.:	2015-003718-25	
BI Trial No.:	1302.3 (INVICTAN®-3)	
BI Investigational Product(s):	BI 695502	
Title:	A single arm, open-label, multicenter, multinational, safety and efficacy Phase IIIb trial of BI 695502 plus mFOLFOX6 in patients with previously untreated metastatic colorectal cancer	
Brief Title:	Open-label, single arm trial of BI 695502 in patients with previously untreated metastatic colorectal cancer	
Clinical Phase:	IIIb	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	Phone: Fax:	
Status:	Final Protocol (Revised Protocol based on global amendment 05)	
Version and Date	**Version: 6.0**	**Date: 17 January 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		BI 695502	
Protocol date: 04 NOVEMBER 2015	**Trial number:** 1302.3		**Revision date:** 17 January 2018

Title of trial:	A single arm, open-label, multicenter, multinational, safety and efficacy Phase IIIb trial of BI 695502 plus mFOLFOX6 in patients with previously untreated metastatic colorectal cancer
Coordinating Investigator:	
Trial site(s):	Multinational, multicenter trial in approximately 50 clinical sites.
Clinical phase:	IIIb
Objective(s):	Primary objective: • The primary objective of this trial is to evaluate the safety and tolerability of BI 695502 in combination with leucovorin/5-fluorouracil/oxaliplatin (mFOLFOX6) and as maintenance therapy (when applicable). Secondary objectives: • To evaluate the following efficacy parameters: Progression-free survival (PFS), objective response rate (proportion of patients with complete response [CR] plus partial response [PR]), overall survival (OS), and duration of response (DOR), time to progression (TTP). Further objectives: • • To evaluate the presence of ADAs and nADAs.
Methodology:	This is a Phase IIIb, open-label, multicenter, multinational, single arm trial. The trial will investigate the safety, efficacy, immunogenicity of BI 695502 in patients with previously untreated metastatic colorectal cancer (mCRC), who will receive BI 695502 in combination with mFOLFOX6 chemotherapy every 2 weeks until disease progression, death, unacceptable toxicity or the end of the trial, whichever occurs earlier. Based on patient tolerability, at least 8 cycles of mFOLFOX6 should be given to all patients. If the Investigator decides to stop oxaliplatin at any time during the study, patients should continue to receive infusional 5FU + leucovorin with BI 695502 until progression. The efficacy analysis will be based upon the evaluation of tumor imaging as per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and as assessed by central imaging review. Starting as of 21 Dec 2017, the Sponsor recommends that patients should be switched from BI 695502 to the reference product bevacizumab (commercially available Avastin®, hereafter referred to as Avastin®) as soon as it is available at the respective clinical site. If Avastin® is not immediately available, the Investigators may temporarily allow continuation on BI 695502. Patients will continue the study with no additional visits in the scheduled visit cycle as per protocol. Patients who discontinue treatment with chemotherapy or BI 695502 or both, but do not have disease progression and have not started a new anticancer therapy, will

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	continue in the trial in the non-treatment period until disease progression or initiation of a new anticancer therapy, whichever occurs first. All patients who receive at least one infusion of BI 695502 will attend a Follow-up visit 30 days after the last administration of BI 695502 or Avastin® whichever occurs later. Patients will attend a long-term Safety Follow-up (SFU) visit 18 weeks after the last administration of trial medication prior to the switch visit. If the patient continues to receive treatment with Avastin® beyond 18 weeks post last BI 695502 dose, then no SFU visit will be performed. After the long-term SFU visit or discontinuation of Avastin® (whichever occurs later), all patients will be monitored for survival every 3 months via telephone call until death or until the trial is closed, whichever occurs earlier. The trial will be closed when all enrolled and treated patients have either died, are lost to follow-up, have withdrawn consent, or for a maximum of 12 months after the last patient enrolled plus the 30-day FU visit, whichever occurs earlier.
No. of patients:	
total entered:	Approximately 120 patients will be enrolled in the trial to receive BI 695502 concentrate for solution for intravenous (i.v.) infusion.
each treatment:	Not applicable.
Diagnosis:	Males and females with histologically confirmed mCRC not amenable to surgical curative treatment and eligible to receive therapy with mFOLFOX6 + bevacizumab.
Main criteria for inclusion:	Patients aged ≥18 (for Japan only: Age ≥20 years at time of signing the informed Consent Form [ICF]) who have received no prior therapy for metastatic disease and have completed any adjuvant/neoadjuvant therapy at least 12 months before trial entry. Patients must have at least one measurable lesion according to RECIST 1.1 that has not been irradiated within 12 weeks prior to enrollment and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. 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:	5 mg/kg every 2 weeks (14 days)
mode of administration:	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:	None.
Additional protocol medication:	Starting as of 21 Dec 2017, the Sponsor recommends that patients should be switched from BI 695502 (5 mg/kg every 2 weeks) 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:	Full description of mFOLFOX6 regimen: • Oxaliplatin 85 mg/m^2 i.v. over 2 hours, Day 1

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	• Leucovorin 400 mg/m^2 i.v. over 2 hours, Day 1 • 5-fluorouracil (5-FU) 400 mg/m^2 i.v. bolus on Day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) i.v. continuous infusion
Duration of treatment:	Treatment with BI 695502 or Avastin® in combination with mFOLFOX6 chemotherapy every 2 weeks until disease progression according to RECIST 1.1, death, unacceptable toxicity, or the end of the trial, whichever occurs earlier. Based on patient tolerability, at least 8 cycles of mFOLFOX6 should be given to all patients. If the Investigator decides to stop oxaliplatin at any time during the study, patients should continue to receive infusional 5FU + leucovorin with BI 695502 or Avastin® until progression. Based on patient tolerability, the doses of chemotherapy drugs may be decreased as per the label or institutional practice.
Endpoints:	Primary safety endpoint: • Patients with any of the following selected adverse events (AEs): o Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions o Thromboembolic events: ▪ Arterial ▪ Venous o Gastrointestinal (GI) perforations o Hypertension o Proteinuria o Pulmonary hemorrhage o All hemorrhages and pulmonary hemorrhages o Wound-healing complications including abscess and fistulas o Posterior reversible encephalopathy syndrome o Ovarian failure. Secondary efficacy endpoints: • PFS is defined as the time from first administration of trial medication until disease progression as assessed by central imaging review according to RECIST 1.1 or death of any cause. • Objective response according to RECIST 1.1 as assessed by central imaging review • DOR defined as the time from first documented CR or PR until time of progression as assessed by central imaging review. • TTP defined as the time from first administration of trial medication to the date of tumor progression, as assessed by central imaging review. • OS defined as the time from first administration of trial medication until death from any cause.
Immunogenicity:	Further Endpoints • ADAs/nADAs at Weeks 0, 4, 8, 16, 24, 32, 40 and 52 and 30-day Follow-up

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	visits and long-term SFU visit.
Pharmacokinetics:	
Safety criteria:	Other safety endpoints • All AEs including AEs related to trial treatment, assessed according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. • All protocol-specified adverse events of special interest. • All AEs potentially related to immunogenicity. Other safety evaluations will include: physical examination, vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), weight, 12-lead electrocardiogram (ECG), and laboratory findings.
Statistical methods:	**Primary safety analysis:** No hypothesis testing will be performed in this single arm trial. All AEs with an onset between start of treatment and end of the residual effect period (REP), a period of 18 weeks after the last dose of trial medication, will be considered. The proportion of patients with at least one AE selected for primary endpoint assessment will be displayed including descriptive 95% confidence intervals (CIs) for the proportion of patients with selected AEs. **Secondary analyses:** PFS will be analyzed descriptively using Kaplan-Meier methodology. The treated set will be used for analysis. The 1-year PFS rate and the median PFS will be estimated with 95% CIs. Objective response rate will be analyzed descriptively with 95% CIs. Duration of response, TTP and OS will be analyzed descriptively using Kaplan-Meier methodology. 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 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 main analyses will cover the period during which patients received BI 695502 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.

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	After the transition from BI 695502 to Avastin®, 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.		

FLOW CHART 1.1 – CYCLE 1 TO CYCLE 13

Trial Period	**Screening**	**Treatment**												
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Cycle	**NA**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Week	**-4 to -1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Day	**-28 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Permitted visit window (days)*	**-**	**-**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
Informed consent	X													
Tumor biopsy/RAS status[1]	X													
Assessment of eligibility	X	X												
Demographics	X													
Medical and surgical history	X													
Infection screen (hepatitis B, hepatitis C), and optional HIV test[2]	X													
TB Test[2]	X													
LABORATORY/SAFETY ASSESSMENTS														
Serum pregnancy test[3]	X													
Urine pregnancy test[3, 4]		X		X		X		X		X		X		X
Urine protein analysis[5]		X		X		X		X		X		X		X
Physical examination (including height at Screening only and weight)[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests (serum chemistry, including DILI if indicated hematology, coagulation urinalysis,)[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[9]	X				X			X			X			X
Previous/concomitant therapy/medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

FLOW CHART 1.1 – CYCLE 1 TO CYCLE 13 (continued)

Trial Period	**Screening**	**Treatment**												
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Cycle	**NA**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Week	**-4 to -1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Day	**-28 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Permitted visit window (days)*	**-**	**-**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
DISEASE ASSESSMENTS														
Tumor assessment (CT[11]/MRI scan)	X[12]					X				X				X
ECOG performance status	X	X				X				X				X
Survival		X----------												
OTHER ASSESSMENTS														
Anti-drug antibodies[14]		X		X		X				X				X
Neutralizing anti-drug antibodies[14]		X		X		X				X				X
TRIAL MEDICATION														
Enrollment[15]		X												
Contact IXRS®	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial medication infusion		X[14]	X	X	X	X	X	X	X	X	X	X	X	X
Chemotherapy administration[16]		X	X	X	X	X	X	X	X	X	X	X	X	X

BMI = body mass index; BSA = body surface area; CT = computerized tomography; DILI = drug induced liver injury ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV human immunodeficiency virus; INR – International normalized ratio, PTT = partial thromboplastin time; IXRS® = Interactive Telephone and Web Response System; MRI = magnetic resonance imaging; NA = not applicable; TB = tuberculosis.

* If a visit occurs outside the specified time window, then the next visit will be based on the number of days from the previous visit, and not the number of days from baseline

1. Tumor histology and RAS status must be confirmed at entry; if not performed/available, and no archival tumor sample is available, a fresh biopsy will be performed if possible and analyzed locally (see Section 5.6.2 for details).
2. Hepatitis B and C testing to be performed at Screening unless obtained within 6 months prior to Screening. Screening for HIV and TB will be performed according to local practice and local regulatory guidance.
3. Only for females of childbearing potential. Serum pregnancy test to be performed at Screening and if a urine pregnancy test is positive.
4. Only for females of childbearing potential. Urine pregnancy test will be performed every 4 weeks.
5. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection as per local laboratory practices. Suspend BI 695502 administration for proteinuria ≥2 g in 24 hours and resume when proteinuria is <2 g in 24 hours. If moderate to severe proteinuria (2+ or greater urine dipstick reading) cannot be controlled within 14 days then the patient should discontinue BI 695502.
6. Will be performed prior to administration of trial medication.
7. Sitting blood pressure (after at least 5 minutes rest), respiratory rate, pulse, and body temperature. Two or more blood pressure readings should be taken at 2 minute intervals and averaged. If the first diastolic readings differ by more than 5 mmHg, then an additional reading should be obtained, and all readings 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 ECGs may be performed every 3 cycles unless clinically indicated. 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.
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 long-term Safety Follow-up 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 contrast product injection of, chest, abdomen and pelvis ± involved area. In case of contrast product injection allergy, an abdomen-pelvic MRI will be performed together with a non-contrast chest CT scan. Tumor assessment will be performed every 8 weeks (±3 days) up to Visit 21, every 12 weeks (±3 days; ±7 days from Visit 28 onwards) from Visit 21 onwards and every 8 weeks (±3 days) during the non-treatment period. Tumor assessments will be done until progression of disease.
12. To be performed within 28 days of enrollment.

14. If sampled on a day when trial medication is administered, anti-drug antibody and neutralizing anti-drug antibody samples should be taken prior to trial medication administration.
15. Cycle 1 treatment to be administered within 4 days after enrollment.
16. Chemotherapy will be administered according to the standard preparation and infusion procedures of each investigational site. See Table 4.1.4.1 for details.

FLOW CHART 1.2 – CYCLE 14 ONWARDS

Visit	**14**	**15**	**16**	**17 to 25**	**26**	**27**	**28 onwards (until PD[1])**	**Switch visit, prior to Avastin® administration[19]**	**Non-treatment period [2,3]**	**30-day FU[4]**	**Long-term SFU[5]**	**Survival[6]**
Cycle	**14**	**15**	**16**	**17 to 25**	**26**	**27**	**28 onwards**					
Week	**26**	**28**	**30**	**32 to 48**	**50**	**52**	**54 onwards**					
Day	**183**	**197**	**211**	**225 to 337**	**351**	**365**	**379**					
Permitted visit window (days)*	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**		**-**	**± 3 days**	**+ 7 days**	
LABORATORY/SAFETY ASSESSMENTS												
Serum pregnancy test[7]						X		X				
Urine pregnancy test[7]		X		X		X	X	X				
Urine protein analysis[8]		X		X		X	X	X				
Physical examination (including weight)	X	X	X	X	X	X	X	X	X	X	X	
BMI	X	X	X	X	X	X	X	X	X	X	X	
BSA	X	X	X	X	X	X	X					
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	
Laboratory tests (serum chemistry, including DILI if indicated, hematology, coagulation and urinalysis,)[10]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[11]			X	X			X	X	X			
Previous and concomitant therapy/medication[12]	X	X	X	X	X	X	X	X	X	X	X	
Adverse events[13]	X	X	X	X	X	X	X	X	X	X	X	
Date of initiation of new anticancer therapy (if applicable)								X	X	X	X	
Survival		X----------										----------X

FLOW CHART 1.2 – CYCLE 14 ONWARDS (CONTINUED)

Visit	**14**	**15**	**16**	**17 to 25**	**26**	**27**	**28 onwards (until PD[1])**	**Switch visit, prior to Avastin administration[19]**	**Non-treatment period [2,3]**	**30-day FU[4]**	**Long-term SFU[5]**	**Survival[6]**
Cycle	**14**	**15**	**16**	**17 to 25**	**26**	**27**	**28 onwards**					
Week	**26**	**28**	**30**	**32 to 48**	**50**	**52**	**54 onwards**					
Day	**183**	**197**	**211**	**225 to 337**	**351**	**365**	**379**					
Permitted visit window (days)*	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**		**-**	**± 3 days**	**+ 7 days**	
DISEASE ASSESSMENTS												
Tumor assessment (CT[14]/MRI scan)				Cycle 17 and 21		X	X	X[15]	X	X[15]		
ECOG performance status[16]				Cycle 17 and 21		X			X			
OTHER ASSESSMENTS												
Anti-drug antibodies[17]				Cycle 17 and 21		X		X		X	X	
Neutralizing anti-drug antibodies[17]				Cycle 17 and 21		X		X		X	X	
TRIAL MEDICATION												
Contact IXRS®[18]	X	X	X	X	X	X	X					
Trial medication infusion[18, 20]	X	X	X	X	X	X	X	X				
Chemotherapy administration[18]	X	X	X	X	X	X	X	X				
End of Trial and Safety Follow up									X			

ADA = anti-drug antibody; BMI = body mass index; BSA = body surface area; CT = computerized tomography; DILI = drug induced liver injury ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IXRS® = Interactive Telephone and Web Response System; MRI = magnetic resonance imaging; NA = not applicable; PD = progressive disease; ; SFU = Safety Follow-up

* If a visit occurs outside the specified time window, then the next visit will be based on the number of days from the previous visit, and not from the number of days from baseline

1. Patients that continue to receive treatment from Cycle 28 and beyond will attend the trial site every 12 weeks, until disease progression or trial closure, whichever occurs earlier.
2. For all patients who discontinue BI 695502 or Avastin®, do not withdraw consent and who do not have disease progression, visits will occur every 8 weeks until initiation of new anti-cancer therapy, disease progression, death, or the end of the trial, whichever occurs earlier
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. Tumor assessments and all AEs (serious and non-serious as well as AEs of special interest), regardless of relatedness, will be collected at these visits. The date of initiation of second-line therapy should be recorded (if applicable).
4. All patients who received at least one infusion of BI 695502 will attend a Follow-up Visit 30 days after the last administration of BI 695502 or Avastin® once they have either completed trial therapy or discontinued from trial treatment.
5. All patients should attend a long-term 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 BI 695502 dose, then no SFU visit will be performed. All patients who prematurely discontinue BI 695502 for reasons other than disease progression must be followed up as per Section 6.2.3.
6. After the long-term SFU visit or discontinuation of Avastin® (whichever occurs later) all patients will be monitored for survival every 3 months via telephone call until death, lost to follow-up, withdrawal of consent, or a maximum of 12 months after the last patient enrolled plus the 30-day FU visit, whichever occurs earlier.
7. Females of childbearing potential only. Urine pregnancy test to be performed every 2 cycles (4 weeks) until Cycle 28 and every 12 weeks thereafter. A serum pregnancy test should be performed if urine pregnancy test is positive.
8. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection as per local laboratory practices. Suspend BI 695502 or Avastin® administration for proteinuria ≥2 g in 24 hours and resume when proteinuria is <2 g in 24 hours. If moderate to severe proteinuria (2+ or greater urine dipstick reading) cannot be controlled within 14 days then the patient should discontinue BI 695502 or Avastin®.
9. Sitting blood pressure (after at least 5 minutes rest), 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.
10. 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. Laboratory tests will be performed every 2 weeks until Cycle 28, every 12 weeks from Cycle 28 onwards and during the non-treatment and follow-up periods
11. Patients should rest for at least 5 minutes in a supine position before ECG evaluations. Two consecutive ECGs may be performed every 3 cycles until Cycle 28 and every 12 weeks from Cycle 28 onwards. 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.
12. Concomitant medication to be recorded every 2 weeks until Cycle 27, every 12 weeks from Cycle 28 onwards and during the non-treatment and follow-up periods
13. All adverse events, regardless of relatedness, will be collected from the time of informed consent until 18 weeks after the last administration of trial medication. Adverse events continuing at the long-term Safety Follow-up 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. Please see Section 5.3.7 for further details on collection of adverse events. Adverse events will be assessed every 2 weeks until Cycle 28, every 12 weeks after Cycle 28 and during the non-treatment and follow-up periods.
14. CT scan with contrast product injection of chest, abdomen and pelvis ± involved area. In case of contrast product injection allergy, an abdomen-pelvic MRI will be performed with a non-contrast chest CT scan. Tumor assessment will be performed every 8 weeks (±3 days) up to Visit 21 and every 12 weeks (±3 days; ±7 days from Visit 28 onwards) from Visit 21 onwards. No CT scan is needed at Visit 28 if the patient received a CT scan at Visit 27. During the non-treatment period CT scans will be performed every 8 weeks (±3 days).
15. To be performed only if a tumor assessment was not performed within the previous 4 weeks. Note: Another unscheduled tumor assessment should be performed 6 weeks after the switch visit and no longer than 13 weeks after this visit.
16. ECOG to be performed every 4 cycles from Cycle 5 to Cycle 21, and at Cycle 27.

18. Chemotherapy will be administered according to the standard preparation and infusion procedures of each investigational site. See Table 4.1.4.1 for details. Based on patient tolerability, the doses of chemotherapy drugs may be decreased as per the label or institutional practice. Trial medication infusion and chemotherapy will be administered every 2 weeks from Cycle 28 onwards. The sites will not be required to contact IXRS after the switch visit while the patient remains on Avastin®. At the time of Avastin® discontinuation, the site must contact IXRS to perform the discontinuation call.
19. 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.
20. 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 will receive Avastin® during the Cycle Visits, as soon as the 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

5-FU	5-Fluorouracil
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BSA	Body surface area
BMI	Body mass index
CA	Competent Authority
CI	Confidence interval
CR	Complete response
CRC	Colorectal cancer
CRO	Contract Research Organization
CT	Computed tomography
CTP	Clinical Trial Protocol
DILI	Drug-induced liver injury
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C
HIV	Human immunodeficiency virus
i.v.	Intravenous
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INR	International normalized ratio
INVICTAN®-3	Trial name
IRB	Institutional Review Board
ISF	Investigator Site File
IXRS	Interactive Telephone and Web Response System

KM	Kaplan-Meier
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	Leucovorin/5-Fluorouracil/Oxaliplatin
MRI	Magnetic resonance imaging
nADA	Neutralizing antidrug antibody
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not evaluable
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PPD	Purified protein derivative
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
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
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TB	Tuberculosis
TSAP	Trial Statistical Analysis Plan
TTP	Time to Progression
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Colorectal cancer (CRC) is the third most common cancer in men (746,000 cases, 10.0% of the total cancers) and the second most common cancer in women (614,000 cases, 9.2% of the total cancers) worldwide. Almost 55% of the cases occur in developed regions. About 694,000 deaths from CRC are estimated worldwide, accounting for 8.5% of all cancer deaths, making it the fourth most common cause of death from cancer (R15-3504).

While surgery is the cornerstone treatment for early stage cancer (stage I–III), chemotherapy is the first treatment option for metastatic disease (stage IV) when metastases are not resectable. Approximately 25% of patients will present with metastases at time of initial diagnosis and almost 50% of patients will develop metastases after initial surgery with or without adjuvant therapy, contributing to the high mortality rates reported for CRC. The CRC-related 5-year survival rate approaches 60% (R15-4644).

Many different trials have shown that the addition of bevacizumab to standard chemotherapy regimens (5-fluorouracil [5-FU]/leucovorin, capecitabine, oxaliplatin) improved outcomes in patients with metastatic CRC (mCRC) in the first-line (R05-2504, R13-1115, R11-2707) and second-line settings (R06-2690, R07-4623, R13-1117, R13-1112).

Avastin® was approved for treatment of mCRC, in first-line setting by the European Medicines Agency (EMA) in January 2005 and by the FDA in February 2004, and was approved by the Food and Drug Administration (FDA) in second-line setting in June 2006.

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 European Union (EU), the United States (US) (R18-0043, R15-1223) and in Japan. BI 695502 is a genetically engineered humanized monoclonal antibody directed against human vascular endothelial growth factor (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 mCRC (US, EU), advanced non-small cell lung cancer (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) (R18-0043, R15-1223). The local approval status for Avastin® can differ in countries outside of the US and the EU.

For a more detailed description of the drug profile refer to the current Investigator's Brochure, which is included in the Investigator Site File (ISF).

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®, 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 sequentially a high degree of similarity (i.e., statistical similarity) between the biosimilar and originator compound, while also demonstrating a high degree of similarity (but not necessarily statistical similarity) for safety and immunogenicity.

The demonstration of equivalent efficacy and safety will be made in the most sensitive indication to comply with the agency advice, i.e., in non-squamous NSCLC using objective response rate as the most sensitive endpoint to detect any meaningful differences.

However, the addition of bevacizumab to chemotherapy has also been shown to be effective in both wild-type and mutated K-ras mCRC (R18-0043, R15-1223, R13-1110).

The results of the Phase I trial (1302.1) have already demonstrated pharmacokinetic similarity between BI 695502, EU-approved Avastin®, and US-licensed Avastin® (see Section 2.3 for details). The demonstration of equivalence in efficacy is being conducted in the most sensitive indication of NSCLC to comply with the regulatory requirements. The value of addition of bevacizumab to chemotherapy has been shown to be effective in mCRC and is the most widely prescribed indication for bevacizumab (R18-0043, R15-1223, R13-1110). While the Sponsor plans to obtain extrapolation across all labeled indications for bevacizumab based on the NSCLC data through the biosimilar regulatory pathway, generation of additional safety and efficacy data of BI 695502 in mCRC will be of value to the treating physician and patients. The trial will be a single arm trial to further assess the safety, tolerability and efficacy of BI 695502 in mCRC.

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 evaluate the safety and tolerability of BI 695502 in combination with mFOLFOX6 and as maintenance therapy (when applicable).

2.2.2 Secondary objectives

The secondary objectives of the trial are:

- To evaluate the following efficacy parameters: Progression-free survival (PFS), objective response rate (proportion of patients with complete response [CR] plus partial response [PR]), overall survival (OS), duration of response (DOR), time to progression (TTP).

2.3 BENEFIT - RISK ASSESSMENT

Patient risk will be minimized by implementing conservative eligibility criteria and 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 in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.6.1.

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 (R18-0043, R15-1223). 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 mCRC 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. 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 5.3.7). 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 anti-hypertensive therapy) are excluded from this trial. Blood pressure will be monitored every 2 weeks during the trial. Patients who develop hypertension should be treated with appropriate anti-hypertensive 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 of patients (R18-0043, R15-1223). The Investigator should discuss fertility preservation strategies with the patient prior to starting treatment in this trial, as appropriate.

Avastin® may cause fetal harm based on the drug's mechanism of action and findings from animal studies. Limited postmarketing reports describe cases of fetal malformations with use of Avastin® in pregnancy; however, these reports are insufficient to determine drug associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Women who are pregnant, nursing, or who plan to become pregnant are excluded from entering the trial. Women of reproductive potential should be advised to use effective contraception during treatment with, and for 6 months after the last dose of Avastin®. Due consideration has been given to previous experience with Avastin® in mCRC patients and toxicity management advice (e.g., for hypersensitivity reactions) is provided in this CTP.

Trial 1302.1 was a Phase I 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 I data described above, BI 695502, as a proposed biosimilar to Avastin®, is expected to show a similar efficacy, safety, immunogenicity and PK profile in patients with mCRC.

While the pivotal Phase III trial in NSCLC (Trial 1302.5) is currently ongoing, the first independent Data Safety Monitoring Board (DSMB) feedback on the safety and efficacy of BI 695502 is anticipated by May 2016. The mCRC trial shall start dosing only upon DSMB recommendation to continue the 1302.5 study without modification. Since May 2016, there have been 5 regularly spaced 1302.5 DSMB meetings, all of which recommended continuation of the trial without modification. Considering that the 1302.3 study is an open-label study, all safety aspects will be regularly monitored by both Sponsor and Contract Research Organization (CRO) during the Medical Quality Review Meeting.

The benefit-risk profile for the patients participating in this trial remains favorable and similar to the originator product. While medical coverage is generally available for such indications in the developed world, it is anticipated that this trial could be more appealing to patients with inadequate or no medical insurance coverage. Generation of such evidence will help patients and physicians to gain trust in the value that biosimilars would bring to our health care systems.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase IIIb, open-label, multicenter, multinational, single arm trial.

Approximately 120 patients with previously untreated mCRC will be enrolled in this trial.

Patients will receive treatment with 5 mg/kg of BI 695502 every 14 days (each cycle) followed by mFOLFOX6 chemotherapy until disease progression (monitored by common radiologic methods and assessed according to Response Evaluation Criteria in Solid Tumors [RECIST 1.1]), death, or unacceptable toxicity or the end of the trial, whichever occurs earlier. Based on patient tolerability, at least 8 cycles of mFOLFOX6 should be given to all patients. If the Investigator decides to stop oxaliplatin at any time during the study, patients should continue to receive infusional 5FU + leucovorin with BI 695502 until progression. Approval from the Sponsor must be obtained prior to implementing any changes to the mFOLFOX6 regimen necessitated by local best practice.

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

The primary endpoint of the trial is the proportion of patients with any of the following selected AEs: anaphylactic reactions/hypersensitivity reactions/infusion-related reactions, arterial and venous thromboembolic events, GI perforations, hypertension, proteinuria, pulmonary hemorrhage, other hemorrhages, wound-healing complications/abscess/fistulas, posterior reversible encephalopathy syndrome, and ovarian failure.

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 (commercially available Avastin®, 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. Patients will continue the study with no additional visits in the scheduled visit cycle as per protocol.

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

All patients who receive at least one infusion of BI 695502 will have a Follow-up visit 30 days after the last dose of BI 695502 or Avastin®, whichever occurs later.

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

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

3.1.1 Administrative structure of the trial

Quintiles will perform Project Management, Clinical Field Monitoring, Medical Monitoring, Data Management, and Statistical Evaluation according to Quintiles Standard Operating Procedures (SOPs). A list of responsible persons and relevant local information can be found in the trial reference manual in the ISF.

A Coordinating Investigator will be nominated and will be responsible for coordinating Investigators at different centers participating in this multicenter trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in the electronic trial master file (eTMF).

3.2 DISCUSSION OF TRIAL DESIGN

This is a Phase IIIb, open-label, multicenter, multinational, single arm trial to investigate safety, efficacy, immunogenicity of BI 695502 in patients with previously untreated mCRC. Patients will receive BI 695502 in combination with mFOLFOX6 chemotherapy every 2 weeks or as monotherapy.

mFOLFOX6 plus bevacizumab is an accepted first-line chemotherapy regimen for patients with mCRC. This regimen was shown to improve outcomes in bevacizumab-naïve patients (R05-2504, R13-1115, R11-2707).

The primary focus of this trial is to evaluate safety and tolerability in mCRC patients treated with BI 695502 in combination with mFOLFOX6 chemotherapy (see Section 2.1 for details on rationale for performing the trial).

3.3 SELECTION OF TRIAL POPULATION

A log of all patients enrolled into the trial (i.e., who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

Patients who do not meet all of the inclusion criteria or meet at least one of the exclusion criteria will not be enrolled, 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 and after approval of the Sponsor's study representative.

Approximately 120 patients will be enrolled in this trial across approximately 50 sites.

3.3.1 Main diagnosis for trial entry

The main requirements for trial entry include adult patients ≥18 years of age (for Japan only: Age ≥20 years at time of signing the informed consent form [ICF]), with histologically confirmed metastatic CRC not amenable to surgical curative treatment, who are eligible to receive therapy with mFOLFOX6 + bevacizumab, have received no prior therapy for metastatic disease and should have completed any adjuvant/neoadjuvant therapy at least 12 months before trial entry. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and must have at least one measurable lesion according to RECIST 1.1 criteria that has not been irradiated within 12 weeks prior to enrollment. Patients will have no known sensitivity to any of the trial drugs or their excipients and must have adequate hepatic, renal, and bone marrow function.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Males and females aged ≥18 years (for Japan only: Age ≥20 years at time of signing ICF) with histologically confirmed mCRC.
2. All patients must sign and date an ICF 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.
3. Metastatic disease not amenable to surgical curative treatment and eligible to receive therapy with mFOLFOX6 + bevacizumab.
4. At least one measurable lesion according to RECIST 1.1 that has not been irradiated within 12 weeks prior to enrollment.
5. ECOG PS 0 or 1.
6. 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 total 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 Cockcroft-Gault formula.
    e. Proteinuria <2 g in 24 hours or an equivalent protein/creatinine ratio of <2000 mg/g creatinine (or <226.0 mg/mmol creatinine)
    f. Absolute neutrophil count >1.5 $x10^9$/L.
    g. Platelet count >100 $x10^9$/L.

h. Hemoglobin ≥9 g/dL (without transfusion within 2 weeks prior to randomization).

7. 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
8. Life expectancy ≥12 months based on clinical investigator's judgment.
9. 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. 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 systemic therapy for metastatic disease. Any adjuvant/neoadjuvant therapy must have been completed >12 months prior to screening.
2. Prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including Avastin® or Avastin® biosimilars.
3. Previous malignancy other than CRC in the last 5 years except for basal cell cancer of the skin or pre-invasive cancer of the cervix.
4. Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 6 weeks prior to start of study treatment. 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.
5. Any unresolved toxicity > Common Toxicity Criteria Grade 1 (except alopecia) from previous anticancer therapy (including radiotherapy).
6. History or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding.
7. 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).
8. 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.
9. Current or recent (within 10 days of first dose of BI 695502) regular use of aspirin (>325 mg/day) or other non-steroidal anti-inflammatory drugs (NSAIDs) with anti-platelet activity or treatment with dipyridamole, ticlopidine, clopidogrel and cilostazol.

10. 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. Intravenous, intramuscular, interarticular or parenteral corticosteroids are restricted within 6 weeks prior to Day 1. The use of corticosteroids as antiemetics for oxaliplatin and 5-FU is allowed according to regular institutional practice (see Table 4.2.2.1: 1 for details).
11. Current or recent (within 10 days of first dose of BI 695502) 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) non-healing wounds, or incompletely healed bone fracture.
12. Patients who are expecting to receive any live vaccine or bacterial vaccinations during the trial, or receive one up to 12 weeks prior to the first dose of trial medication.
13. 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 anti-hypertensive therapy (see Section 5.3.2).
14. Any surgical procedure within 28 days of first dose of BI 695502 or anticipated elective surgery during the trial (see Table 4.2.2.1: 1 for details).
15. History of active gastroduodenal ulcer(s) within 18 months of study enrolment.
16. History of abdominal fistula as well as non-GI fistula, GI perforation or intra-abdominal abscess within 6 months prior to screening.
17. Active or chronic hepatitis B or C, ongoing human immunodeficiency virus (HIV) infection, or tuberculosis (TB) (see Section 5.3.3). Screening for HIV and TB to be performed according to local practice and local regulatory guidance.
18. Treatment in 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.
19. 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 study).
20. Known hypersensitivity to the trial drug or its excipients.
21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

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.

If a patient discontinues (drops out or withdraws after enrollment) from this trial, the patient will not be replaced.

An individual patient will be discontinued from trial treatment if:

- Investigator decision because of an intolerable AE or a clinically significant laboratory value including but not limited to:
  - Progressive disease
  - Life-threatening reaction, including anaphylaxis, hypersensitivity reaction, renal failure, severe cardiopulmonary event and severe muco-cutaneous reaction
  - GI perforation (including fistula formation in the GI tract, intra-abdominal abscess)
  - Tracheoesophageal or any Grade 4 fistula
  - Fistula formation involving an internal organ
  - Wound dehiscence and wound healing complications requiring medical intervention

  In these cases the trial medication is to be discontinued and appropriate measures are to be taken. The Sponsor or Sponsor designee is to be notified immediately.
- Serious hemorrhage (i.e., requiring medical intervention)
- Severe arterial thromboembolic events
- Life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism
- Hypertensive crisis or hypertensive encephalopathy
- RPLS/ Posterior Reversible Encephalopathy Syndrome (PRES)
- Nephrotic syndrome
- Necrotizing fasciitis
- Congestive heart failure, any degree
- Severe hypertension, moderate or severe proteinuria, severe infusion reactions if the event cannot be adequately controlled within 14 days
- Initiation of a new treatment (i.e. another chemotherapy or radiotherapy at any time)
- 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 5.3.7).
- 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 (i.e., withdraws consent).
- 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.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow-up as outlined in Flowchart 1.2 and Section 6.2.3.

For all patients, the reason for withdrawal (e.g., AEs) must be recorded in the eCRF. These data will be included in the trial database and reported.

For details of pregnancy reporting and follow-up procedures, see Section 5.3.7.

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 case of the third reason).

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product

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

Table 4.1.1: 1 Trial medication

Substance:	BI 695502
Pharmaceutical formulation:	Concentrate for solution for infusion
Manufacturer:	Boehringer Ingelheim
Unit strength:	400 mg/16 mL solution in a single use vial
Excipients:	disodium phosphate dihydrate, sodium dihydrogenphosphate dihydrate, trehalose dihydrate, polysorbate 20 and water for injection.
Route of administration:	Intravenous (i.v.)

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. All patients will continue the study with no additional visits in the scheduled visit cycle as per protocol.

4.1.2 Method of assigning patients to treatment groups

This is an open-label, single arm trial. All patients will receive BI 695502 in combination with mFOLFOX6 chemotherapy every 2 weeks. Based on patient tolerability, the doses of chemotherapy drugs may be decreased as per the label or institutional practice.

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. All patients will continue the study with no additional visits in the scheduled visit cycle as per protocol.

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 mCRC, in combination with fluoropyrimidine-based chemotherapy. The dose of BI 695502 selected for this trial is based on the clinically effective dose of Avastin®.

The 5 mg/kg dose of Avastin® is the dose recommended by the National Comprehensive Cancer Network (NCCN) in this indication and in combination with mFOLFOX6.

The primary focus of this trial is to assess safety in patients with untreated mCRC, following multiple infusions of BI 695502 in combination with mFOLFOX6. The recommended dose of Avastin®, administered as an intravenous (i.v.) infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks. In this trial, patients will receive 5 mg/kg BI 695502 i.v. once every 2 weeks (R18-0043) as recommended by the NCCN. The dose administered to each patient is to be recalculated at each visit based on their body weight at that visit. The same applies to the Avastin® administration after the switch from BI 695502.

Patients will continue to receive treatment every 2 weeks until disease progression, death, unacceptable toxicity, or the end of the trial, whichever occurs earlier. Based on patient tolerability, at least 8 cycles of mFOLFOX6 should be given to all patients. If the Investigator decides to stop oxaliplatin at any time during the study, patients should continue to receive infusional 5FU+ leucovorin with BI 695502 (before the switch visit) or Avastin® (after the switch visit) until progression, unacceptable toxicity or end of the trial, whichever occurs earlier. Based on patient tolerability, the doses of chemotherapy drugs may be decreased as per the label or institutional practice.

4.1.4 Drug assignment and administration of doses for each patient

BI 695502 will be provided by the Sponsor. Avastin® will be provided, or financially covered, by the Sponsor.

BI 695502 or Avastin® infusion will be administered first, i.e., prior to the administration of mFOLFOX6 chemotherapy. 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 SAE).

The recommended initial dose for the first BI 695502 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.

After the patient is switched to Avastin®, 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.

Cycle 1 treatment is to be administered within 4 days after enrollment.

BI 695502 or 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 or 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.

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 or Avastin® plus chemotherapy is provided in Table 4.1.4: 1.

Table 4.1.4: 1 BI 695502 or Avastin® plus mFOLFOX6

Immunochemotherapy regimen	Dose	Mode	Day 1 of cycle	Day 2 of cycle	Day 3 of cycle
BI 695502 or Avastin®	5 mg/kg	i.v.	X		
Oxaliplatin	85 mg/m^2 over 2 hours	i.v.	X		
Leucovorin	400 mg/m^2 over 2 hours	i.v.	X		
5-FU	400 mg/m^2 on Day 1 then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) continuous infusion	i.v.	X	X	X

5-FU = 5-fluorouracil

Upon availability of Avastin® at the clinical site, BI 695502 will be replaced by Avastin® following the administration procedure and treatment regimen as described in the Avastin® label, with the exception of the use of filters which must be used according to the BI 695502 administration procedure.

4.1.4.1 Chemotherapy

Administration of chemotherapy will be according to the standard preparation and infusion procedures of each investigational site. The formula used to calculate body surface area (BSA) should be recorded on the eCRF at each visit.

For mFOLFOX6 chemotherapy, oxaliplatin 85 mg/m^2 i.v. over 2 hours on Day 1, leucovorin 400 mg/m^2 i.v. (or levoleucovorin 200 mg/m^2 i.v.) over 2 hours on Day 1, 5-FU 400 mg/m^2 i.v. bolus on Day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) i.v. continuous infusion (R13-1134).

Further details on the chemotherapy regimen are provided in Appendix 10.3.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial. See Section 3.2 for detailed discussion on trial design.

4.1.5.2 Unblinding and breaking the code

Not applicable since this is an open-label trial with only one treatment group.

4.1.6 Packaging, labeling, and re-supply

For details of packaging and the description of the label, refer to the ISF. Avastin® will be provided as commercially labeled drug. Relabeling 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 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. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

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 Investigator/pharmacist or the designated person will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB)/ethics committee.
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site.
- 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 clinical trial protocol.
- Availability of the proof of a medical license for the principal Investigator, if applicable.
- Availability of Form FDA 1572 for sites in US.

The Investigator/pharmacist or the 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 disposal 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 and trial patients. Once patients are switched from BI 695502 to Avastin®, the date of administration, the batch number, and expiry dates of Avastin® are to be recorded.

The Investigator/pharmacist or the designated person will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor and/or the appointed CRO, the Investigator/pharmacist or the designated person must verify that no remaining supplies are in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

There are no special emergency procedures to be followed.

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

BI 695502 or Avastin® should be permanently discontinued in patients with GI perforations (including fistula formation in the GI tract, intra-abdominal abscess), tracheoesophageal or any Grade 4 fistula, 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 and life-threatening (Grade 4) venous thromboembolic events(including pulmonary embolism); hypertensive crisis or hypertensive encephalopathy; RPLS/PRES; nephrotic syndrome; necrotizing fasciitis; or congestive heart failure of any grade.

Patients with severe hypertension, moderate to severe proteinuria, or severe infusion reactions will not receive further treatment with BI 695502 or Avastin® 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. BI 695502 or Avastin® 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 BI 695502 or Avastin®.

Based on patient tolerability, subsequent doses of chemotherapy drugs may be decreased as per the label or institutional practice.

Prophylactic anti-emetics or other pre-medications may be administered per standard of care prior to chemotherapy administration.

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 prior to prescription.

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 treatment

Treatment	Restriction
mFOLFOX6 chemotherapy	Refer to Appendix 10.3
Radiotherapy	No radiotherapy will be allowed at any time during the trial
Other anticancer regimens	Patients should not have received previous systemic treatment for their mCRC. Patients who have received adjuvant chemotherapy are eligible if the last administration of the prior adjuvant regimen occurred >12 months prior to Screening. Other anticancer treatment is not permitted.
Intravenous, intramuscular, intra-articular, or parenteral corticosteroids	Not permitted within 6 weeks prior to Day 1 or throughout the trial. The use of corticosteroids as antiemetics for oxaliplatin and 5-FU is allowed 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. The use of corticosteroids as antiemetics for oxaliplatin and 5-FU is allowed according to regular institutional practice.
Oral or parenteral anticoagulants	Full-dose oral or parenteral anticoagulants or other thrombolytic agents for therapeutic (as opposed to prophylactic) purposes (including coumadin or warfarin) are not permitted within 10 days of the first dose of BI 695502 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 are not permitted within 10 days of first dose of BI 695502 or throughout the trial. Acetaminophen (paracetamol) as well as natural and synthetic opioids can 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 is not permitted. 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.
Surgical procedures	Invasive procedures (major surgical procedure, open biopsy or significant traumatic injury) are not permitted within 28 days prior to the first dose of BI 695502 (see details below). Surgery incision should be fully healed. Placement of a vascular access device is not considered as a major surgical procedure if performed more than 24 hours prior to BI 695502 administration.
Calcium/magnesium	Caution in the concomitant or prophylactic use of calcium or magnesium due to the possibility of reduced response rate to mFOLFOX6 treatment.
Live/attenuated vaccine	Not permitted within 12 weeks prior to the Screening Visit or throughout the trial.

Table 4.2.2.1: 1 Prior and concomitant treatment (continued)

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.
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

Any surgical procedure (including biopsy for RAS determination) is not permitted within 28 days prior to the first dose of BI 695502 or for the duration of the trial. If it is not possible to arrange a biopsy during the screening period then the patient can be re-screened after the procedure has been undertaken.

For elective surgery during the trial, the interval between termination of the BI 695502 or 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 (except for biopsy if required for determination of RAS status) will not be enrolled into the trial.

4.2.2.2 Restrictions on diet and life style

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

4.2.2.3 Restrictions regarding women of childbearing potential

Women who are pregnant, nursing, or who plan to become pregnant while in the trial will be excluded from the trial. Women of childbearing potential must be ready and able to use highly effective methods of birth control. See Section 3.3.2 and Section 3.3.3 for details.

In addition, male patients with female partners of childbearing potential must also agree to use a medically acceptable method of contraception during the trial and for 6 months after the last dose of trial medication.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary endpoint

The primary safety endpoint of the trial is patients with any of the following selected AEs:
- Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions.
- Thromboembolic events:
    - Arterial
    - Venous
- GI perforations
- Hypertension
- Proteinuria
- Pulmonary hemorrhage
- All hemorrhages and pulmonary hemorrhages
- Wound-healing complications including abscess and fistulas
- Posterior reversible encephalopathy syndrome
- Ovarian failure

5.1.2 Secondary endpoints

The secondary efficacy endpoints of the trial are:
- PFS is defined as the time from first administration of trial medication until disease progression as assessed by central imaging review according to RECIST 1.1 or death of any cause.
- Objective Response according to RECIST 1.1 as assessed by central imaging review.
- DOR defined as the time from first documented CR or PR until time of progression as assessed by central imaging review.
- TTP defined as the time from first administration of trial medication to the date of tumor progression as assessed by central imaging review.
- OS defined as the time from first administration of trial medication until death from any cause.

5.1.3 Further endpoints

The further endpoints of the trial are:
- ADAs/nADAs at Weeks 0, 4, 8, 16, 24, 32, 40 and 52 and 30-day Follow-up visits and long-term SFU visit.
- All AEs including AEs related to trial treatment, assessed according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
- All AEs potentially related to immunogenicity.
- All protocol-specified adverse events of special interest (AESIs).

5.2 ASSESSMENT OF EFFICACY

A central review of all patient images will be performed. Details will be described in the imaging charter. The results of the central review imaging data (independent assessments of objective response) will be used for the secondary efficacy analysis. The results of the Investigator assessment will be used for sensitivity analysis (see Section 7.3.2.1).

5.2.1 Progression-free survival

PFS: proportion/amount of patients who have neither progressed as per central imaging review nor died censored on the date of last radiological tumor assessment. Progression-free survival is defined as the time from first administration of trial medication until disease progression as assessed by central review or death. Disease progression is assessed according to RECIST 1.1 (see Appendix 10.1).

5.2.2 Objective response

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 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
- PR
- 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 will be listed in the imaging charter).

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 and Flow chart 1.2.

Tumor assessments should be performed prior to trial treatment administration. 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. Tumor assessment will be performed every 8 weeks (±3 days) up to Visit 21. From Visit 21 onwards tumor assessment will be performed every 12 weeks (±3 days; ±7 days from Visit 28 onwards). This means that no CT scan is needed at Visit 28 if the patient received a CT scan at Visit 27. During the non-treatment period CT scans will be performed every 8 weeks (±3 days) weeks.

A CT scan with i.v. contrast product injection will be performed on the, chest, abdomen and pelvis ± involved area. In case of a contrast product injection allergy, an abdomen-pelvic MRI will be performed with a non-contrast chest CT scan.

5.2.3 Duration of response

Duration of response (DOR) is the time from first documented CR or PR until time of progression as assessed by central review.

5.2.4 Time to progression

Time to Progression (TTP) is defined as the time from first administration of trial medication to the date of tumor progression as assessed by central review.

5.2.5 Overall survival

Overall survival (OS) is defined as the time from first administration of trial medication until death from any cause.

5.3 ASSESSMENT OF SAFETY

5.3.1 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 and an optional rectal examination, as per the local practice, 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.

5.3.2 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 5.3.6).

5.3.3 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:
• aPTT, INR at screening and subsequent visits
• Neutrophil count and creatinine clearance at every visit
• Monocytes (abs, %), eosinophils (abs, %), basophils (abs, %) at every visit
• Reticulocyte count at every visit

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.

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 may be 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 hepatitis C virus (HCV) and/or positive antibody. If any of these tests are positive, the result should be confirmed by a positive hepatitis virus RNA.
- HIV and TB (QuantiFERON Gold assay or purified protein derivative [PPD] skin test) screening 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 5.3.6), 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.

5.3.4 Electrocardiogram

Two consecutive resting 12-lead electrocardiograms (ECG) 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 the Investigator or designee.

5.3.5 Other safety parameters

5.3.5.1 Tuberculosis assessment

Screening for HIV and TB should be performed according to local practice and local regulatory guidance. There should be no radiographic or clinical evidence of active TB. Thus, although a PPD skin test or the QuantiFERON®-TB Gold Assay may be used to assess TB status at Screening, none of these tests are mandatory. Local practice and local regulatory guidance should be followed.

Purified protein derivative skin test

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

QuantiFERON®-TB Gold Assay or T-SPOT Assay

QuantiFERON Gold or T-SPOT assay may be used to assess TB status at Screening.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event
An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
An SAE is defined as any AE which:

- results in death,
- is life-threatening; this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- 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.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Japan only: The following events will be handled as "deemed serious for any other reason". An AE which possibly leads to disability will be reported as an SAE.

AEs considered "Always Serious"

Every new occurrence of cancer of new histology must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

In accordance with the EMA initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

A copy of the latest list of "Always Serious AEs" will be provided to you upon request. The list of these AEs can be found in the ISF. These events should always be reported as SAEs as described earlier in this section.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, see Section 5.3.7.

The following are considered as AESIs:

1. Hepatic injury

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

Patients showing the following laboratory abnormalities need to be followed up according to Section 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 x 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 the baseline value combined with an elevation of total bilirubin ≥2 x the baseline value measured in the same blood draw sample.
- Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 x ULN.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analyzed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed and an SAE form should be completed and sent to the Sponsor.

2. Anaphylactic reactions.
3. GI perforations.
4. 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).

Local tolerability
The assessment of injection site reactions will be done by the investigator/designee who will assess the presence of: 'swelling', 'hardening', 'heat', 'redness', 'pain', 'itching', 'bruising', or 'other symptoms'. If any injection site reactions are observed, these findings should also be reported on the AE eCRF page.

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

Causal relationship of AEs
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.
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.
Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g., preexisting or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g., Stevens-Johnson syndrome).
- An indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g., pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of

drug administration; an allergic reaction weeks after discontinuation of the drug concerned).

- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

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

5.3.7 Adverse event collection and reporting

AE collection
The following must be collected and documented on the appropriate eCRFs by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP)/Long-term SFU, all AEs (serious and non-serious), and AESIs. If in an individual patient only vital status information is collected after the long term SFU or discontinuation from Avastin® (whichever occurs later), from then on and until the individual patient's end of trial the Investigator does not need to actively monitor the patient for AEs but should only report fatal AEs, relevant SAEs and relevant AESIs of which the Investigator may become aware of. However, if a patient remains in the non-treatment period beyond 18 weeks post last dose of trial medication prior to the switch visit (i.e., beyond the long term SFU), all AEs, SAEs and AESI will continue to be collected until disease progression, initiation of new anti-cancer therapy, death, or the end of the trial. Once disease progression, initiation of new anti-cancer therapy is confirmed and only vital status information is collected, report fatal AEs, relevant SAEs and relevant AESIs of which the Investigator may become aware.

The REP is defined as 126 days/18 weeks after the last trial medication administration prior to the switch visit. All AEs which occur through the treatment phase and throughout the REP will be considered as on treatment, please see Section 7.3.3. Events which occur after the REP will be considered as post treatment events. All AEs will be reported up until the end of the long-term SFU visit (18 weeks after the last dose of BI 695502) or until discontinuation from Avastin®, whichever occurs later.

AE reporting to Sponsor and timelines
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the Sponsor's/Sponsor's designee unique entry point (specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific

occasions the Investigator could inform the Sponsor/Sponsor designee directly via telephone. This does not replace the requirement to complete and fax the BI SAE form.

Japan only: All SAEs and AESIs must be reported immediately to the head of the trial site.

With receipt of any further information for these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required
For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication, and any possible interactions between the investigational drug(s) and a non-investigational product.

The following should also be recorded as an (S)AE in the eCRF and SAE form (if applicable):

- Worsening of other pre-existing conditions (see also Exemption of SAE reporting below)
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior to trial inclusion, they will be considered as baseline conditions.

All (S)AEs, including those persisting after trial completion, must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a female patient has been enrolled into the clinical trial, after having taken trial medication, the Investigator must report immediately (within 24 hours) any potential drug exposure during pregnancy (DEDP) to the Sponsor/Sponsor designee unique entry point (specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used. The pregnant study participant must be withdrawn from the study.

This applies also to the rare cases of pregnancy of a female partner of a male patient that has been enrolled into the clinical trial, after having taken trial medication. If a female partner of a male patient is confirmed as being pregnant, an ICF for a Pregnant Partner will be provided to the female partner to allow pregnancy follow-up.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor/Sponsor designee unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

As pregnancy itself is not to be reported as an AE. In the absence of an (S)AE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is a SAE and/or AESI associated with the pregnancy a SAE form must be completed in addition.

Exemptions to SAE reporting
Protocol-specified outcome events should be collected on the appropriate eCRF page only.

Disease Progression in oncology trials is a trial endpoint for analysis of efficacy and as such is exempted from reporting as a (S)AE. Progression of the patient's underlying mCRC (underlying disease) 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 in 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 trial medication and the progression of the underlying malignancy, the event must be reported as a (S)AE 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 by the Quintiles Medical Monitor.

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

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Immunogenicity assessment

For all ADA/nADA samples, the day and time of sampling will be accurately recorded.

Wherever possible, ADA/nADA blood samples will be taken at the same time as blood is drawn for other analyses to limit repeated venipuncture. The ADA/nADA samples should be obtained from the forearm not used in the BI 695502 or Avastin® i.v. administration.

In the event of early withdrawal from treatment, every effort should be made to take ADA/nADA samples as part of the early withdrawal procedures, if possible, with date and time of sample and time of dose prior to this sample recorded. Every effort should be made to take ADA/nADA samples at the SFU visit or at 18 weeks after the last administration of BI 695502 prior to the switch visit.

5.6.2 Tumor biopsy

Tumor histology and RAS status will be confirmed before enrolment; if not performed/available, and no archival tumor sample is available, a fresh biopsy will be performed, if possible, and analyzed locally.

5.7 APPROPRIATENESS OF MEASUREMENTS

The RECIST 1.1 guideline (R09-0262) is well established and scientifically accepted and will be used for the evaluation of objective 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 mCRC patients.

6. INVESTIGATIONAL PLAN

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

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 with the maximum time window of ±3 days unless otherwise specified:

- Administration of BI 695502 will occur on Day 1 of each cycle (every 2 weeks).
- Administration of chemotherapy will start on Day 1 of each cycle (see Table 4.1.4.1).
- Each subsequent cycle will occur within 3 days (±3 days) of completion of the previous cycle, including after the switch from BI 695502 to Avastin®.
- During the Switch visit prior to infusion with Avastin®, the assessments as described in Flow Chart 1.2 will be performed.
- The 30-day Follow-up visit will be performed 30 days (±3 days) after the last BI 695502 or Avastin® dose, whichever occurs later.
- Non-treatment period: visits will be performed every 8 weeks until initiation of new treatment or death for patients who discontinue BI 695502 or Avastin® 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.
- The long-term SFU visit will be performed 18 weeks (+7 days) after the last dose of trial medication prior to the switch visit. If the patient continues to receive treatment with Avastin® beyond the 18 weeks post last BI 695502 dose, then no SFU visit will be performed.

Clinical assessments will be performed within 3 days before trial medication infusion. Laboratory samples must be drawn prior to infusions of 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.

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 27 cycles of treatment during the course of the trial, plus the 30-day Follow-up and long-term 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	31	108.5
Hematology	2	31	62
INR/PT/PTT	2.7	31	83.7
ADAs	3	11	33
nADA	5	11	55
Infection screen	12	1	12
TB	3	1	3
Approximate total			**396.2**

ADAs = antidrug antibodies; nADA = neutralizing ADAs; 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 period Visit 0 (Week -4 to -1)
Once the patient has provided informed consent (before any trial-specific procedures or assessments are performed), the trial site will enter the screened patient into the system using the Interactive Telephone and Web Response System (IXRS®). Once the patient meets all inclusion criteria and none of the exclusion criteria (see Section 3.3), the patient will be enrolled into the trial.

The following assessments will be performed/collected:

- Tumor biopsy (performed and assessed locally) and RAS status assessment.
- Demographic information (including sex, date of birth, ethnicity and race), medical and surgical history, and smoking status.
- Hepatitis B and hepatitis C (unless status has previously been confirmed within 6 months prior to Screening) and HIV test (should be performed only if required per local practice and local regulatory guidance).
- TB test (PPD skin test or QuantiFERON TB Gold test or T-SPOT 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) (see Section 5.3.1).

- Measurement of body mass index (BMI). The formula used to measure BSA will be recorded.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.3.2).
- Laboratory testing (serum chemistry, hematology, coagulation and urinalysis; see Section 5.3.3).
- 12-lead ECG (see Section 5.3.4).
- Previous and concomitant therapies/medications (see Section 4.2).
- Assessment of AEs (see Section 5.3.6).
- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and the involved area, if applicable) (see Section 5.2.2). To be performed within 28 days of enrolment.
- ECOG PS.
- Contact IXRS®.

6.2.2 Treatment period(s)

Cycle 1 (Day 1)

Eligible patients will be enrolled and treatment will be administered 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).
- Urine protein analysis.
- Physical examination, including weight (kg) (see Section 5.3.1).
- Measurement of BMI. The formula used to measure BSA will be recorded.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.3.2).
- Laboratory testing (serum chemistry, hematology, coagulation and urinalysis; see Section 5.3.3).
- Previous and concomitant medications (see Section 4.2).
- Assessment of AEs (see Section 5.3.6).
- ECOG PS.
- Survival.
- Blood samples for the level of ADAs/nADAs, sample should be taken prior to trial medication administration (see Section 5.6.1).
-

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

Cycle 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26

- Physical examination, including weight (kg) (see Section 5.3.1).
- Measurement of BMI. The formula used to measure BSA will be recorded.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.3.2).
- Laboratory testing (serum chemistry, hematology, coagulation and urinalysis; see Section 5.3.3).
- 12-lead ECG every three cycles (per the Flow chart 1.1 and Flow chart 1.2).
- Concomitant therapies/medications (see Section 4.2).
- Assessment of AEs (see Section 5.3.6).
- Survival.
- Trial medication infusion (see Section 4.1.4).
- Administration of chemotherapy (see Table 4.1.4.1).
- Contact IXRS®. Not required from the switch visit onwards. Note: at the time of Avastin® discontinuation, contact IXRS to perform the discontinuation call.

Cycles 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27.

- Urine pregnancy test for women of childbearing potential (serum pregnancy test to be performed in case of positive urine pregnancy test) (serum pregnancy test at Cycle 27).
- Urine protein analysis.
- Physical examination, including weight (kg) (see Section 5.3.1).
- Measurement of BMI. The formula used to measure BSA will be recorded.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature (see Section 5.3.2).
- Laboratory testing (serum chemistry, hematology, coagulation and urinalysis; see Section 5.3.3).
- 12-lead ECG (every 3 cycles per the Flow chart 1.1 and Flow chart 1.2).
- Concomitant medications (see Section 4.2).
- Assessment of AEs (see Section 5.3.6).
- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and the involved area, if applicable) (see Section 5.2.2). To be performed every 8 weeks from Cycle 5 to Cycle 21. From Cycle 21 onwards, it should be done every 12 weeks.
- ECOG PS. To be performed every 4 cycles from Cycle 5 to Cycle 21 and at Cycle 27.
- Survival.
- Blood samples for the level of ADAs/nADAs, sample should be taken prior to trial medication administration (see Section 5.6.1). Samples to be collected at Cycles 3, 5, then every 4 cycles to Cycle 21 and at Cycle 27.
-

- Trial medication infusion (see Section 4.1.4).
- Administration of chemotherapy (see Table 4.1.4.1).

- Contact IXRS®. Not required from the switch visit cycle onwards. Note: at the time of Avastin® discontinuation, contact IXRS to perform the discontinuation call.

Cycle 28 onwards

Patients that continue to receive treatment from Cycle 28 and beyond will attend the trial site every 12 weeks for the following assessments:

- Measurement of BMI. The formula used to measure BSA will be recorded
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.3.2).
- Physical examination, including weight (kg) (see Section 5.3.1).
- Urine pregnancy test for women of childbearing potential (serum pregnancy test to be performed in case of positive urine pregnancy test).
- Urine protein analysis.
- Laboratory testing (serum chemistry, hematology coagulation and urinalysis; see Section 5.3.3).
- Concomitant therapies/medications (see Section 4.2).
- Assessment of AEs (see Section 5.3.6).
- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and the involved area, if applicable) (see Section 5.2.2). To be performed every 12 weeks or per the Investigator's discretion. This means that no CT scan is needed at Visit 28 if the patient received a CT scan at Visit 27.
- Trial medication infusion (see Section 4.1.4). To be performed every 2 weeks.
- Administration of chemotherapy (see Table 4.1.4.1). To be performed every 2 weeks.
- Contact IXRS®. To be performed every 2 weeks. Not required from the switch visit onwards. Note: at the time of Avastin® discontinuation, contact IXRS to perform the discontinuation call.
- 12-lead ECG (see Section 5.3.4)

Switch Visit, prior to Avastin® administration:

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

- Physical examination, including weight (kg) (see Section 5.3.1).
- Urine pregnancy test for women of childbearing potential (serum pregnancy test to be performed in case of positive urine pregnancy test).
- Urine protein analysis.
- Measurement of BMI. The formula used to measure BSA will be recorded.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature (see Section 5.3.2).
- Laboratory testing (serum chemistry, hematology, coagulation and urinalysis (see Section 5.3.3).
- 12-lead ECG

- Concomitant therapies/medications (see Section 4.2).
- Assessment of AEs (see Section 5.3.6).
- 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) (see Section 5.2.2).
  Note: Another unscheduled tumor assessment should be performed 6 weeks after the switch visit and no longer than 13 weeks after this visit.
- Survival.
- Blood samples for the level of ADAs/nADAs (see Section 5.6.1). (only one sample between 2 hours and 5 minutes prior to the start of infusion needs to be taken)
-

Subjects are allowed to be re-screened up to two times and must be re-consented before each re-screening occurs.

6.2.3 Follow-up Period and Trial Completion

30-day Follow-up Visit

The following will be performed/collected:

- Physical examination, including weight (kg) (see Section 5.3.1).
- Measurement of BMI.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature (see Section 5.3.2).
- Laboratory testing (serum chemistry, hematology, coagulation and urinalysis (see Section 5.3.3).
- Concomitant therapies/medications (see Section 4.2).
- Assessment of AEs (see Section 5.3.6).
- Date of initiation of new anticancer therapy, if applicable.
- 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) (see Section 5.2.2).
- Survival.
- Blood samples for the level of ADAs/nADAs (see Section 5.6.1).
- .

In addition, all patients who receive at least one infusion of BI 695502 or Avastin® and who discontinue the trial treatment at any time after Day 1 (but do not withdraw their consent) will be required to have all of the evaluations for the Follow-up visit 30 days after the last trial medication administration (BI 695502 or Avastin®, whichever occurs later).

Non-treatment period

For all patients who discontinue trial medication for reasons other than progressive disease, but do not withdraw consent, the following will be performed/collected every 8 weeks until death or initiation of a new treatment, whichever occurs earlier.

- Physical examination, including weight (kg) (see Section 5.3.1).
- Measurement of BMI.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.3.2).
- Laboratory testing (serum chemistry, hematology, coagulation and urinalysis; see Section 5.3.3).
- 12-lead ECG (see Section 5.3.4).
- Concomitant therapies/medications (see Section 4.2).
- Assessment of AEs (see Section 5.3.6).
- Date of initiation of new anticancer therapy, if applicable.
- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and involved area, if applicable) (see Section 5.2.2) at a minimum of every 8 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 to 9 weeks according to clinical judgment until disease progression, death, or the end of the trial, whichever occurs first. The following will be performed/collected:

- Tumor assessment (CT/MRI scan of chest and abdomen, including adrenals and involved area, if applicable) (see Section 5.2.2).
- Assessment of AEs (see Section 5.3.6).
- Date of disease progression (if applicable).
- Survival

Long-term Safety Follow-up Visit

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

The following will be performed/collected:

- Physical examination, including weight (kg) (see Section 5.3.1).

- Measurement of BMI.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.3.2).
- Laboratory testing (serum chemistry, hematology, coagulation and urinalysis; see Section 5.3.3).
- Concomitant therapies/medications (see Section 4.2).
- Assessment of AEs (see Section 5.3.6).
- Date of initiation of second-line therapy (if applicable).
- Survival.
- Blood samples for the level of ADAs/nADAs (see Section 5.6.1).
-

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 until death, lost to follow-up, withdrawal of consent, or a maximum of 12 months after the last patient enrolled plus the 30-day FU visit, whichever occurs earlier.

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 single arm, open-label, multicenter trial. The primary objective is to evaluate safety and tolerability of BI 695502.

The primary endpoint will be patients with any of the selected AEs (see Section 5.1.1).

Secondary objectives comprise the evaluation of efficacy parameters and further safety. A further objective is the evaluation of immunogenicity

No formal hypothesis testing will be performed. The analysis of the data will be performed descriptively.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing will be performed. Where confidence intervals or p-values are presented, they will be interpreted in an exploratory fashion only.

7.3 PLANNED ANALYSES

All patients treated with at least one dose of trial medication (treated set) will be included in efficacy and safety evaluations. Efficacy and safety analyses will be based on the treated set.

The main analyses will cover the period during which patients received BI 695502 and data will be analyzed to the extent available also taking differences in exposure to BI 695502 into account, i.e. using censoring of data and exposure corrected adverse events rates. These methods will be defined in the TSAP. Adverse events will be presented by underlying treatment and taking the corresponding exposure into account.

After the transition to commercially available Avastin®, the impact of switching will be assessed in an exploratory manner 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.

7.3.1 Primary endpoint analyses

7.3.1.1 Primary safety analysis

The primary endpoint of the study is patients with any of the selected AEs defined in Section 5.1.1.

All AEs with an onset between start of treatment and end of the REP, a period of 18 weeks after the last dose of trial medication, will be considered. The proportion of patients with at

least one AE selected for primary endpoint assessment will be displayed including descriptive 95% confidence intervals (CIs) for the proportion of patients with selected AEs. See Section 7.3.3 for details on safety analysis. The proportion of patients for the AE categories will be presented.

7.3.2 Secondary endpoint analyses

Objective response according to RECIST 1.1 as assessed by central imaging review will be analyzed using objective response rate, defined as proportion of patients with complete response [CR] plus partial response [PR]. Objective response rate will be summarized using descriptive statistics including descriptive 95% CIs. Additionally, the response categories will be analyzed descriptively. See Section 5.2.2 for the definition of response categories and objective response.

For other secondary endpoints listed below, descriptive analyses using Kaplan Meier (KM) methodology will be performed.

Date of PD will be the date of radiological diagnosis of PD for patients progressed according to central review assessment.

For PFS calculation, patients who have neither progressed as per central imaging review nor died will be censored on the date of last radiological tumor assessment (see Section 7.5.1).

For TTP and DOR evaluation, patients who have not progressed as per central imaging review will be censored on the date of last evaluable tumor assessment.

For OS, OS time will be censored at the last date that the patient is known to be alive.

The PFS will be analyzed descriptively using KM methodology. The KM survival rate will be presented graphically. The 1-year PFS rate and median PFS will be estimated with two-sided 95% CI. The CI for 1-year PFS rates will be determined using Greenwood's variance estimate (R14-3846). The CI for the median will be calculated according to the Brookmeyer and Crowley method (R09-6372).

7.3.3 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.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. All AEs with an onset between start of treatment and end of

the REP, a period of 18 weeks after the last dose of trial medication, will be assigned to the treatment period for evaluation and will be considered as treatment-emergent AEs. In the context of switching from BI 695502 to Avastin®, TEAE definitions will be specified in the TSAP.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Severity of AEs will be reported using the NCI-CTCAE version 4.0 criteria. For all 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.
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 18 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. 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 vital signs, weight, physical examination and ECG parameters, compared to findings before start of treatment, will be summarized.

7.3.4 Immunogenicity analyses

If data allow, the antibody response, antibody titer and neutralizing antibody response will be summarized as appropriate (frequency/proportions for ADA positive samples, descriptive statistics for titer and frequency/proportions of characterization of the neutralizing potential of the ADA for ADA positive samples assayed) by scheduled assessments (Week 0, Week 4, Week 8, Week 16, Week 24, Week 32, Week 40 and Week 52, and 30-day Follow-up visits and long-term SFU visit) and overall (for ADA positive subjects only).

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7.4 INTERIM ANALYSES

No interim analysis is planned for this study.

7.5 HANDLING OF MISSING DATA

7.5.1 Efficacy endpoints

For the primary analysis, the rules described in Table 7.5.1: 1 for censoring and assignment of progression date will be applied.

Table 7.5.1: 1 Censoring and handling of missing data for PFS

Situation	Outcome	Date of Progression or Censoring
No baseline assessment	Censored	Date of first administration of trial medication
Consecutive missed radiological assessments	Censored	Date of last radiological assessment of measured lesions
New anticancer treatment started	Censored	Date of last radiological assessment of measured lesions
No progression/no death	Censored	Date of last radiological assessment of measured lesions
Progression according to RECIST 1.1 and not censored for any reason above	Progressed	Date of radiological assessment that demonstrates progression
Death and not censored for any reason above	Progressed	Date of death

For other efficacy endpoints, rules for handling of missing data will be specified in the Trial Statistical Analysis Plan (TSAP) if necessary.

7.5.2 Safety and other endpoints

Adverse events with missing relationship will be considered as drug related. Other missing safety data will be not be imputed.

7.6 RANDOMIZATION

This is an open-label, single arm trial. No randomization will be performed.

7.7 DETERMINATION OF SAMPLE SIZE

This is an exploratory trial. No formal statistical hypothesis will be tested or powered for. Based on historical data (R10-2544, R11-2707, R13-5293), a proportion of about 30% to 50% of patients are expected to experience an AE of the primary endpoint. For these

proportions, a sample size of N=120 patients will lead to a width of the CI for the AE rate of 16.2% to 17.6% as shown in Table 7.7: 1 below.

Table 7.7: 1 95% Wilson Confidence interval for proportion of patients with primary endpoint AE

Assumed AE rate	Lower bound	Upper bound
30%	22.5%	38.7%
40%	31.7%	48.9%
50%	41.2%	58.8%

Furthermore, the sample size of N=120 allows to observe relatively rare AEs with high probability as shown in Table 7.7: 2.

Table 7.7: 2 Probability to observe at least 1 AE with a given probability of occurring.

Underlying probability of event	Probability to observe at least 1 case
1%	70.0%
2%	91.1%
3%	97.4%
5%	99.8%

Therefore the sample size of N=120 is chosen for this trial.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP and relevant BI SOPs, and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

Japan only: The rights of the Investigator/trial site and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract/trial site's contract. As a general rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF.

8.1 TRIAL 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/Independent Ethics Committee (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.

Partner pregnancy: If a female partner of a male patient is confirmed as being pregnant, an ICF for a Pregnant Partner will be provided to the female partner to allow pregnancy follow-up.

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 the regulatory and legal requirements of the participating country.

Japan only: The Investigator must give a full explanation of the study procedures to trial patients using the patient information form, which avoids the use of technical terms and expressions. The patient will be given sufficient time to consider participation in the trial. The Investigator will obtain the patient's written consent on the informed consent form after confirming that the patient understands its 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. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's instructions.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB/IEC 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

Electronic Case Report Forms for individual patients will be provided by the Sponsor. 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 reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

For the eCRF, the following data need to be derived from source documents:

- Patient identification (gender, date of birth)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date (mandatory), and end date (if available))
- SAEs (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)

- Originals or copies of laboratory results (in validated electronic format, if available)
- Completion of patient's participation in the trial
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g., medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

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. eCRF 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 Clinical Research Associate, on site monitor and auditor may review all eCRF, 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 period of records (Japan only)

Trial site(s):
The trial site(s) must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and trial site's contract with the Sponsor.

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 fulfil 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.

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 product (mFOLFOX6), the reference document for fluorouracil is the EU Summary of Product Characteristics (SPC) and for leucovorin and oxaliplatin the United Kingdom (UK) SPC for each product should be used.
The current versions of these reference documents are provided in the ISF. No AEs are classified as listed for trial design.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of SAEs, e.g. suspected unexpected serious adverse reactions to health authorities and IEC/IRB, will be done according to local regulatory requirements. When there is no evidence suggesting a causal relationship between the trial medication and the progression of the underlying malignancy, 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 END OF TRIAL

The end of the trial is defined as when all enrolled and treated patients have either died, are lost to follow-up, or have withdrawn consent, or for a maximum of 12 months after the last patient enrolled plus the 30-day FU visit, whichever occurs earlier.

The IEC/CA in each participating EU member state needs to be notified about the end of the trial 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 should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reasons, 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.

9. REFERENCES

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9.2 UNPUBLISHED REFERENCES

Not applicable.

10. APPENDICES

10.1 GUIDELINES FOR EVALUATION OF OBJECTIVE 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 1302.3 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 enrollment.

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 (TL) and lesions irradiated within 12 weeks of enrollment.

- 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 TLs.

Target lesions:

A maximum of five measurable lesions (with a maximum of two lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs 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 1302.3 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 intravenous (i.v.) contrast media administration is the preferred method. MRI 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 1302.3 trial, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs 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 1302.3 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 1302.3 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 1302.3 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 1302.3 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 1302.3 trial, tumor markers will not be used for objective response assessments as per RECIST 1.1.

Cytology and histology

In the 1302.3 trial, histology will not be used as part of the objective 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 (SD) (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 1302.3 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 trial. 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.

OBJECTIVE 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 28 days (see Flow chart 1.1) before the start of trial treatment. Follow-up assessments will be performed every 8 weeks (± 3 days) after enrollment 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 five measurable lesions, with a maximum of two 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 >5 mm, 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., 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 TLs since baseline. Any pathological lymph nodes selected as TLs 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 TLs, 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 TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides not NE as a TL 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 NTLs 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 NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit.

To achieve ‘unequivocal progression’ on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more NTLs 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; NA = not applicable (only relevant if there were no target lesions/non-target lesions at baseline); NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

CENTRAL REVIEW

Radiological examinations performed in the conduct of this trial for RECIST 1.1 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 OR AVASTIN® PREPARATION AND ADMINISTRATION

Supply

BI 695502 will be provided as a concentrate for solution for infusion 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 or Avastin®; therefore, the vials are intended for single use only. BI 695502 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 (PVC) or polyolefin bags/lines have been observed for BI 695502, only bags/lines made of these materials are to be used for 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 tubing include a 0.2 µm infusion filter	

BR = Polybutadiene; DEHP = di-(2-ethylhexyl)phthalate; PE = Polyethylene; PP = Polypropylene; PUR = Polyurethane; PVC = Polyvinyl chloride; 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 or Avastin® for Intravenous Administration

The recommended dose is 5 mg/kg every 2 weeks when used in combination with i.v. 5-FU-based chemotherapy. The dose of BI 695502 or 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. The necessary amount of BI 695502 will be withdrawn and diluted in 0.9% of 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 respecting the mandatory concentration of 16.5 mg/mL. 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.

After 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 mFOLFOX6 as outlined in earlier sections of the protocol.

In case of any toxicity > grade 2 (according to the NCI CTCAE version 4.0), chemotherapy will be discontinued.

Neurotoxicity related to oxaliplatin requires particular attention. The National Comprehensive Cancer Network (NCCN) recommends to discontinue oxaliplatin in case of significant neurotoxicity with other drugs maintained until disease progression.

However, 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 eCRF page.

Based on patient tolerability, the doses of chemotherapy drugs may be decreased as per the label or institutional practice.

10.4 CLINICAL EVALUATION OF LIVER INJURY

10.4.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.3.6.1 (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, ceruloplasmin, α-1 antitrypsin, transferrin, amylase, lipase, fasting glucose, cholesterol, triglycerides, cholinesterase, INR, aPTT.

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 judgment and Good Clinical Practice (GCP).

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		22 April 2016
EudraCT number		2015-003718-25
BI Trial number		1302.3
BI Investigational Product(s)		BI 695502
Title of protocol		A single arm, open-label, multicenter, multinational, safety and efficacy Phase IIIb trial of BI 695502 plus mFOLFOX6 in patients with previously untreated metastatic colorectal 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		Title page: Study Title, Brief title and Coordinating Investigator details
Description of change		Locally advanced removed Contact details changed
Rationale for change		To allow all patients with untreated metastatic colorectal cancer to be included in the study Administrative change of contact details added
Section to be changed		Synopsis: Study title
Description of change		Locally advanced removed
Rationale for change		To allow all patients with untreated metastatic colorectal cancer to be included in the study
Section to be changed		Synopsis: No of Patients: total entered
Description of change		Removal of number of patients to be entered in Japan
Rationale for change		Local information not required in the global protocol
Section to be changed		Synopsis: Main criteria for inclusion

Description of change		Text changed from: Patients aged ≥18 (for Japan only: Age ≥20 years at Visit 1) to: Patients aged ≥18 (for Japan only: Age ≥20 years at time of signing the informed consent form [ICF]) Requirement for locally advanced disease removed Text updated to state the patients must have at least one measurable lesion according to RECIST 1.1, **that has not been irradiated within 12 weeks prior to enrollment**
Rationale for change		To align with study flow chart, to allow all patients with metastatic disease to enter the study and to restrict entry of patients who have recently undergone radiotherapy
Section to be changed		Synopsis: Statistical Methods
Description of change		Provision of an interim analysis has been deleted The subsection Further analyses has been deleted to remove repetition
Rationale for change		No interim analysis is needed for this study
Section to be changed		Flow Chart 1.1
Description of change		Assessment of DILI (if needed) and coagulation parameters added. Row for INR/PTT deleted Footnotes added to state that a Central Laboratory will be used for hematology, clinical biochemistry urinalysis and coagulation tests Footnotes amended to state that: screening biopsy should be obtained locally, that sitting BP is measured after at least 5 minutes rest, that two consecutive ECGs should be taken, that tumor assessments will be performed every 8 weeks up to Visit 28, every 12 weeks from Visit 28 onwards and every 8 weeks in the non-treatment period; CT scans of the neck are now deleted; A new footnote also states that if a visit occurs outside the specified time window,

		then the next visit will be based on the number of days from the previous visit, and the number of days from not from baseline
Rationale for change		To include completion of the DILI checklist for patients with elevated LFTs and to include regular assessment of coagulation parameters To permit centers to take local biopsy samples if archival material is not available To align ECG evaluations with those in Study 1302.5 To reduce the number of CT scans that are required To add clarity on the timing and procedures for study assessments
Section to be changed		Flow Chart 1.2 – Cycle 14 onwards
Description of change		Assessment of DILI (if needed) and coagulation parameters added. Footnotes added to state that a Central Laboratory will be used for hematology, clinical biochemistry urinalysis and coagulation tests ECG assessments were aligned with 3 cycle frequency. Urine pregnancy and protein analysis added at Week 27 Concurrent medication check added at Cycle 28 onwards Footnotes amended to increase the visit interval during the non-treatment phase from 8 weeks to 12 weeks, to state that two consecutive ECGs should be taken, to specify that sitting BP is measured after at least 5 minutes rest, and to clarify the procedure for PK sampling Footnotes also clarify that from Cycle 28 onwards CT scans will be performed every 12 weeks. CT scans of the neck have been deleted. During the non-treatment period CT scans will be performed every 8 weeks Footnote added to state that if a visit occurs outside the specified time window, then the

		next visit will be based on the number of days from the previous visit, and the number of days from not from baseline
Rationale for change		To align assessments with those stated in the study design sections of the protocol and with Protocol 1302.5 To reduce the number of assessments and CT scans required after Cycle 27 To add clarity on the timing and procedures for study assessments
Section to be changed		2.1 Rationale for Performing the Trial
Description of change		Text changed to state that… generation of additional safety and efficacy data of BI 695502 in mCRC will be **of value to the treating physician and patients**
Rationale for change		To add clarity to the rationale
Section to be changed		2.3 Benefit-Risk Assessment
Description of change		The following paragraph has been added: Avastin® may cause fetal harm based on the drug's mechanism of action and findings from animal studies. Limited postmarketing reports describe cases of fetal malformations with use of Avastin® in pregnancy; however, these reports are insufficient to determine drug associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Women who are pregnant, nursing, or who plan to become pregnant are excluded from entering the trial. Women of reproductive potential should be advised to use effective

		contraception during treatment with, and for 6 months after the last dose of Avastin®.
Rationale for change		To alert Investigators of the risks of fetal harm in women taking Avastin and to update the protocol in line with the revised labelling (Dec 2015)
Section to be changed		3.1: Overall Design
Description of change		Provision of an interim analysis has been deleted Proposed number of Japanese patients deleted. Provision for changes to the mFOLFOX6 regimen to be allowed following agreement by the Sponsor
Rationale for change		No interim analysis is needed for this study Regional information removed from the protocol Changes to mFOLFOX regimen may be required in centers where leucovorin is not obtainable
Section to be changed		3.3: selection of Trial Population
Description of change		Text added to state that re-screening can only occur after approval of the Sponsor The number of subjects planned for Japan has been deleted
Rationale for change		Administrative and to remove country specific information.
Section to be changed		3.3.1 Main diagnosis for trial entry
Description of change		Text changed from: Patients aged ≥18 (for Japan only: Age ≥20 years at Visit 1) to: Patients aged ≥18 (for Japan only: Age ≥20 years at time of signing ICF) Text changed to state that patients measurable lesions must not have been irradiated within 12 weeks prior to enrollment 'Locally advanced' removed to allow patients with metastatic CRC to enter the study
Rationale for change		To align with study flow chart and to exclude recently irradiated patients To extend the population eligible for study entry
Section to be changed		3.3.1 Main diagnosis for trial entry
Description of change		The description of the main diagnosis for trial entry was modified from:

		subjects who 'have **not** completed any adjuvant/neoadjuvant therapy at least 12 months before trial entry to: *subjects* '**should** have completed any adjuvant/neoadjuvant therapy at least 12 months
Rationale for change		To align text with Exclusion criterion 1 and text in Table 4.2.2.1:1
Section to be changed		3.3.2 Inclusion criteria
Description of change		Inclusion criterion 1 has been changed from: Patients aged ≥18 (for Japan only: Age ≥20 years at Visit 1) to: Patients aged ≥18 (for Japan only: Age ≥20 years at time of signing ICF) 'Locally advanced' removed to allow patients with metastatic CRC to enter the study Criterion 6 re-ordered to align with Study 1302.5 INR criterion revised in line with Study 1302.5 and added as a separate criterion Text changed to state exclude patients with measurable lesions that have been irradiated within 12 weeks prior to enrollment
Rationale for change		To align with study flow chart and exclude recently irradiated patients. To extend the population eligible for study entry
Section to be changed		3.3.2 Inclusion criteria
Description of change		Inclusion criterion 6d has been changed from: Hemoglobin ≥9 g/dL (without transfusion within 2 weeks prior to randomization) to: Hemoglobin ≥9 g/dL (without transfusion within 2 weeks prior to screening). Criterion 6g has been amended to specify **total** bilirubin Criterion 6h has been clarified to include subjects with non-clinically significant deviations in INR ≤1.4 or PTT within normal limits Criterion 7 has been amended to specify life expectancy should be based on the clinical Investigators judgment
Rationale for change		To align with the single arm open label study design and to more clearly specify subject inclusion criteria

Section to be changed		3.3.3 Exclusion criteria
Description of change		Exclusion criterion 4 has been amended as follows: Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment. 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. The following text has been added to exclusion criterion 10: Intravenous, intramuscular, interarticular or parenteral corticosteroids are restricted within 6 weeks prior to Day 1. The use of corticosteroids as antiemetics for oxaliplatin and 5-FU is allowed according to regular institutional practice In Criterion 12: 3 months has been replaced by 12 weeks Criterion 15 has been changed to state that history of active gastroduodenal ulcer refers to within 18 month of study inclusion
Rationale for change		To provide more detailed information about exclusion of patients with brain metastases To provide consistency with information provided in Table 4.2.2.1:1 and to allow these drugs to be given for antiemetic use in line with regular Institutional practice in each country / study center participating in the study 12 weeks stated for consistency with subsequent sections of the protocol To allow inclusion of patients with history of gastroduodenal ulcer more than 18 months ago
Section to be changed		Section 3.3.4 Removal of patients from therapy or assessments

Description of change		Text added to state that: if pregnancy occurs the sponsor designee is to be notified immediately New chemotherapy or radiotherapy added as an additional criterion
Rationale for change		Safety monitoring No new chemotherapy or radiotherapy to be allowed during the study
Section to be changed		Section 4.1.3 Selection of doses in the trial
Description of change		Text added to state that: The dose administered to each patient is to be recalculated at each visit based on their body weight at that visit.
Rationale for change		To account for potential weight loss during the study
Section to be changed		Section 3.3.4 Removal of patients from therapy or assessments
Description of change		The criteria for patient discontinuation have been expanded
Rationale for change		To align with Protocol 1302.5 and with Sections 4.1.4 and 4.2.1 of this protocol
Section to be changed		Section 4.1.4 1 Chemotherapy
Description of change		The text now states that: The formula used to calculate BSA should be recorded on the eCRF at each visit
Rationale for change		To account for the variety of formulas that can be used to estimate BSA and to account for different study personnel at a given site estimating BSA at different visits
Section to be changed		Section 4.2.2 Restrictions
Description of change		Radiotherapy at any time during the study has been added as a restriction in Table 4.2.2.1:1
Rationale for change		To prevent concomitant radiotherapy during the study
Section to be changed		Section 4.2.2 Restrictions
Description of change		The following changes have been made to Table 4.2.2.1:1 concerning corticosteroid use. For ‘Intravenous intramuscular, intra-articular, or parenteral corticosteroids’ and for ‘Oral, inhaled or topical corticosteroids’ the following sentence has been added to the restrictions: The use of corticosteroids as antiemetics for oxaliplatin and 5-FU is allowed according

		to regular institutional practice
Rationale for change		To allow these drugs to be given for antiemetic used in line with regular Institutional practice in each country / study center participating in the study
Section to be changed		Section 4.2.2 Restrictions
Description of change		The restrictions in Table 4.2.2.1:1 concerning the use of oral or parenteral anticoagulants have been rewritten as follows: Full-dose oral or parenteral anticoagulants or other thrombolytic agents for therapeutic (as opposed to prophylactic) purposes (including coumadin or warfarin) are not permitted within 10 days of the first dose of BI 695502 or throughout the trial. Text has been added to state that: All patients will have a biopsy taken and RAS determination performed during the 28-day screening period, before the first dose of study drug. If it is not possible to arrange a biopsy during the screening period then the patient can be re-screened after the procedure has been undertaken
Rationale for change		To bring the text in line with exclusion criterion 11 To ensure that study drug is not given within 28 days of any surgical procedure needed to obtain a biopsy
Section to be changed		Section 4.2.2 Restrictions
Description of change		The text in Table 4.2.2.1:1 has been amended to indicate that treatment with dipyridamole, ticlopidine, clopidogrel and cilostazol are **not permitted** within 10 days of first dose of BI 695502 or throughout the trial
Rationale for change		This brings the text in line with exclusion criterion 9
Section to be changed		Section 4.2.2 Restrictions
Description of change		The text in Table 4.2.2.1:1 has been amended to indicate that treatment within a clinical trial within 4 weeks prior to initiation of trial treatment **is not permitted**.
Rationale for change		This brings the text in line with exclusion criterion 18
Section to be changed		Section 4.2.2 Restrictions

Description of change		The text in Table 4.2.2.1:1 concerning surgical procedures now states that any surgical incisions should be fully healed
Rationale for change		Safety
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		The text has been added to ensure that investigators do not prescribe concomitant medication prior to discussing with the Sponsor.
Rationale for change		To improve consistency throughout the study and protect patient safety
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		The text has been added to state that acetaminophen (paracetamol) as well as natural and synthetic opioids can be used as pain relievers and to provide guidance on the use of bisphosphonates
Rationale for change		To improve consistency across studies and protect patient safety
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		The text has been amended to clarify no surgical procedure including that for RAS determination is permitted within 28 days of the first dose of trial drug
Rationale for change		To align with other sections of the protocol
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		5.2.2 Objective response
Description of change		The text relating to CT scans has been amended as follows: Tumor assessment will be performed every 8 weeks (±3 days) up to Visit 27. From Visit 28 onwards tumor assessment will be performed every 12 weeks (±3 days). This means that no CT scan is needed at Visit 28 if the patient received a CT scan at Visit 27. During the non-treatment period CT scans will be performed every 8 weeks (±3 days) weeks. CT scans of the neck have been excluded
Rationale for change		To reduce the number of CT scans and other assessments required during the non-

		treatment period
Section to be changed		5.3.3 Safety laboratory parameters
Description of change		The laboratory parameters to be evaluated have been added to the text. Text has been added to the infection screen for hepatitis B and C to state that if any of these tests are positive, the result should be confirmed by a positive hepatitis B virus DNA. The text also clarifies that HIV and TB screen will be analyzed locally and that coagulation assessments for study inclusion should also be analyzed locally whenever possible. Active hepatitis C is defined as positive hepatitis C virus (HCV) and/or positive antibody. If any of these test are positive, the result should be confirmed by a positive hepatitis virus RNA
Rationale for change		To add clarity
Section to be changed		5.3.4 Electrocardiogram
Description of change		The text has been amended to state that two consecutive ECGs will be taken
Rationale for change		To align with Study 1302.5
Section to be changed		5.3.6 Assessment of adverse events
Description of change		The following text has been deleted These laboratory findings constitute a hepatic injury alert and the patients showing these laboratory abnormalities need to be followed up according to the "DILI checklist" provided in the ISF
Rationale for change		To remove repetition
Section to be changed		5.3.6 1 Definitions of AEs - AESIs
Description of change		A full definition of TEAEs suggestive of hepatic injury has been provided to assist investigators in deciding whether the DILI checklist needs to be completed. Investigators are also instructed to complete an SAE form for these subjects A section has been added to define the procedure for assessing and reporting local tolerability
Rationale for change		To align with Study 1302.5
Section to be changed		5.3.7 Adverse event collection and reporting
Description of change		<u>Pregnancy</u> The text for reporting pregnancy has been updated

		Instructions have also been added for the completion of an Informed Consent Form for a Pregnant Partner within 24 h in the event that a female partner of a male study patient is confirmed as being pregnant. It has also been specified that pregnant study participants must be withdrawn from the study.
Rationale for change		To clarify procedures to be adopted in the case of pregnancy and make provision for female partners who become pregnant to be followed up as part of the study procedures
Section to be changed		5.6.2 Tumor biopsy
Description of change		This section has been amended to state that tumor histology and RAS status will be confirmed during the screening period; if not performed/available, and no archival tumor sample is available, a fresh biopsy will be performed, if possible, and analyzed locally.
Rationale for change		To clarify study procedures and align with entry criteria
Section to be changed		Section 6.1 Visit Schedule
Description of change		The visit frequency for the non-treatment period has been changed to 8 weeks Blood volumes have been updated in Table 6.1:1
Rationale for change		To reduce the number of assessments and CT scans required after Cycle 27 To align blood volumes with the study schedule
Section to be changed		6.2.1 Screening Period
Description of change		This section has been amended to state that biopsies can be performed locally, that the formula used to estimate BSA should be recorded, and to include coagulation tests
Rationale for change		To clarify study procedures
Section to be changed		6.2.2 Treatment period
Description of change		This section has been amended to state that patients will continue to receive treatment

		every 2 weeks from Cycle 28 onwards and that they will attend the trial site every 12 weeks for assessment (the study flow chart has been amended accordingly) The formula used to estimate BSA should be recorded and to include coagulation tests. the frequency of CT scans have been aligned to the study schedule It is also specified that subjects are allowed to be re-screened up to two times and must be re-consented before each re-screening occurs.
Rationale for change		To clarify study procedures
Section to be changed		6.2.3 Follow up period and Trial Completion
Description of change		The text has been modified to state that subjects will be assessed every 8 weeks (instead of every 12 weeks) For the follow-up visit , the text now specifies that tumor assessment is to be performed only if a tumor assessment was not performed within the previous 4 weeks
Rationale for change		To clarify study procedures and reduce the number of CT scans and other assessments required during the non-treatment period
Section to be changed		7.3.3 Safety analyses
Description of change		The text now states that Laboratory values will be graded according to the NCI-CTCAE version 4.0 and reported by frequency. (i.e. for each treatment group has been deleted)
Rationale for change		To add clarity to the procedures
Section to be changed		7.4: Interim Analysis
Description of change		Provision of an interim analysis has been deleted
Rationale for change		No interim analysis is needed for this study
Rationale for change		This is a single-arm open label study

Section to be changed		8.1 Trial Approval, Patient Information and Informed Consent
Description of change		Text relating to the pregnant partner consent form has been added as follows: Partner pregnancy: If a female partner of a male patient is confirmed as being pregnant, an Informed Consent Form for a Pregnant Partner will be provided to the female partner to allow pregnancy follow-up. Text relating to informed consent in Japan has been modified for clarity
Rationale for change		To make provision for female partners who become pregnant to be followed up as part of the study procedures. To clarify and improve the translation of the procedure for informed consent to be adopted in Japanese centers
Section to be changed		8.4.2 Expedited reporting to health authorities and IEC/IRB
Description of change		The following text has been added to better define cases where disease progression does not require expedited reporting: When there is no evidence suggesting a causal relationship between the trial medication and the progression of the underlying malignancy, 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.
Rationale for change		To make consistent with Section 5.3.7
Section to be changed		10.1 Guidelines for evaluation of an objective response
Description of change		Special cases now excludes radiotherapy during the study
Rationale for change		No radiotherapy will be allowed during the study
Section to be changed		10.2 Guidelines for BI695502 preparation and administration
Description of change		The guidelines have been updated to align with product labeling and with study 1302.5.
Rationale for change		Administrative
Section to be changed		10.3 Chemotherapy Regimens and Recommendations for Dose Modifications

		in Cases of Toxicity
Description of change		The version of the NCI CTCAE has been added to the following sentence: In case of any toxicity > grade 2 (according to the NCI CTCAE version 4.0), chemotherapy will be discontinued.
Rationale for change		For consistency with Section 7.3.3
Section to be changed		10.4.2 Procedures
Description of change		The text has been updated to state that a copy of the DILI checklist should be provided in addition to an SAE form for patients with suspected liver injury Clinical chemistry now includes coagulation tests
Rationale for change		To align with preceding sections of the protocol

Number of global amendment		2
Date of CTP revision		25 May 2016
EudraCT number		2015-003718-25
BI Trial number		1302.3
BI Investigational Product(s)		BI 695502
Title of protocol		A single arm, open-label, multicenter, multinational, safety and efficacy Phase IIIb trial of BI 695502 plus mFOLFOX6 in patients with previously untreated metastatic colorectal 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		Flow Chart 1.1
Description of change		Separate line added to show schedule of assessments for BSA BSA added to list of abbreviations in table footnote Footnote numbers 13 and 14 aligned Typo in IXRS corrected in footnote
Rationale for change		For added clarity
Section to be changed		Flow Chart 1.2
Description of change		Chart corrected to make provision for measurement of vital signs and weight at Week 28 onwards for measurement of BMI at Week 28 onwards and during non-treatment period Separate line added to schedule for BSA measurement BSA and IXRS added to list of abbreviations in table footnote Measurement of weight specified as part of physical examination
Rationale for change		To add clarity and make consistent with Section 6.2
Section to be changed		Abbreviations
Description of change		BSA added to list of abbreviations

Rationale for change		To add clarity
Section to be changed		5.3.3 Safety laboratory parameters
Description of change		The following text has been deleted: International normalized ratio and partial thromboplastin time will be measured at screening only.
Rationale for change		To ensure that all coagulation tests are collected post screening
Section to be changed		6.2 Details of trial procedures at selected visits. 6.2.2 Treatment period
Description of change		Physical examination (including weight), measurement of BMI, BSA and vital signs added to Cycle 28 onwards
Rationale for change		For consistency with Flow Chart 1.2
Section to be changed		6.2 Details of trial procedures at selected visits. 6.2.3 Follow-up period
Description of change		Coagulation added to list of laboratory tests at 30-day follow-up, non-treatment period and long-term safety follow-up visits. Measurement of BMI added to non-treatment period
Rationale for change		For consistency with Flow Chart 1.2

Number of global amendment		3
Date of CTP revision		13 April 2017
EudraCT number		2015-003718-25
BI Trial number		1302.3
BI Investigational Product(s)		BI 695502
Title of protocol		A single arm, open-label, multicenter, multinational, safety and efficacy Phase IIIb trial of BI 695502 plus mFOLFOX6 in patients with previously untreated metastatic colorectal 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		5.3.1, Physical Examination
Description of change		The rectal examination was made optional.
Rationale for change		The rectal examination was made optional since it is not routinely done in all the US practices as part of physical examination and to allow the use of alternate reliable diagnostic methods if needed.

Number of global amendment		4
Date of CTP revision		26 October 2017
EudraCT number		2015-003718-25
BI Trial number		1302.3
BI Investigational Product(s)		BI 695502
Title of protocol		A single arm, open-label, multicenter, multinational, safety and efficacy Phase IIIb trial of BI 695502 plus mFOLFOX6 in patients with previously untreated metastatic colorectal 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		Title page
Description of change		The trial number has been updated to: 1302.3 (INVICTAN®-3).
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.
Section to be changed		Flow chart 1.1. Flow chart 1.2.
Description of change		The following footnote was added: Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection as per local laboratory practices. Suspend BI 695502 administration for proteinuria ≥2 g in 24 hours and resume when proteinuria is <2 g in 24 hours. If moderate to severe proteinuria (2+ or greater urine dipstick reading) cannot be controlled within 14 days then the patient should discontinue BI 695502.
Rationale for change		To clarify how to manage proteinuria in patients with a 2+ or greater urine dipstick reading.

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: 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 ECGs is optional.
Section to be changed		Flow chart 1.1. Flow chart 1.2. 5.2.2, Objective response.
Description of change		Text updated to clarify that tumor assessment will be performed every 8 weeks (±3 days) up to Visit 21, every 12 weeks (±3 days; ±7 days from Visit 28 onwards) from Visit 21 onwards and every 8 weeks (±3 days) during the non-treatment period. In addition, the following text was added to the footnote in Flow chart 1.2: No CT scan is needed at Visit 28 if the patient received a CT scan at Visit 27.
Rationale for change		To clarify the timing of tumor assessments; specifically, to highlight that tumor assessment is not required at Visit 28 if the patient received a tumor assessment at Visit 27.

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Section to be changed		4.1.4, Drug assignment and administration of doses for each patient
Description of change		The following text was added: Slight variations in BI 695502 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		5.3.4, Electrocardiogram.
Description of change		The first paragraph in the section was updated to: Two consecutive resting 12-lead electrocardiograms (ECG) 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.
Rationale for change		To clarify that the second of the consecutive ECGs is optional.
Section to be changed		9.1, Published references.
Description of change		Details for references R15-2488, R15-4640, R10-2544 and R13-5293 were updated.
Rationale for change		Administrative update.
Section to be changed		10.2, Guidelines for BI 695502 preparation and administration.
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.
Rationale for change		The use of polyethylene bags for infusion of BI 695502 is now permitted in this trial. The use of polybutadiene infusion sets is common in day-to-day clinical practice. The use of infusion sets made of polybutadiene

		for administration of BI 695502 is now permitted in this trial.
Section to be changed		10.2, Guidelines for BI 695502 preparation and administration.
Description of change		The mandatory concentration of BI 695502 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. The following text was added: 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 the risk for the patient.

Number of global amendment		5
Date of CTP revision		17 January 2018
EudraCT number		2015-003718-25
BI Trial number		1302.3
BI Investigational Product(s)		BI 695502
Title of protocol		A single arm, open-label, multicenter, multinational, safety and efficacy Phase IIIb trial of BI 695502 plus mFOLFOX6 in patients with previously untreated metastatic colorectal 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 the protocol
Description of change		Text has been revised where applicable to state “BI 695505 or Avastin®” instead of BI 695502
Rationale for change		To clarify where applicable that the trial medication may be either BI 695502 or Avastin® as a result of the switch
Section to be changed		Synopsis, 3.1, 4.1.1, 4.1.2, Flow chart 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.

Section to be changed		Synopsis, Flow chart 1.2, 3.1, 6.1, 6.2.3
Description of change		The text has been modified to state that the 30-day follow-up visit will take place after the last administration of BI 695502 or Avastin®, whichever occurs later
Rationale for change		To clarify that the 30-day FU visit will take place after the last dose of medication in the trial, which could be either BI 695502 or Avastin® after the swtich visit
Section to be changed		Synopsis, 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. 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. Patients who are still being seen at the site every 3 weeks will not need an additional SFU visit.
Section to be changed		Synopsis, Flow chart 1.2, 6.2.3, 8.6
Description of change		The end of trial definition has been updated to take account of patients that may continue to receive Avastin beyond the 18-week SFU visit.
Rationale for change		To update the end of trial definition to accurately reflect the updated trial design
Section to be changed		Synopsis, 4.1.4, Appendix 10.2
Description of change		Text has been added to state that filters must be used for Avastin® administration
Rationale for change		To ensure patients safety, filters must be used for all Avastin® infusions the same as for BI 695502 administration
Section to be changed		Synopsis, 7.3
Description of change		Text has been added to describe the period covered by the main analyses plus that

		appropriate censoring methods will be applied at the time of switching. 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
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
Rationale for change		To provide detailed information on what assessments need to be performed at the Switch Visit
Section to be changed		2.3
Description of change		Text has been added to state that 5 DSMB meetings have taken place during the 1302.5 study to date
Rationale for change		To provide further information on the DSMB meetings that have occurred in study 1302.5 and that all meetings recommended the continuation of the trial without modification
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.
Section to be changed		4.1.6
Description of change		Text has been added to state that Avastin® will be provided as commercially labeled drug and that relabeling for trial purposes is not required
Rationale for change		To clarify Avastin® supply and labeling
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 not need to 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		5.6.1
Description of change		The text has been updated to clarify the shipping process for nADA samples.
Rationale for change		To ensure consistency in the shipment frequency for nADA samples between the protocol and the laboratory manual

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 assessments to be performed
Section to be changed		Table 6.1: 1
Description of change		The blood volumes have been updated to include the addition sampling for the Switch visit
Rationale for change		To update the total estimated blood volumes.
Section to be changed		6.2.2
Description of change		Text has been added to state that the sites will not be required to contact IXRS after the switch onwards, but when the patient discontinues treatment, IXRS should be contacted to perform the discontinuation call.
Rationale for change		To clarify the process for contacting IXRS after the switch visit
Section to be changed		7.3.3
Description of change		Text has been added to describe that TEAE definitions after the switch visit will be defined in the TSAP
Rationale for change		To clarify that the definition of TEAEs after switching will be clarified in the TSAP and not explained in the protocol
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		8.4.1
Description of change		Text has been added to provide the reference documents for the evaluation of listedness for Avastin®
Rationale for change		To provide the reference documents for the evaluation of listedness for new trial

		medication, Avastin®
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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Document Name: clinical-trial-protocol-version-06

Title: A single arm, open-label, multicenter, multinational, safety and efficacy Phase IIIb trial of BI 695502 plus mFOLFOX6 in patients with previously untreated metastatic colorectal cancer

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Pharmacokinetics		18 Jan 2018 10:52 CET
Approval-Team Member Medicine		18 Jan 2018 10:53 CET
Author-Trial Clinical Monitor		18 Jan 2018 10:56 CET
Author-Trial Statistician		18 Jan 2018 11:25 CET
Approval-Therapeutic Area		18 Jan 2018 15:27 CET
Verification-Paper Signature Completion		23 Jan 2018 16:43 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed