Clinical Trial Protocol

	Document Number:	**c09542349-05**
EudraCT No.: **EU Trial No:**	2016-000612-14	
BI Trial No.:	1297.4	
BI Investigational Product(s):	BI 695501	
Title:	BI 695501 versus Humira® in patients with active Crohn's disease: a randomized, double-blind, multicenter, parallel group, exploratory trial comparing efficacy, endoscopic improvement, safety, and immunogenicity	
Lay Title:	BI 695501 versus Humira in patients with active Crohn's disease: a trial comparing efficacy, endoscopic improvement, safety, and immunogenicity	
Clinical Phase:	III	
Trial Clinical Monitor:	Tel.:	
Coordinating Investigator:		
Status:	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date:	Version: 3.0	Date: 12 Dec 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**NA**	
Name of active ingredient:		**BI 695501**	
Protocol date: 30 May 2016	**Trial number:** 1297.4		**Revision date:** 12 Dec 2017

Title of trial:	BI 695501 versus Humira® in patients with active Crohn's disease: a randomized, double-blind, multicenter, parallel-group, exploratory trial comparing efficacy, endoscopic improvement, safety, and immunogenicity
Coordinating Investigator:	
Trial site(s):	Multinational, multicenter trial in approximately 125 clinical sites across approximately 15 countries in the US and the EU
Clinical phase:	III
Objective(s):	Primary Objective: The primary objective of this trial is to compare the clinical efficacy of BI 695501 with EU-approved Humira® in patients with active Crohn's disease (CD). Secondary Objectives: The secondary objectives of this trial are to compare the efficacy and safety of BI 695501 with EU-approved Humira across the induction and maintenance phases.
Methodology:	This is an exploratory, randomized, 56-week, double-blind, parallel arm, multiple dose, active comparator trial of BI 695501 and EU-approved Humira, with a 48-week treatment period and a 10-week follow-up period (starting after the last dose of trial medication at Week 46) in patients with moderately to severely active CD and a primary endpoint assessment at Week 4. The treatment phase of the trial will encompass 2 parts, the induction period, ranging from baseline to Week 4, and the maintenance period, from Week 4 to Week 48.

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	Patients who meet the inclusion and exclusion criteria will be randomly assigned in a blinded fashion to either BI 695501 or EU-approved Humira with a 1:1 allocation ratio in the first phase of this trial (induction). Each patient will receive a loading dose of 160 mg of BI 695501 or EU-approved Humira (Day 1), followed by 80 mg of BI 695501 or EU-approved Humira 2 weeks later (Day 15), thereafter 40 mg of BI 695501 or EU-approved Humira every second week. Initial randomization will be stratified according to prior exposure to infliximab (yes/no) and to screening SES-CD (<16 or ≥16). No caps will be put on any of these strata. At Week 4, clinical response will be assessed and only patients who are classified as responders by achieving a decrease in CDAI ≥70 will continue on trial and enter the maintenance phase. The hematocrit value required to determine CDAI score at Week 4 will be assessed locally and confirmed via central laboratory assessment. Patients who are originally randomized to EU-approved Humira will switch to BI 695501 at Week 24. In addition, every effort should be made for all patients who complete the total 48-week treatment period or who discontinue the trial medication early during the maintenance phase, to have an End of Treatment Visit as soon as possible after completion/discontinuation and to return for a Safety Follow-up Visit 10 weeks after the last dose of trial medication.
No. of patients:	
total entered:	Approximately 130 evaluable patients will be randomized
each treatment:	Initially patients will be allocated to treatment in a 1:1 ratio to receive BI 695501 or EU-approved Humira
Diagnosis :	Moderately to severely active CD, for more than 4 months
Main criteria for inclusion:	Adult patients, between 18 and 80 years of age, with moderately to severely active CD (CDAI 220-450), confirmed by endoscopy or radiologic evaluation for more than 4 months. Evidence of mucosal ulceration has to be documented by recorded ileocolonoscopy during trial screening.
Test product:	BI 695501, solution for s.c. injection in single-use pre-filled syringe (PFS) (40 mg/0.8 mL)
dose:	After randomization at Day 1: four PFS, corresponding to 160 mg of the test product At Day 15: two PFS corresponding to 80 mg of the test product At Day 29: one PFS corresponding to 40 mg of the test product and thereafter, every 2 weeks, 40 mg of the test product via PFS
mode of administration:	subcutaneous injection

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Comparator product:	EU-approved Humira, solution for s.c. injection in single-use PFS (40 mg/0.8 mL or 40 mg/0.4 mL)
dose:	After randomization at Day1: four PFS, corresponding to 160 mg of the comparator product At Day 15: two PFS corresponding to 80 mg of the comparator product At Day 29: one PFS corresponding to 40 mg of the comparator product and thereafter, every 2 weeks, 40 mg of the comparator product via PFS
mode of administration:	subcutaneous injection
Duration of treatment:	The trial will consist of a screening period of up to a maximum of 28 days and a 48-week treatment period. Each patient will be treated with either BI 695501 or EU-approved Humira for 4 weeks (induction) and responders will be treated in the maintenance phase for an additional 44 weeks. Patients who are originally randomized to EU-approved Humira will switch to BI 695501 at Week 24. A 10-week safety follow-up period without treatment is implemented.
Endpoints	Primary endpoint: • Proportion of patients in each treatment group with a clinical response (CDAI decrease of ≥70 compared with baseline) at Week 4 Secondary endpoints: <u>Efficacy</u> • Proportion of patients in each treatment group with a clinical response (CDAI decrease of ≥70 compared with baseline) at Week 24 • Proportion of patients in each treatment group in clinical remission (CDAI <150) at Week 24

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Safety

- Proportion of patients with AEs, SAEs, and AESIs
- Proportion of patients with infections/serious infections (seriousness of infection defined as requirement of i.v. antibiotics for treatment and/or meeting seriousness criteria to be qualified as an SAE)
- Proportion of patients who experience hypersensitivity reactions
- Proportion of patients who experience DILI
- Proportion of patients with injection-site reactions

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Safety criteria:	Safety assessments include continuous AE monitoring and local tolerability assessment, physical examination, vital signs (blood pressure, pulse rate, and body temperature), TB test (IGRA), 12-lead ECG, injection site reaction assessment, and laboratory tests.
Statistical methods:	This trial is intended to generate additional information for the comparison of BI 695501 with EU-approved Humira in patients with active Crohn's disease. The statistical model for the analysis of the primary endpoint will be a log-linked binomial regression model. The model will include the stratification factors (prior exposure to infliximab [yes/no] and baseline SES-CD [<16 or ≥16]) and treatment as fixed, categorical effects.. For the primary and secondary endpoints, point estimates (risk difference for binary endpoints) together with their 90% and 95% CIs will be calculated, but will be interpreted in a descriptive manner. The safety population will consist of all patients who receive at least one (full or partial) dose of either of the trial treatments during any dosing period. The analysis of AEs will be based on the concept of treatment-emergent AEs. That means that all AEs with an onset after the first dose of trial medication up to a period of 10 weeks after the last dose of the trial medication will be assigned to the current treatment for evaluation.

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	Adverse events that start before first drug intake and deteriorate under treatment will also be considered as treatment-emergent. Other AEs will be assigned to the appropriate trial phases, i.e., screening or post-treatment. Safety endpoints and AESIs will be presented descriptively; in addition RR and risk difference together with 95% CIs will be presented.		

FLOW CHART A: SCREENING AND INDUCTION PERIOD

Trial Period	**Screening**		**Induction**			**EoT[2]**	**SFU[2]**
Visit	**1**	**1.1**	**2[1]**	**3**	**4**		
Week	**-4 to -2**	**-1**	**0 (Baseline)**	**2**	**4**	**-**	**14**
Day	**-28 to -14**	**-9**	**1**	**15**	**29**	**-**	**99**
Permitted visit window (days)	**-**	**±2**	**-1/+2**	**±1**	**±1**	**±3**	**+7**
Informed consent	X						
Assessment of eligibility	X	X	X				
Demographics	X						
Medical and surgical history, incl. history of opportunistic infection	X						
LABS/SAFETY ASSESSMENTS							
Infection screen: hepatitis B (HBsAg), hepatitis C (antiHCV), and HIV test (where mandated by local authorities)	X						
Chest X-ray[3]	X						
TB testing (IGRA)[4]	X					X	
CRP/fecal calprotectin	X		X		X	X	
Pregnancy test[5]	X		X			X	X
Physical examination (incl. height and weight)[6]	X		X			X	X
Vital signs[7]	X		X	X	X	X	X
Laboratory tests (serum chemistry, hematology, urinalysis)[8]	X		X		X	X	X
Stool studies to evaluate for enteric pathogens	X						
12-lead electrocardiogram	X				X	X	X
Previous and concomitant therapy	X	X	X	X	X	X	X
Adverse events[9]	X	X	X	X	X	X	X
EFFICACY ASSESSMENTS							
CDAI evaluation[10]		X	X		X	X	
Endoscopy (mucosal ulceration, SES-CD)		X					

TRIAL MEDICATION							
Contact IRT[12]	X		X	X	X[13]		
Randomization			X[1]				
Trial medication administration[14]			X	X	X		

; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CDAI: Crohn's disease activity index; SES-CD: Simple Endoscopic Score for Crohn's Disease; CRP: C-reactive protein; EoT: End of Treatment; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IGRA: interferon-gamma release assay; IRT: Interactive Response Technology;
SFU: safety follow-up; TB: tuberculosis; ULN: upper limit of normal.

[1] Patients will be randomized to each treatment in a 1:1 ratio (BI 695501: EU-approved Humira).

[2] Patients who do not achieve a clinical response at Week 4 will be excluded from the maintenance period and will have their EoT visit at Week 4. Every effort should be made for all patients who discontinue to return for a Safety Follow-up Visit 10 weeks after their last dose of trial medication.

[3] A chest X-ray is to be taken at Screening. Alternatively, results from a chest X-ray taken within 12 weeks of Screening can be used.

[4] Patients must have a negative TB screening assessment, including an IGRA (e.g., QuantiFERON® TB Gold). In addition, a TB test will be performed at Week 24 before switch from EU-approved Humira to BI 695501, at EoT visit, and may be performed at any time during the trial if the investigator considers it clinically necessary.

[5] Females only: a serum pregnancy test at Screening and a urine pregnancy test on Day 1 (baseline); a urine pregnancy test will be performed at the applicable visits thereafter.

[6] Height to be measured at Screening only; weight at every physical examination.

[7] Includes measurement of blood pressure and pulse rate (both sitting after 5 minutes rest). The patient's body temperature will also be recorded.

[8] Findings of ALT or AST >1.5 times the ULN or hemoglobin <8.0 g/dL at Screening are criteria for exclusion.

[9] Adverse events will be collected from the time of informed consent. Adverse events continuing at the EoT Visit must be followed to resolution or follow-up as agreed by the investigator and medical monitor. For patients who complete the trial or who discontinue the trial early, new AEs will be captured until the end of the 10-week safety follow-up period.

[10] CDAI determination: where applicable, exclude the day of bowel preparation for colonoscopy due to misleading impact on assessment of pain and liquid stool frequency. The CDAI evaluation at Visit 1.1 will be performed based on the CDAI diary provided to the patient at Visit 1 (a minimum of 7 days must be allowed between visits for completion of the diary). For subsequent CDAI evaluations, the diary will be provided to the patient at the previous planned visit. At Visit 4 (Week 4), the hematocrit value to determine CDAI score will be assessed locally and confirmed via central laboratory assessment. At visits where no physical examination is performed, weight must be measured for use in CDAI determination.

[12] IRT will be contacted prior to every trial medication administration visit.

[13] Contact IRT to confirm whether or not patient has achieved a clinical response (CDAI decrease ≥70). Patients who are non-responders will have an EoT visit and every effort should be made to ensure that they return for a Safety Follow-up visit 10 weeks after their last dose of trial medication. Patients achieving a clinical response at Week 4 will be eligible to continue in the trial (maintenance period) as shown in Flow Chart B.

[14] Trial medication should be administered every 2 weeks (±1 day up to Visit 4). Patients will receive each dose of trial medication at the trial site until Week 22, trial medication will be administered by suitably qualified, designated unblinded trial personnel (Third party blinding). All assessments and procedures should be performed prior to trial medication administration, unless otherwise stated.

FLOW CHART B: MAINTENANCE PERIOD

Visit	**4**[1]	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Week	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**
Day	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**
Permitted visit window (days)	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
LABS/SAFETY ASSESSMENTS										
TB testing (IGRA)										
CRP/fecal calprotectin	X				X					
Pregnancy test[3]			X				X			
Physical examination (incl. weight)										
Vital signs[4]	X		X		X		X		X	
Laboratory tests (serum chemistry, hematology, urinalysis)	X		X				X			
12-lead electrocardiogram	X		X							
Previous and concomitant therapy	X		X		X		X		X	
Adverse events[5]	X		X		X		X		X	
EFFICACY ASSESSMENTS										
CDAI evaluation[6]	X				X					

TRIAL MEDICATION										
Contact IRT[9]	X	X	X	X	X	X	X	X	X	X
Switch from EU-approved Humira to BI 695501[10]										
Trial medication administration[11]	X	X	X	X	X	X	X	X	X	X

AE: adverse event; CDAI: Crohn's disease activity index; SES-CD: Simple Endoscopic Score for Crohn's Disease; CRP: C-reactive protein; EoT: End of Treatment; IGRA: interferon-gamma release assay; IRT: Interactive Response Technology; SFU: safety follow-up; TB: tuberculosis; Wk: Week.

1 Visit 4 (Week 4) in this flow chart applies only for patients assessed as achieving a clinical response (CDAI decrease ≥70). Non-responders will follow the visit schedule for Week 4, EoT, and SFU presented in Flow Chart A.

2 Patients who discontinue the trial early will, at discontinuation, have an EoT visit equivalent to the Week 48 assessments, but without an endoscopy. A Safety Follow-up visit will be performed 10 weeks after the EoT visit. Every effort should be made for all patients who complete the total 48-week treatment period to return for a Safety Follow-up Visit at Week 56.

3 Females only: a serum pregnancy test at Screening and a urine pregnancy test on Day 1 (baseline); a urine pregnancy test will be performed at the applicable visits thereafter.

4 Includes measurement of blood pressure and pulse rate (all sitting after 5 minutes rest). The patient's body temperature will also be recorded.

5 Adverse events will be collected from the time of informed consent. Adverse events continuing at the EoT Visit must be followed to resolution or follow-up as agreed by the investigator and medical monitor. For patients who complete the trial or who discontinue the trial early, new AEs will be captured until the end of the 10-week safety follow-up period.

FLOW CHART B: MAINTENANCE PERIOD (CONT'D)

Visit[1]	**14**	**15**	**16**	**17**	**18**	**19, 20, 21**	**22**	**23, 24, 25**	**EoT**[2]	**SFU**[2]
Week	**24**	**26**	**28**	**30**	**32**	**34, 36, 38**	**40**	**42, 44, 46**	**48**	**56**
Day	**169**	**183**	**197**	**211**	**225**	**239, 253, 267**	**281**	**295, 309, 323**	**337**	**393**
Permitted visit window (days)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**
LABS/SAFETY ASSESSMENTS										
TB testing (IGRA)	X								X	
CRP/fecal calprotectin	X								X	
Pregnancy test[3]	X				X		X		X	X
Physical examination (incl. weight)	X								X	X
Vital signs[4]	X		X		X		X		X	X
Laboratory tests (serum chemistry, hematology, urinalysis)	X				X		X		X	X
12-lead electrocardiogram	X								X	X
Previous and concomitant therapy	X		X		X		X		X	X
Adverse events[5]	X		X		X		X		X	X
EFFICACY ASSESSMENTS										
CDAI evaluation[6]	X								X	
Endoscopy (mucosal ulceration, SES-CD)									X[7]	

TRIAL MEDICATION										
Contact IRT[9]	X	X	X	X	X	X	X	X		
Switch from EU-approved Humira to BI 695501[10]	X									
Trial medication administration[11]	X	X	X	X	X	X	X	X		

6 CDAI determination: exclude the day of bowel preparation for colonoscopy due to misleading impact on assessment of pain and liquid stool frequency. Patients will be required to complete a CDAI diary (provided at the previous visit) for the last 7 days prior to CDAI evaluation. At Visit 8 (Week 12), the hematocrit value from the central laboratory assessment at Visit 6 (Week 8) will be used to determine CDAI score. At visits where no physical examination is preformed, weight must be measured for use in CDAI determination.

7 Only applicable for patients who complete the 48-week treatment period

9 IRT will be contacted prior to every trial medication administration visit.

10 At Week 24, all patients on EU-approved Humira will switch to BI 695501.

[11] Trial medication should be administered every 2 weeks (±1 day up to Visit 4 and ±3 days from Visit 5 onwards). Patients will receive each dose of trial medication at the trial site until Week 22, trial medication will be administered by suitably qualified, designated unblinded trial personnel (Third party blinding); for remaining doses (Week 24 onwards), any suitably trained trial personnel may administer the trial medication since all patients will be receiving BI 695501. The last dose of BI 695501 will be at Week 46 for patients who remain on treatment throughout the trial. All assessments and procedures should be performed prior to trial medication administration, unless otherwise stated.

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
CD	Crohn's disease
CDAI	Crohn's disease activity index
CI	confidence interval
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EoT	End of Treatment
EudraCT	European Clinical Trials Database
FAS	full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon-gamma release assay
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	intrauterine device
i.v.	intravenous
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Drug Regulatory Activities

MTX	methotrexate
nAb	neutralizing anti-drug antibody
NRI	non-responder imputation
PFS	pre-filled syringe
PK	pharmacokinetics
PPS	per-protocol set
RA	rheumatoid arthritis
REP	residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RR	risk ratio
SAE	serious adverse event
SAF	safety analysis set
s.c.	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SmPC	summary of product characteristics
SOP	Standard Operating Procedure
sTNF	soluble tumor necrosis factor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
tmTNF	transmembrane tumor necrosis factor
TNF	tumor necrosis factor
TSAP	Trial Statistical Analysis Plan
ULN	upper limit of normal

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Crohn's disease is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract characterized by abdominal pain, fever, and bloody or mucus-containing diarrhea (R13-2231). The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the ileum and colon (40%), followed by the small bowel only (30%), and the colon only (25%) (R13-2232, R13-2233). It occurs in a relatively young population, most commonly developing in people between the ages of 20 and 29, and there is no marked sex difference (R13-2231, R15-0886). Although the etiology of CD is still unknown, it is widely accepted that it is caused by a combination of environmental, immune, and bacterial factors in genetically susceptible individuals (R16-1919, R16-1918, R16-1917).

The incidence of CD in Europe and North America is approximately 161 to 319 cases per 100,000 people (R13-2231) and is less common in Asia and Africa (R16-1920, R16-1923). Historically, CD has been more common in the developed world (R16-1922); however, rates have been increasing, particularly in the developing world, since the mid-1970s (R16-1923, R16-1922).

Because of myriad symptoms, clinical status is measured using clinical indexes. The most widely used in clinical trials is the CDAI (R97-2689). At the mucosal level, the extent of disease can be graded following ileocolonoscopy according to the SES-CD (R14-2969, R15-6247).

Current treatment options

Medical treatment for CD has two main goals: achieving remission and, once that is accomplished, maintaining remission (prevention of flares). Treatment is, thus, aimed at controlling the ongoing inflammation in the intestine, the cause of IBD symptoms.

Medical therapy used in clinical practice includes 5-ASA and antibiotics (for colonic disease), corticosteroids, immunosuppressant drugs, and biologic agents. The latter is the newest class of drugs to be used in IBD and includes three of the available anti–TNF-alpha agents (infliximab, adalimumab, certolizumab pegol), as well as vedolizumab (Entyvio®) and natalizumab (Tysabri®). Biologic therapies offer a distinct advantage in the treatment of IBD since their mechanism of action is targeted. Unlike corticosteroids, which tend to suppress the entire immune system and thereby produce major side effects, biologic agents act more selectively. However, immunosuppression-related side effects, such as an enhanced incidence of infections, are also described for biologic agents.

Nutritional support also has a role as primary therapy or as adjunct to other treatment. When medical treatment is unsuccessful or with certain complications, surgery is indicated. More than 70% of patients with ileal disease will require surgery at least once during the course of their disease. Due to therapeutic failures and serious side effects of present therapies, alternatives continue to be needed.

1.2 DRUG PROFILE

BI 695501 is a monoclonal antibody being developed as a proposed biosimilar to the TNF-alpha blocker, adalimumab (US-licensed Humira and EU-approved Humira). Adalimumab is a recombinant humanized monoclonal IgG1 antibody specific to human TNF-alpha. It has human-derived heavy and light chain variable regions and human IgG1:kappa constant regions and is produced in a mammalian cell expression system (R15-5978, R15-4915).

For a more detailed description of the BI 695501 profile, please refer to the current IB, and for Humira, to the SmPC or US Prescribing Information.

Humira binds specifically to TNF-alpha (not to TNF-beta) and blocks its interaction with the p55 and p75 cell surface TNF receptors. Humira has also been shown to lyse cells expressing surface TNF *in vitro* in the presence of complement and modulate biological responses that are induced or regulated by TNF, including changes in adhesion molecules responsible for leukocyte migration (endothelial leukocyte adhesion molecule-1, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1) (R15-5978).

In contrast to rheumatological indications, where binding and neutralization of soluble TNF is the prominent feature of adalimumab's pharmacodynamic activity, clinical efficacy in IBD requires additional effects attributable to interaction of adalimumab with tmTNF, subsequently leading to reverse signaling (T cell apoptosis, inhibition of cytokine release from macrophages) and induction of complement dependent cytotoxicity / antibody-dependent cell-mediated cytotoxicity. The contribution of each of these effects is still a matter of scientific debate.

Humira (adalimumab) has received regulatory approval for CD in the US, the EU, and many other countries (R15-5978, R15-4915).

Humira has a generally favorable clinical safety profile, and is not associated with AEs that would suggest a high risk to patients participating in this trial. In patients treated with Humira, most common adverse reactions (incidence >10%) include infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash, abdominal pain, musculoskeletal pain, nausea, and vomiting. Allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

Cases of hepatitis B virus reactivation have been reported in patients receiving anti-TNF therapy. Some cases have been fatal, the majority of which were in patients concomitantly receiving other immunosuppressive medications.

Tuberculosis reactivation or new TB infections have been observed in patients receiving Humira and other TNF-inhibitors, including patients who had previously received treatment for latent or active TB.

In the controlled portions of clinical trials of some TNF-blockers, including Humira, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. Malignancies were rare side effects in clinical trials of Humira, with non-melanoma skin cancer and lymphoma most frequently reported; other malignancies included breast, colon, prostate, lung, and melanoma.

Humira was evaluated in over 1500 adult patients with moderately to severely active CD (CDAI ≥220 and ≤450) in trials that were performed prior to approval, with some patients followed for at least 3 years of open-label adalimumab. In the European Medicines Agency SmPC, three randomized, double-blind, placebo-controlled studies were reported for Humira, which assessed the efficacy and safety of Humira for the treatment of CD (R15-4915).

The analytical similarity between BI 695501 and US-licensed Humira was assessed in a single-dose PK study in the cynomolgus monkey and a local tolerance study in rabbits. Additionally, the PK similarity between BI 695501, US-licensed Humira and EU-approved Humira was assessed in a Phase I clinical trial (1297.8) in healthy volunteers. The results of these studies are provided in the IB.

The PK similarity of BI 695501 to US-licensed Humira and EU-approved Humira was demonstrated in a healthy volunteer study (c03070713). Single s.c. doses of 40 mg BI 695501, US-licensed Humira and EU-approved Humira were generally well tolerated by healthy male subjects. There were no notable differences between the 3 treatment arms with respect to safety, tolerability, and immunogenicity. Including both Phase I studies, a total of 175 subjects were exposed to BI 695501.

Overall, the AEs seen in healthy subjects for BI 695501 and both EU-approved Humira and US-licensed Humira were in line with the known safety profile presented in the US prescribing information for Humira (R15-5978) and in the SmPC for EU-approved Humira (R15-4915).

A Phase III trial (1297.2) in patients with moderate to severe RA is ongoing. A total of 645 patients with moderate to severe RA were included in this blinded trial and are being treated with either BI 695501 or US-licensed Humira, monitored by an IDMC.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The CD trial 1297.4 is intended to generate comparative PK, efficacy, safety, and immunogenicity data in an indication where these modes of adalimumab's action are important. The aim is to explore similarity of sTNF and tmTNF-related effects, initially established by the extrapolation approach which is based on comparative analytical testing and preclinical models, and has allowed extrapolation across indications.

The 1297.4 trial will also address switching between EU-approved Humira and BI 695501, as well as treatment of infliximab pre-treated patients after secondary resistance, both scenarios reflecting daily clinical practice in the future.

The primary outcome measure is defined as CDAI at Week 4,

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to compare the clinical efficacy of BI 695501 with EU-approved Humira in patients with active CD.

The secondary objectives of this trial are to compare the efficacy and safety of BI 695501 with EU-approved Humira across the induction and maintenance phases, as covered by CDAI and safety monitoring.

2.3 BENEFIT - RISK ASSESSMENT

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

Patient risk will be minimized in this trial by implementing conservative eligibility criteria.

Adverse events, body temperature, vital signs, ECGs, and safety laboratory results as well as immunogenicity will be monitored at different time points during the trial and during the long-term safety follow-up period up to 10 weeks after the last administration of trial medication.

Although rare, a potential for 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.

All safety aspects will be regularly monitored by both the sponsor and a CRO during the Medical Quality Review Meetings.

To avoid a risk of reactivating TB and other infections, TB tests (IGRA), HBsAg (qualitative), hepatitis B antibody (qualitative), hepatitis C antibodies (qualitative), HIV-1 and HIV-2 antibody (qualitative) will be performed to exclude patients testing positive.

In the controlled portions of clinical trials of some TNF-inhibitors, including Humira, more cases of malignancies have been observed among TNF-inhibitor-treated adult patients compared to control-treated adult patients. Therefore, a possibly increased risk for the development of malignancies cannot be excluded.

The PK similarity of BI 695501 to US-licensed and EU-approved Humira was established in the Phase I trial 1297.8 (c03070713). Additionally, there were no notable differences with respect to safety, tolerability, and immunogenicity between BI 695501 and US-licensed and EU-approved Humira in this Phase I trial, and the dose of 40 mg BI 695501 was safe and well tolerated in healthy male volunteers. The observed blinded AE profile in the Phase III trial 1297.2 has thus far revealed no unexpected safety. The review of safety data by the IDMC to date has not suggested any clinically relevant differences in safety profile between Humira and BI 695501.

There have been no major clinically relevant findings with respect to clinical laboratory evaluation, vital signs, ECGs, or injection site reactions (including anaphylactic or allergic reactions). 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 695501, as a proposed biosimilar to Humira, is expected to show a similar efficacy, safety, immunogenicity, and PK profile in patients with CD.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is an exploratory, randomized, 56-week, double-blind, parallel arm, multiple dose, active comparator trial of BI 695501 and EU-approved Humira, with a 48-week treatment period and a 10-week follow-up period (starting after last dose of trial medication at Week 46) in patients with moderately to severely active CD, and a primary endpoint assessment at Week 4.

The trial will consist of a Screening period of up to a maximum of 28 days, a 48-week treatment period consisting of an induction period from Baseline to Week 4 and a maintenance period from Week 5 to Week 48, and a 10-week safety follow-up period (starting after last dose of trial medication at Week 46).

Approximately 130 evaluable patients with moderately to severely active CD will be randomized into the trial. Patients will be randomly assigned to receive either BI 695501 or EU-approved Humira according to the randomization ratio and the stratification factors as described in Section 7.6. Each patient will receive a loading dose of 160 mg of BI 695501 or EU-approved Humira (Day 1), followed by 80 mg of BI 695501 or EU-approved Humira 2 weeks later (Day 15), and thereafter 40 mg of BI 695501 or EU-approved Humira every 2 weeks until the end of the treatment period (Week 46; with End of Treatment [EoT] evaluations at Week 48). Trial medication will be administered by s.c. injection.

At Week 4, patients will be assessed and those who are classified as responders (CDAI decrease of ≥70 compared to baseline) will continue on trial and enter the maintenance phase. Patients who are originally randomized to EU-approved Humira will switch to BI 695501 at Week 24.

Patients will undergo up to 27 visits (including 13 trial medication administration only visits) over the duration of the trial (56 weeks). The trial procedures to be undertaken at each visit are shown in Flow Chart A and Flow Chart B.

The primary endpoint of the trial is the proportion of patients in each treatment group with a clinical response (CDAI decrease of ≥70 compared to baseline) at Week 4. The primary analysis will take place when the last patient has completed the Week 4 assessments. For more details, please refer to Section 7.4.1.

Patients who discontinue the trial will, at discontinuation, have an EoT visit (see Flow Chart A and Flow Chart B). Every effort should be made for all patients who complete the total 48-week treatment period or who discontinue the trial medication early, to return for a Safety Follow-up Visit 10 weeks after their last dose of trial medication.

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

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

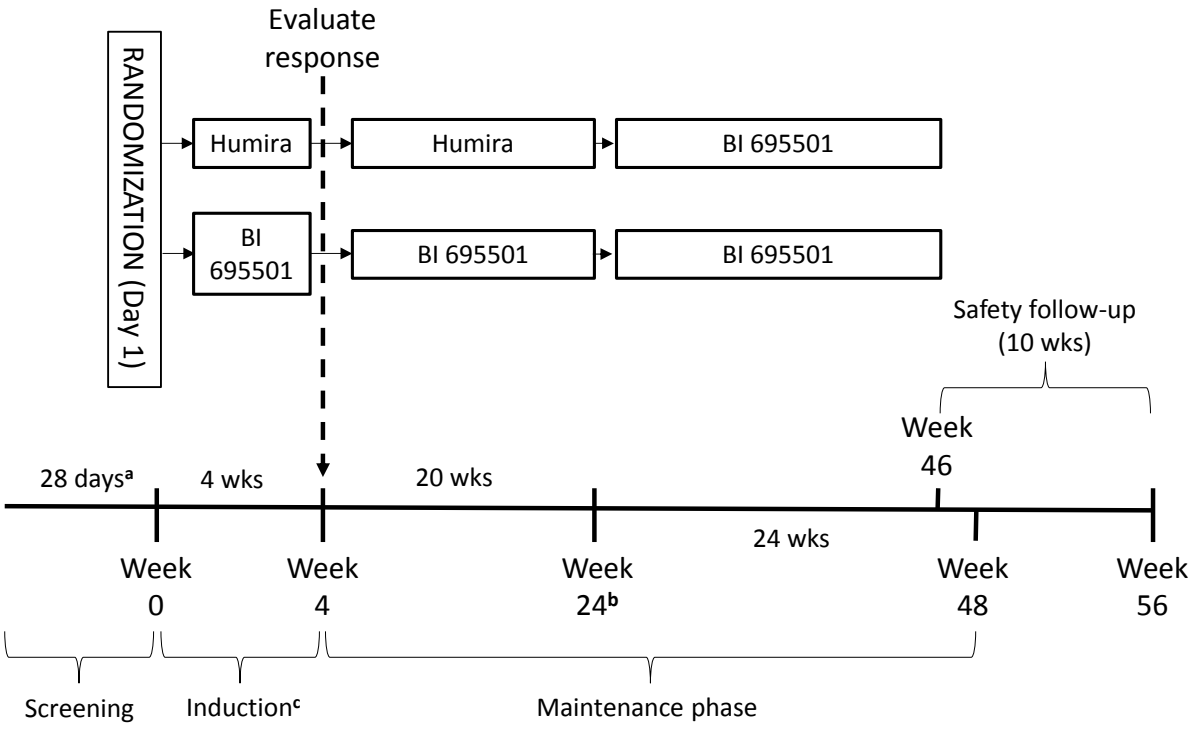


Figure 3.1: 1 Overview of trial design

wks: weeks.
Note: In the figure, Humira represents EU-approved Humira.

a Screening period of 28 days to include 2 visits (Visit 1 during the period Day -28 to Day -14 and Visit 1.1 on Day -9 ± 2 days).

b At Week 24, patients initially randomized to EU-approved Humira will switch to receive BI 695501 for the remainder of the treatment period.

c Induction phase will comprise the following doses of trial medication: a loading dose of 160 mg on Day 1 and a second dose of 80 mg at Week 2 (Day 15). Evaluation of clinical response will be performed at the Week 4 visit and only responders will continue in the trial.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim. Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for the planning, conduct, and reporting of the trial outsourced to a CRO in accordance with the applicable regulations and Boehringer Ingelheim/CRO SOPs.

The CRO will perform Project Management, Clinical Field Monitoring, Medical Monitoring, Data Management, Statistical Evaluation, and Medical Writing according to CRO 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 to coordinate 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 at the CRO.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The current trial is being performed to compare the clinical efficacy of BI 695501 with EU-approved Humira in patients with moderately to severely active CD. Additionally, the safety of BI 695501 will be assessed during long-term treatment and after switching from EU-approved Humira.

This is an exploratory, randomized, 56-week, double-blind, parallel arm, multiple dose, active comparator trial of BI 695501 and EU-approved Humira, with a 48-week treatment period and a 10-week follow-up period (starting from Week 46), in patients with moderately to severely active CD.

Patients will be randomized according to a 1:1 ratio to either BI 695501 or EU-approved Humira in a blinded fashion. At Week 4, patients will be assessed and those who are classified as responders, by achieving a decrease in CDAI ≥70, will continue the trial and enter the maintenance phase.

3.3 SELECTION OF TRIAL POPULATION

In view of the TNF-blocking mechanism of adalimumab, care has been taken to exclude patients likely to be at greater risk of severe infection, severe immunosuppression or severe heart failure (see Section 3.3.3).

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.

3.3.1 Main diagnosis for trial entry

Patients must have moderately to severely active CD (CDAI 220-450), confirmed by endoscopy or radiologic evaluation for more than 4 months, with evidence of mucosal ulceration documented by recorded ileocolonoscopy during trial screening.

Please refer to Section 8.3.1 (Source documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Males and females aged ≥18 and ≤80 years at Screening who have a diagnosis of moderate to severely active CD, confirmed by endoscopy or radiologic evaluation, for

more than 4 months with evidence of mucosal ulceration. Patients must have all of the following:

   a. CDAI score of ≥220 and ≤450
   b. A diagnosis of CD confirmed by ileocolonoscopy during Screening
   c. Presence of mucosal ulcers in at least one segment of the ileum or colon and a SES-CD score ≥7 (for patients with isolated ileal disease SES-CD score ≥4), as assessed by ileocolonoscopy and confirmed by central independent reviewer(s) before randomization

2. Anti-TNF naïve patients or patients previously treated with infliximab who had initially responded and who meet one of the following criteria:
   a. Responded and developed secondary resistance due confirmed anti-infliximab ADA formation, which caused infliximab depletion
   b. Responded and became intolerant
3. Willing to undergo up to 3 endoscopies
4. For participants of reproductive potential (males and females[1]), a reliable means of contraception has to be used throughout trial participation. Acceptable methods of birth control include, for example, birth control pills, IUDs, surgical sterilization, vasectomized partner, and double barrier method (for example male condom in combination with female diaphragm/cervical cap plus spermicidal foam/gel/film/cream/suppository). All patients (males and females of childbearing potential) must also agree to use an acceptable method of contraception for 6 months following completion or discontinuation from the trial medication.
5. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

1. Patients with ulcerative colitis or indeterminate colitis
2. Patients with symptomatic known obstructive strictures
3. Surgical bowel resection performed within 6 months prior to Screening or planned resection at any time while enrolled in the trial
4. Patients with an ostomy or ileoanal pouch
5. Patients with short bowel syndrome

[1] Women of childbearing potential are defined as:
- having experienced menarche,
- not postmenopausal (12 months with no menses without an alternative medical cause), and
- not permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

6. Patients currently receiving total parenteral nutrition
7. Patients who have received any investigational chemical agent in the past 30 days or 5 half-lives prior to Screening (whichever is longer)
8. Patients who have received any biological treatment (other than TNF inhibitors) or investigational biological agent with the exception of infliximab within 6 months prior to Screening
9. Patients who have previously used infliximab and have never clinically responded
10. Patients who have previously received treatment with adalimumab, or who have participated in an adalimumab or adalimumab biosimilar clinical trial
11. Patients who have received systemic antibiotic, antiviral, or antifungal treatment(s) within 3 weeks prior to Screening for any non-Crohn's related infections
12. Patients taking combined budesonide and prednisone (or equivalent) at 4 weeks prior to randomization
13. Patients who have undergone therapeutic enemas within 2 weeks prior to Screening
14. Patients who have received cyclosporine (i.v. or oral), tacrolimus, sirolimus (rapamycin), thalidomide, or mycophenolate mofetil within 8 weeks prior to Screening
15. Patients who have received live vaccines within 3 months prior to Screening
16. Patients with a history of clinically significant drug or alcohol abuse within 1 year prior to Screening that, in the investigator's opinion, makes them an unreliable trial subject or unlikely to complete the trial
17. History of severe allergy or hypersensitivity, including allergy to the trial medication, its excipients or device materials (e.g., natural rubber or latex)
18. Patients with a poorly controlled medical condition such as: uncontrolled diabetes with documented history of recurrent infections, unstable ischemic heart disease, congestive heart failure, recent cerebrovascular accidents, or any other condition which, in the opinion of the investigator or the sponsor, would put the patient at risk by participation in the trial
19. Have a stool culture or other examination positive for an enteric pathogen, including *Clostridium difficile* toxin, in the last 4 months unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen
20. Patients with a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly
21. Patients with any known malignancy or a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ, or cervical carcinoma in situ that has been treated with no evidence of recurrence, within 5 years prior to Screening)
22. History or current evidence of listeria, HIV, an immunodeficiency syndrome, central nervous system demyelinating disease, or TB

23. Positive serology for hepatitis B or hepatitis C, or a positive TB test (IGRA e.g., QuantiFERON® TB Gold) at Screening
24. Laboratory or other analyses at Screening (Visit 1) that show any of the following clinically relevant results, as assessed by the investigator:
    a. ECG with any clinically significant abnormalities
    b. AST or ALT >1.5 times upper limit of the reference range
    c. Hemoglobin <8.0 g/dL
    d. Platelets <100,000/µL
    e. Leukocyte count <4000/µL
    f. Total bilirubin ≥3 mg/dL
    g. Creatinine clearance <60 mL/min
25. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
26. Previous enrolment and treatment in this trial
27. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s)
28. Women who are pregnant at Screening (Visit 1), nursing, or who plan to become pregnant while in the trial and for 6 months after the last dose of trial medication

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An excessive withdrawal rate from the trial can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

Patients who do not meet all of the inclusion criteria or who meet one or more of the exclusion criteria will not be randomized, will be considered screen failures. The primary reason for the screen failure will be recorded on the eCRF. Patients may be rescreened if the investigator considers that the reason for screen failure may be resolved after a suitable period.

Patients have the right to withdraw from this trial at any time for any reason.

Two situations can occur in this trial and need to be documented accordingly:

a) An individual patient is to be withdrawn from the trial if:

- The patient decides to discontinue participation in the trial by withdrawal of consent. In this case, no more investigations will be performed. The patient does not have to justify the decision.

b) Based on assessment by the investigator, an individual patient is to be discontinued from treatment with the investigational compound if:

- Lack of efficacy: absence of a clinical response at Week 4, defined as a decrease in CDAI of ≥70.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- Development of a toxicity or AE which warrants treatment discontinuation including, but not limited to, SAEs or SUSARs.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy).
- The patient has an AE that is categorized as a serious infection (infections requiring i.v. antibiotics or meeting the regulatory definition of an SAE [including, but not limited to systemic fungal infections, HIV, hepatitis B, hepatitis C]).
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

If a patient permanently discontinues from trial medication for any reason, every effort should be made for the patient to attend the EoT Visit as soon after trial discontinuation as possible. For patients who discontinue the trial medication early (and do not withdraw consent), every effort should be made to follow the patients for efficacy assessments Week 48, wherever possible. In addition, every effort should be made for all patients who complete the total 48-week treatment period or who discontinue the trial early, to return for a safety follow-up visit 10 weeks after the last dose of trial medication.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow-up as outlined in Flow Chart A or Flow Chart B, as appropriate, 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.

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 for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the CTP, or the contract 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 INVESTIGATIONAL TREATMENTS

The trial medication will be provided by Boehringer Ingelheim or a designated CRO.

4.1.1 Identity of the Investigational Medicinal Products

BI 695501 and EU-approved Humira will be used in this trial. Details of the trial medication are provided in Table 4.1.1: 1 and Table 4.1.1: 2.

Table 4.1.1: 1 Test product

Substance:	BI 695501
Pharmaceutical formulation:	Solution for injection in PFS
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	40 mg / 0.8 mL
Posology	160 mg on Day 1 (after randomization); 80 mg on Day 15 (Week 2); 40 mg every 2 weeks from Week 4 to Week 46 inclusive (and from Week 24 to Week 46 inclusive for patients switching from EU-approved Humira)
Route of administration:	subcutaneous injection

Table 4.1.1: 2 Reference product

Substance:	EU-approved Humira (adalimumab)
Pharmaceutical formulation:	Solution for injection in PFS
Source:	
Unit strength:	40 mg / 0.8 mL or 40 mg / 0.4 mL
Posology	160 mg on Day 1 (after randomization); 80 mg on Day 15 (Week 2); 40 mg every 2 weeks from Week 4 to Week 22 inclusive
Route of administration:	subcutaneous injection

BI 695501 will be provided in sterile, preservative-free, non-pyrogenic, single-use PFS containing 40 mg of BI 695501 per 0.8 mL. On Day 1, four PFS will be used (total of 160 mg); on Day 15 (Week 2), two PFS will be used (total of 80 mg); and thereafter (Week 4, then every 2 weeks until Week 46 if patient is eligible to enter the maintenance phase; also

from Week 24 to Week 46 for patients who switch from EU-approved Humira), one PFS will be used per injection.

EU-approved Humira will be provided in sterile, preservative-free, non-pyrogenic, single-use PFS containing 40 mg of adalimumab per 0.8 mL or 40 mg of adalimumab per 0.4 mL (old and new formulations, respectively, approved to be comparable). On Day 1, four PFS will be used (total of 160 mg); on Day 15 (Week 2), two PFS will be used (total of 80 mg); and thereafter (Week 4, then every 2 weeks until Week 22 if patient is eligible to enter the maintenance phase), one PFS will be used per injection.

Any unused product or waste material will be disposed of in accordance with local requirements.

4.1.2 Selection of doses in the trial

In the US and EU, Humira has received health authority approval for the treatment of CD, RA, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis. The doses of BI 695501 and EU-approved Humira selected for this trial follow the approved posology of Humira for the treatment of CD (a loading dose of 160 mg, followed 2 weeks later by a dose of 80 mg, then 2 weeks later and subsequently every 2 weeks by 40 mg, all by s.c. injection).

4.1.3 Method of assigning patients to treatment groups

Once patients have completed screening, have met all of the inclusion criteria and not met any of the exclusion criteria, randomization will occur on Day 1 through a standard randomization visit call, using the IRT system. Patients will be randomized to each treatment in a 1:1 ratio (BI 695501: EU-approved Humira) according to the stratification factors defined in Section 7.6.

Each PFS of trial medication will be labeled with the trial code and a unique medication identification number. The IRT system will be used for the randomization, allocation, and supply of trial medication throughout the trial. The IRT will assign each patient unique medication numbers for each drug administration (each syringe will have a unique medication number). Details of the IRT system will be provided in the ISF.

4.1.4 Drug assignment and administration of doses for each patient

Each patient will receive 160 mg (loading dose) of BI 695501 or EU-approved Humira at the Baseline Visit (Day 1) followed by 80 mg of BI 695501 or EU-approved Humira 2 weeks later (Day 15/Week 2), and then 40 mg of BI 695501 or EU-approved Humira at Week 4 (primary endpoint).

At Week 4 (Day 29), patients achieving a clinical response (defined as a decrease in CDAI ≥70) will continue receiving their randomized treatment (40 mg BI 695501 or EU-approved Humira every 2 weeks) in a blinded fashion. The hematocrit value required to determine CDAI score at Week 4 will be assessed locally and confirmed via central laboratory

assessment. At Week 24, patients originally randomized to EU-approved Humira will switch to receive 40 mg BI 695501 every 2 weeks. All patients will then continue to receive BI 695501 at the same dose until Week 46.

Patients not achieving a clinical response at Week 4 will not receive any further treatment with trial medication, but will be followed up for safety after 10 weeks (Safety Follow-up Visit).

Prefilled syringes will be used for the administration (see Section 4.1.1) and all patients will receive their injections at the trial site throughout the trial until Week 22, and BI 695501/EU-approved Humira will be administered by a dedicated, unblinded member of trial personnel (third party blinding). From Week 24 onwards, when all patients will be receiving BI 695501when all patients will be receiving BI 695501, any suitably trained trial personnel may administer the medication to the patient. However, patients and other trial personnel must remain blinded with respect to the initial assignment to EU-approved Humira or BI 695501.
After the first injection in the induction period (Visit 2) and the injection at Visit 14 (when patients originally randomized to EU-approved Humira will switch to receive BI 695501), patients will remain at the clinical site for at least 1 hour for observation of any AEs.

Dose modification is not permitted during this trial. If a patient misses a dose of trial medication then the dose should be administered as soon as possible, in accordance with the visit schedule presented in Flow Chart A and Flow Chart B.

In the event of an anaphylactic or other serious allergic reaction, the administration of trial medication will be discontinued immediately and appropriate therapy instituted. Every effort should be made to ensure that patients who discontinue trial medication are followed up as described in Section 3.3.4.1.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is a double-blind trial, therefore patients, investigators, and everyone involved in trial conduct (except the trial personnel administering the trial medication – third party blinding) will remain blinded with regard to the randomized treatment assignments until after database lock. The unblinded trial personnel receiving, handling, and administering the trial medication will not be involved in any other trial assessments or procedures.

Details of blinding procedures are described in Appendix 10.1, Medication Blinding Procedures.

The randomization code will be kept secret by Clinical Trial Support up to database lock.

The secondary packaging (boxes containing PFS) will be identical for both BI 695501 and EU-approved Humira, allowing the blinding of the site pharmacy during the first 22 weeks of

treatment. Thereafter, all patients will receive BI 695501 and the drug supplies will not require blinding via secondary packaging.

The data will be unblinded at the time point of the primary analysis (see Section 7.4.1), only for individuals involved in the primary analysis and reporting.

Access to the randomization code will be controlled and documented. All persons directly involved in the conduct of the trial will have no access to the treatment allocation prior to final database lock.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator / Pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. If unblinding is required in the interest of the safety of a patient, and time allows, the investigator will discuss the matter with the Medical Advisor before unblinding whenever possible. If the code is broken for a patient (via the IRT) the sponsor must be informed immediately. The reason for unblinding must be documented in the patient's source documents and the appropriate eCRF along with the date and the initials of the person who broke the code.

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

Due to the requirements to report SUSARs, it may be necessary for a representative from the Boehringer Ingelheim Pharmacovigilance group to access the randomization code for individual patients during trial conduct. The access to the code will only be given to authorized Pharmacovigilance representatives and will not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by Boehringer Ingelheim or a designated CRO. They will be packaged and labelled in accordance with the principles of GMP. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

All trial medications must be kept in a secure place with limited access under appropriate storage conditions and handled according to GMP and GCP. The medication must be stored in a refrigerator at a controlled temperature (2 to 8°C [36 to 46°F]) and must not be frozen. A temperature log will be kept at the trial site, and will be completed (with a minimum and maximum reading) on each working day. Syringes will be kept in the outer carton in order to protect from light. Detailed storage conditions will be described on the trial medication labels.

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.

4.1.8 Drug accountability

Drug supplies will be provided by the sponsor.

Pharmacy personnel at each trial site will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the CTP by the IRB/IECs
- 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
- Availability of the curriculum vitae of the Principal Investigator
- Availability of a signed and dated CTP
- Availability of the proof of a medical license for the Principal Investigator
- Availability of Form 1572 (for sites in the US)

The pharmacist or other designated person must maintain records of the product's delivery to the trial site, the inventory at the site, the administration to each patient, and the return to the sponsor or warehouse/drug distribution center or alternative disposal of unused products. If applicable, the sponsor or warehouse/drug distribution center will maintain records of the disposal. Unused trial medication will be destroyed in accordance with local requirements.

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. The designated person will maintain records that document adequately that the patients were administered 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 appointed CRO, the designated person must verify that no remaining supplies are in the possession of the investigator.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Patients will continue to take their usual prescribed concomitant medications, as allowed by this CTP, from their usual source.

There are no specific rescue drugs foreseen for the treatment of AEs. There are no special emergency procedures to be followed.

In case of AEs requiring treatment, the investigator can authorize an appropriate therapy. In such cases, patients will be treated as necessary and, if required, kept under supervision at the

trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the trial or must refer them for appropriate ongoing care according to local guidelines and daily practice, respectively.

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.

Patients must be instructed not to take any new medications or to change the dose regimen of any existing medication (including over-the-counter products, herbal medications, and complementary therapies) without first consulting the investigator. All changes must be noted in the concomitant medication section of the eCRF.

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 adhere to the restrictions listed in Table 4.2.2.1: 1.

All concomitant medications will be recorded in the appropriate sections of the eCRF, including dose and day of administration.

Table 4.2.2.1: 1 Prior and concomitant treatments

Treatment	Restriction
Crohn's-related concomitant treatments	No escalations are permitted during the trial. No reductions are permitted with the exception of corticosteroids.
5-ASA, mesalamine, sulfasalazine, or Crohn's-related antibiotics	If receiving treatment prior to entry to the trial, the dose must have been stable for a minimum of 4 weeks prior to randomization (Day 1) and must remain stable throughout the trial.
Corticosteroids	If receiving current treatment with corticosteroids, the dose must not exceed 20 mg/day of prednisone or equivalent. The dose must have been stable for a minimum of 2 weeks prior to randomization (Day 1) and must remain stable throughout the induction period of the trial (i.e., until Week 4). At Week 4, patients who are receiving prednisone or budesonide may begin a taper if qualifications are met.
Budesonide	If receiving current treatment with budesonide, the dose must not exceed 6 mg/day and must have been stable for a minimum of 2 weeks prior to randomization (Day 1).
Budesonide and prednisone (combination therapy)	Not permitted throughout the trial.
Infliximab and other biologic therapies	Not permitted within 8 weeks (infliximab) and 6 months (other biologics) prior to randomization (Day 1) and throughout the trial.
Adalimumab and other TNF	Treatment not permitted at any time.
Azathioprine, 6-mercaptopurine, or MTX	If receiving these treatments, the dose must have been stable for a minimum of 4 weeks prior to randomization (Day 1) and must remain stable throughout the trial. Additionally, patients receiving these medications must have been on azathioprine, 6-mercaptopurine, or MTX for at least 12 weeks prior to randomization (Day 1).
Live/attenuated vaccine	Not permitted within 3 months prior to randomization (Day 1), for the duration of the trial, or for 70 days after the last dose of trial medication.
Cyclosporine, tacrolimus, and mycophenolate mofetil	Not permitted 8 weeks prior to Screening and throughout the trial.
Any drug/therapy that has not received regulatory approval for any indication	Not permitted within 6 months (or 30 days for chemical agents) or a minimum of five half-lives, whichever is longer, prior to randomization (Day 1) and throughout the trial.
Enemas (except when related to routine endoscopy or radiographic studies)	Not permitted within 2 weeks prior to randomization (Day 1) and throughout the trial.

In addition to the above restrictions, adalimumab is prohibited throughout the safety follow-up period.

Surgical bowel resection is not permitted within 6 months prior to randomization (Day 1), or at any time throughout the trial. If patients need surgery during the trial, they must discontinue.

4.2.2.2 Restrictions on diet and life style

Male patients with female partner(s) of childbearing potential must agree to use a medically acceptable method of contraception during the trial and for 6 months after the last dose of trial drug.

4.2.2.3 Restrictions regarding women of childbearing potential

A serum β-hCG test will be performed at Screening in women of childbearing potential. Thereafter, a local urine pregnancy test will be performed as indicated in the flow charts (see Flow Chart A and Flow Chart B). Any woman with a confirmed positive pregnancy test during screening is not eligible for the trial. A positive urine pregnancy test during the treatment periods of the trial requires immediate interruption of trial treatment until a serum β-hCG test is performed and found to be negative. If the serum β-hCG test is positive, the patient must be discontinued from trial medication.

Women of childbearing potential must use the contraception methods described in the patient information and in Section 3.3.2.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication by the dedicated trial personnel considered qualified to perform the s.c. injections. The measured plasma concentrations will provide additional confirmation of compliance.

Patients who are non-compliant (for instance, who do not attend scheduled visits or violate trial restrictions) may be discontinued from the trial treatment by the investigator after consultation with the sponsor or sponsor's representative, and the eCRF will be completed accordingly.

5. VARIABLES AND THEIR ASSESSMENT

Please refer to Flow Chart A and Flow Chart B for the schedule of assessments for the trial.

The trial endpoints are listed in Section 5.1 below. Efficacy assessments are described in more detail in Section 5.2, safety assessments in Section 5.3, PK sample collection in Section 5.4, and immunogenicity assessments in Section 5.6.

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

The primary endpoint is:

- Proportion of patients in each treatment group with a clinical response (CDAI decrease of ≥70 compared with baseline) at Week 4

5.1.2 Secondary Endpoint(s)

Secondary endpoints are:

Efficacy
- Proportion of patients in each treatment group with a clinical response (CDAI decrease of ≥70 compared with baseline) at Week 24
- Proportion of patients in each treatment group in clinical remission (CDAI <150) at Week 24

Safety
- Proportion of patients with AEs, SAEs, and AESIs (e.g., serious infections, allergic reactions, abscesses, fistula, strictures)
- Proportion of patients with infections/serious infections (seriousness of infection defined as requirement of i.v. antibiotics for treatment and/or meeting seriousness criteria to be qualified as an SAE)
- Proportion of patients who experience hypersensitivity reactions
- Proportion of patients who experience DILI
- Proportion of patients with injection-site reactions

5.2 ASSESSMENT OF EFFICACY

The assessments described in the following sections will be made at the time points indicated in Flow Chart A and Flow Chart B.

5.2.1 CDAI

Evaluation of CDAI will be performed by the investigator at the visits indicated in the Flow Chart A and Flow Chart B.

The CDAI is a validated instrument to measure disease severity in CD (R97-2689). It is the most widely used clinical index for the evaluation of disease activity and remission in inflammatory CD in clinical trials. It has been recommended by the International Organization for the study of IBD and the European Crohn's and Colitis Organization for

defining CD activity (R02-0112, R15-4343) and has been accepted by the regulatory authorities (R13-2623).

The CDAI score is composed of eight factors as shown in Table 5.2.1: 1. The patient is required to keep a symptom diary for 4 of these 8 variables (number of liquid stools, abdominal pain, general well-being, and use of antidiarrheal drugs) for 7 consecutive days before each CDAI evaluation. Hematocrit results are integral to the CDAI calculation and will be assessed at each visit by the central laboratory as part of the safety laboratory analyses (see Section 5.3.3). The Visit 1 hematocrit results will be used for the calculation of CDAI at Visit 1.1 in order to determine eligibility of the patient to be included in the trial. At Week 4, the hematocrit value required to determine CDAI score will be assessed locally and confirmed via central laboratory assessment. At Visit 8 (Week 12), the hematocrit value from the central laboratory assessment at Visit 6 (Week 8) will be used to determine CDAI score. At visits where CDAI evaluation is performed and no physical examination is planned, body weight must be measured for use in CDAI determination.

The CDAI score is a sum of the eight factors after adjustment with a weighting factor; CDAI scores range from 0 to approximately 600. The day of bowel preparation for colonoscopy and the day of colonoscopy will be excluded from the CDAI assessment. This is to prevent misleading influences (pain and liquid stool frequency) on CDAI evaluation.

Table 5.2.1: 1 Calculation of CDAI

Variable	Description	Scoring	Multiplier
Number of liquid stools	Sum of 7 days		×2
Abdominal pain	Sum of 7 days' ratings	0 = none 1 = mild 2 = moderate 3 = severe	×5
General well-being	Sum of 7 days' ratings	0 = generally well 1 = slightly under par 2 = poor 3 = very poor 4 = terrible	×7
Extra-intestinal complications	Number of complications listed	Arthritis/arthralgia, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphtous stomatitis, anal fissure/fistula/abscess, fever > 37.8°C	×20
Antidiarrheal drugs	Use in the previous 7 days	0 = no 1 = yes	×30
Abdominal mass		0 = no 2 = questionable 5 = definite	×10
Hematocrit	Expected–observed hematocrit	Men: 47 observed Women: 42 observed	×6
Body weight	Ideal/observed ratio	[1 − (actual weight/standard weight)] × 100	×1 (not < −10)

Adapted from R97-2689.

5.2.2 Endoscopy

Endoscopies will be performed for the evaluation of SES-CD and mucosal ulceration at the visits indicated in Flow Chart A

Lesions detected by endoscopy (ileocolonoscopy) will be scored by means of the validated SES-CD, as described below. The same endoscopist at the trial site will complete the SES-CD for each endoscopy immediately after the procedure. The investigator (or designate) will record each endoscopy and send the video to the central imaging laboratory. A central reading of all endoscopies will be performed by an independent blinded reviewer and the findings scored using SES-CD. Eligibility at Screening must be confirmed using the centrally read scores prior to randomization.

The results for SES-CD and mucosal ulceration will be returned to the trial site from the central imaging laboratory for entry into the appropriate eCRF.

5.2.2.1 SES-CD

The SES-CD was developed as a reproducible measure that could be used to assess response to therapy in CD (R14-2969, R15-6247) using an endoscopic index capable of assessing the severity of mucosal lesions in colonic or ileocolonic CD. The scoring system is represented in Table 5.2.2: 1 below. The index is relatively complex and must be performed by an experienced endoscopist who has been trained in the precise and specific data recording procedure required.

Table 5.2.2.1: 1 Scoring system for SES-CD

	Ileum	Right colon	Transverse colon	Left colon	Rectum	**Total**
Presence and size of ulcers (0-3)	0-3	0-3	0-3	0-3	0-3	**0-15**
Extent of ulcerated surface (0-3)	0-3	0-3	0-3	0-3	0-3	**0-15**
Extent of affected surface (0-3)	0-3	0-3	0-3	0-3	0-3	**0-15**
Presence and type of narrowings (0-3)	0-3	0-3	0-3	0-3	0-3	**0-11**
					SES-CD =	**0-56**

Source: R14-2969.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A physical examination will be performed at the visits indicated in Flow Chart A and Flow Chart B.

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 assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, and neurological systems, thyroid gland, musculoskeletal system/limbs, respiratory tract, and abdomen. Clinically relevant abnormal findings will be reported as baseline conditions or AEs.

Body weight will also be measured. Height will be measured at Screening only.

5.3.2 Vital Signs

Vital signs will be assessed at the visits indicated in Flow Chart A and Flow Chart B.

Blood pressure 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.

The investigator must 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 other tests will be taken at the times indicated in Flow Chart A and Flow Chart B.

The laboratory parameters listed in Appendix 10.2 will be measured.

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 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 and stool samples will be analyzed by a central laboratory. The central laboratory vendor 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, reference ranges, and blood sample volumes can be found in the Laboratory Manual.

At Week 4, in order to assess clinical response during the visit, the hematocrit value required to determine CDAI score will be assessed locally and subsequently confirmed via central laboratory assessment.

Pregnancy testing will be performed by a central laboratory using serum at Screening or by a local laboratory using urine at all applicable visits thereafter.

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

5.3.4 Electrocardiogram

A 12-lead ECG (I, II, III, aVR, aVL, aVF, V1 – V6) will be recorded using a computerized electrocardiograph at the visits indicated in Flow Chart A and Flow Chart B.

All ECGs will be recorded for 10-second duration after the patients have rested for at least 5 minutes in a supine position. ECG assessment will always precede all other trial procedures at the same time point (except blood drawing from an i.v. cannula which is already in place) to avoid impact of sampling on the ECG quality.

The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the patient's medical file.

The investigator or a designate will evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal. Additionally, any occurrence of re- or depolarization disorders, arrhythmic disorders or other abnormalities will be assessed. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at Screening) if judged clinically relevant by the investigator. Any ECG abnormalities, judged as clinically relevant, will be monitored carefully and, if necessary, the patient will be removed from the trial and will receive the appropriate medical treatment. Additionally, evaluation of these ECGs will be performed by a board certified cardiologist.

Information about the details of ECG collection and the parameters assessed will be provided in the ISF.

5.3.5 Other safety parameters

5.3.5.1 Tuberculosis assessment

A chest X-ray will be reviewed by the investigator or designee at Screening. If chest radiographs have been taken within 12 weeks of the Screening Visit then the chest radiographs do not need to be repeated (as long as they show no clinically significant abnormality and no signs or symptoms suggestive of lung disease that would exclude the patient from the trial). The results must be entered into the eCRF.

An IGRA (e.g., QuantiFERON®-TB Gold) will be used to assess TB status at Screening and, for patients who continue to the maintenance phase, at Visit 14 Week 24 (before switch from EU-approved Humira to BI 69550 and at EoT (Week 48 or earlier for patients who discontinued treatment during the maintenance phase). In the event of an indeterminate result at Screening, the test should be repeated. If a second indeterminate result is obtained then the patient must be excluded from the trial participation.

In the event of an indeterminate or positive result during the study, the test should be repeated and if a result is positive, then the patient will discontinue receiving the study treatment and followed up for safety. The patient will be referred to the specialist as required by local regulations.

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 medicinal 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 AE 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, referring to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if more severe,
- requires inpatient hospitalization or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is 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.

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer 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 European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further 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.

The latest list of "Always Serious AEs" will be provided in the ISF. These events should always be reported as SAEs as described above.

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. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs (see above).

The following are considered as AESIs:

- Hepatic injury

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

  - an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
  - marked peak aminotransferase (ALT and/or AST) elevations ≥10 fold ULN

  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.

  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.

  For further details see Appendix 10.4.

- Anaphylactic reactions

- Serious infection (defined as infections requiring i.v. antibiotics or meeting the regulatory definition of an SAE)

- Hypersensitivity reactions.

Protocol-specified AESIs can be classified as serious or non-serious but all AESIs must be reported in an expedited manner similar to SAEs on an SAE form (i.e., non-serious AESIs must be reported on the SAE form and follow SAE reporting timelines).

Intensity of AEs

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

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 AE. An adverse reaction, in contrast to an AE, 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 etiologies that could explain the event (e.g., pre-existing 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 trial drug treatment continues or remains unchanged.

5.3.6.2 Adverse event collection and reporting

AE Collection

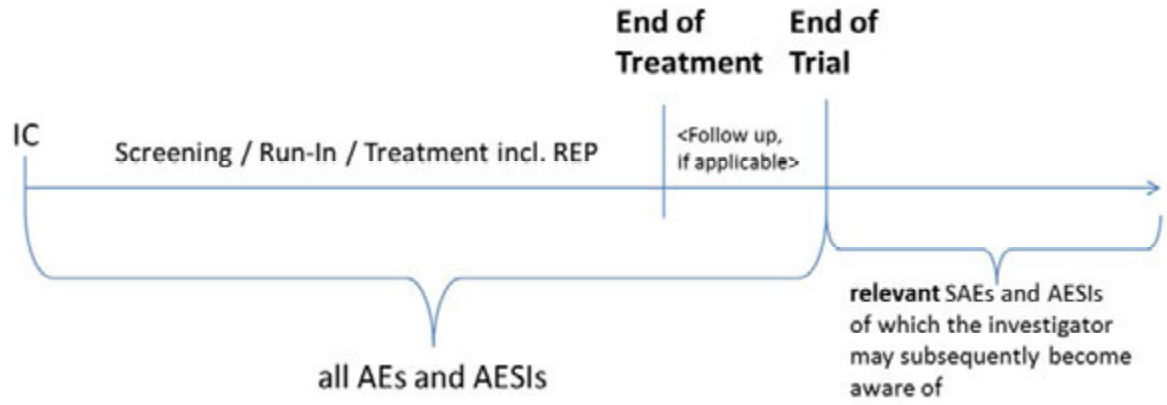
The investigator shall maintain and keep detailed records of all AEs in their patient files.

The following must be collected and documented on the appropriate eCRF(s) by the investigator:

- From signing the informed consent onwards through the REP (defined as 10 weeks after last administration of trial medication), until the individual patient's end of trial:
    - All AEs (serious and non-serious) and all AESIs

  However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e., if further visits incl. telephone visits, or vital status assessments are planned) from then on and until the individual patient's end of the trial, the investigator must report related SAEs and related AESIs.
- After the individual patient's end of trial:
    - The investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware.

The above instructions are summarized schematically below.



The REP is defined as 10 weeks after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment (see Section 7.3.4). Events which occurred after the REP will be considered as post-treatment events.

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's 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's designee upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to 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. The investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug(s) and a non-investigational medicinal product/auxiliary medicinal product.

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

- Worsening of the underlying disease or of other pre-existing conditions
- 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 trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial 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 patient has been enrolled into this clinical trial and has taken trial medication, the investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's/sponsor's designee's 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 outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's/sponsor's designee's 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 B).

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

5.7 APPROPRIATENESS OF MEASUREMENTS

The primary efficacy endpoint (CDAI decrease of ≥70 compared to baseline) is a standard outcome criterion that is widely accepted for regulatory purposes to demonstrate efficacy on signs and symptoms of CD.

Therefore, the appropriateness of all measurements applied in this trial is assured and is in line with guidance from regulatory authorities (R13-2623).

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

A schedule of assessments is provided in Flow Chart A and Flow Chart B.

Visits will be scheduled as close as possible to the preplanned schedule:

- A visit window of -1/+2 days is permitted for Visit 2 (Day 1)
- A visit window of ±1 day is permitted for Visit 3 to Visit 4
- A visit window of ±3 days is permitted for Visit 5 to Visit 25, and EoT
- A visit window of +7 days is permitted for safety follow-up Visit
- Trial medication will be administered every 2 weeks (±1 day up to Visit 4 and ±3 days from Visit 5 onwards).

On trial medication administration days, all assessments should be performed prior to administration, unless otherwise specified. Laboratory samples must be drawn prior to trial medication injection.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in Flow Chart A, Flow Chart B, and the respective protocol sections. Refer to Section 5 for explanations of procedures.

6.2.1 Screening and run-in period(s)

The Screening period in this trial will comprise two separate visits. Once the patient has provided informed consent (before any trial-specific procedures or assessments are performed), meets the inclusion criteria and does not meet any of the exclusion criteria (see Section 3.3), the trial site will enter the screened patient into the system using the IRT.

Screening Visit 1, Day -28 to Day -14

The following will be performed/collected:

- Demographic information (including gender, date of birth, ethnicity, and race), and medical and surgical history (including CD history and history of opportunistic infection)
- Infection screen (HBsAg, antiHCV, and HIV test, per the investigator's discretion and/or where mandated by local authorities)
- Chest X-ray, unless taken within the previous 12 weeks (see Section 5.3.5.1)
- TB test (IGRA e.g., QuantiFERON® Gold assay; see Section 5.3.5.1)
- Stool studies to evaluate for enteric pathogens (see Section 5.3.3)
- Serum pregnancy test for women of childbearing potential
- Physical examination, including height (cm) and weight (kg) (see Section 5.3.1)
- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2)
- Laboratory testing (serum chemistry, hematology, and urinalysis; see Section 5.3.3)

- 12-lead ECG (see Section 5.3.4)
- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)

Following completion of the above screening procedures at Visit 1, patients who are eligible to continue will receive a patient CDAI diary to complete their daily symptoms during the 7-day period immediately before Visit 1.1. Sites must ensure that sufficient time is allowed between Visit 1 and Visit 1.1 to allow completion of the CDAI diary.

Screening Visit 1.1, Day -9

At Visit 1.1, the patient CDAI diary will be reviewed by the investigator in order to assess the CDAI score. The hematocrit result and weight measurement from Visit 1 must be used to calculate the CDAI score at Visit 1.1 (see Section 5.2.1). Only patients with moderate to severe CD, defined as CDAI score ≥220 and ≤450 will undergo an endoscopy at Visit 1.1 (see Section 5.2.2). Evidence of mucosal ulcers in at least one segment of the ileum or colon and a SES-CD score ≥7 (or ≥4 for patients with isolated ileal disease) must be confirmed by central independent reviewer(s) prior to randomization.

Once patients have completed screening at Visit 1.1, have met all the inclusion criteria and have not met any of the exclusion criteria, randomization will occur on Day 1 (-1/+2) through a standard randomization visit call, using the IRT system. Patients will be randomized to each treatment in a 1:1 ratio (BI 695501: EU-approved Humira) according to the stratification factors. Patients will be randomly assigned in a blinded fashion to BI 695501 or EU-approved Humira as described in Section 4.1.3 and Section 7.6.

6.2.2 Treatment period(s)

Prior to Week 24, BI 695501/EU-approved Humira will be administered by a suitably qualified, designated unblinded trial personnel. From Week 24 onwards, when all patients will be receiving BI 695501, it will not be necessary for the trial personnel administering the medication to be unblinded. However, patients and other trial personnel must remain blinded with respect to the initial assignment to EU-approved Humira or BI 695501. All administrations of trial medication will be performed at the trial site. Trial medication will be administered every 2 weeks (-1/+2 days at Visit 2, ±1 day up to Visit 4 and ±3 days from Visit 5 onwards).

Baseline, Visit 2 (Day 1)

Eligible patients will be randomized and will receive their first administration of trial medication on Day 1.

The following will also be performed/collected:

- Physical examination, including weight (kg) (see Section 5.3.1)
- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2)

- Laboratory testing (serum chemistry, hematology, and urinalysis; see Section 5.3.3)
- Urine pregnancy test (in addition to a serum pregnancy test at Screening)
- Evaluation of CDAI (see Section 5.2.1)

- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)

- Contact IRT and administer first trial medication injection (see Section 4.1.4)

Visit 3 (Day 15)

The following will be performed/collected:

- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2)
- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)
- Contact IRT and administer trial medication

Visits 4 and 14 (Days 29 and 169, respectively)

The following will be performed/collected:

- Physical examination, including weight (kg) (Visit 14 only; see Section 5.3.1)
- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2)
- Laboratory testing (serum chemistry, hematology, and urinalysis; see Section 5.3.3)
- Urine pregnancy test for women of childbearing potential (Visit 14 only)
- Local hematocrit testing (Visit 4 only; to be used for CDAI evaluation)
- Evaluation of CDAI (see Section 5.2.1)

- TB test (IGRA e.g., QuantiFERON Gold assay; at Visit 14 only)
- 12-lead ECG (see Section 5.3.4)
- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)

- Contact IRT and administer trial medication

At Visit 14, patients initially randomized to EU-approved Humira will switch to receive BI 695501. From Visit 14 onwards, all patients will be receiving BI 695501.

Visits 6, 10, 18 and 22 (Days 57, 113, 225 and 281, respectively)

The following will be performed/collected:

- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2)
- Laboratory testing (serum chemistry, hematology, and urinalysis; see Section 5.3.3)
- Urine pregnancy test for women of childbearing potential
- 12-lead ECG (Visit 6 only; see Section 5.3.4)
- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)
- Contact IRT and administer trial medication

Visit 8 (Day 85)

The following will be performed/collected:

- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2)

- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)
- Evaluation of CDAI (see Section 5.2.1)

- Contact IRT and administer trial medication

At this visit, the hematocrit value from the central laboratory assessment at Visit 6 (Day 57) will be used to determine CDAI score.

Visits 12 and 16 (Days 141 and 197, respectively)

The following will be performed/collected:

- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2)
- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)
- Contact IRT and administer trial medication

Trial medication administration only visits

Visits 5, 7, 9, 11, 13, 15, 17, 19, 20, 21, 23, 24, and 25 are for administration of trial medication only and the following will be performed:

- Contact IRT and administer trial medication

End of Treatment Visit

The following will be performed/collected:

- TB test (IGRA e.g., QuantiFERON® Gold assay)
- Physical examination, including weight (kg) (see Section 5.3.1)
- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2)
- Laboratory testing (serum chemistry, hematology, and urinalysis; see Section 5.3.3)
- Urine pregnancy test for women of childbearing potential
- 12-lead ECG (see Section 5.3.4)
- Evaluation of CDAI (see Section 5.2.1)
- CRP (see Section 5.2.3)

- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)

Patients who discontinue the trial at any time after Day 1 (but do not withdraw their consent) will be required to have all of the evaluations for the EoT Visit as soon as after trial discontinuation as possible (except TB test, which is not required for those discontinuing before the maintenance phase, which is only required for patients who complete the 48-week treatment period).

The patient who early discontinued from the trial will receive treatment as deemed appropriate by the investigator and in accordance with the applicable guidance.

6.2.3 Follow-up period and trial completion

Every effort should be made for all patients who complete the total 48-week treatment period or who discontinue the trial early, to return for a Safety Follow-up Visit 10 weeks after last dose of trial medication (at Week 56 for patients who complete the full treatment period).

Safety follow-up visit

The following will be performed/collected:

- Physical examination, including weight (kg) (see Section 5.3.1)
- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2)
- Laboratory testing (serum chemistry, hematology, and urinalysis; see Section 5.3.3)
- Urine pregnancy test for women of childbearing potential
- 12-lead ECG (see Section 5.3.4)
- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)

- End of participation

Unscheduled visit assessments

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomized, double-blind, parallel arm, multiple dose, multicenter, multinational, active comparator trial of BI 695501 and EU-approved Humira.

The primary objective of this trial is to compare the clinical efficacy of BI 695501 with EU-approved Humira in patients with active CD at the end of the induction phase at Week 4 by means of the RR.

The primary endpoint (Section 5.1.1) will be analyzed using a log-linked binomial model, which will include stratification factors as covariates (i.e., prior exposure to infliximab [yes/no] and screening SES-CD (<16 or ≥16).

7.2 NULL AND ALTERNATIVE HYPOTHESES

This exploratory trial is intended to generate additional data in patients with active CD. Therefore, no formal confirmatory hypotheses for the primary efficacy analysis are defined.

7.3 PLANNED ANALYSES

The primary analysis set will be the FAS according to the intention to treat principle. The FAS will consist of all randomized patients who receive at least one dose of trial medication, and have all efficacy measures relevant for the CDAI, measured at baseline and at least once post-baseline.

A PPS of patients who have followed the CTP in all essential criteria will be created for sensitivity analyses. Patients included in the FAS who have important protocol violations relevant for efficacy prior or at Week 4 will be excluded from the PPS. Protocol violations will be assessed on a case-by-case basis. A protocol violation will be considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint. Important protocol violations may include:

- Incorrect trial medication taken until Week 4
- Violation of treatment compliance until Week 4
- Violation of inclusion/exclusion criteria
- Further details on the definition of the different analysis sets will be provided in the TSAP.

All patients treated with at least one (full or partial) dose of either of the trial treatments during any dosing period will be included in the safety evaluation (SAF).

7.3.1 Primary endpoint analyses

Primary efficacy analysis:

The primary analyses will be performed on the FAS. Patients will be assigned to the treatment they were randomized to receive.

The primary analysis of the observed proportion of patients with a clinical response (CDAI decrease of ≥70 compared with baseline) at Week 4 will be based on log-linked binomial model. No missing data imputation for primary analysis endpoint need to be taken into account due to FAS definition. However, for pre-specified criteria non-responder imputation (NRI) will be applied (see Section 7.5).

The statistical model can be described as follows:

- (M1) Response to treatment at Week 4 = treatment + prior infliximab exposure + screening SES-CD

This model includes the stratification factor, prior exposure to infliximab, and treatment as fixed, categorical effects and it will be investigated whether the baseline SES-CD will be included as a continuous or as a categorical effect:

- Treatment (BI 695501, EU-approved Humira)
- Prior exposure to infliximab (Yes/No)
- Baseline SES-CD (<16 or ≥16)

The relative risk estimate together with its 90% and 95% CI (ratio scale) will be produced.

Further efficacy analyses:

As sensitivity analyses to the primary analysis, the primary endpoint will also be analyzed on the PPS with NRI.

The following explorative hypotheses are not intended to support any biosimilarity claim for BI 695501; however, the framework of non-inferiority testing will be used to compare efficacy of BI 695501 versus EU-approved Humira in a descriptive way.

The following hypotheses will be investigated:

- H_0: RR of proportion of patients with a clinical response (CDAI decrease of ≥70 compared with baseline) at Week 4 (BI 695501 versus EU-approved Humira) is less than or equal to 0.76
- H_1: RR of proportion of patients with a clinical response (CDAI decrease of ≥70 compared with baseline) at Week 4 (BI 695501 versus EU-approved Humira) is greater than 0.76

Two-sided 90% CI will be used for the comparison.

The applied margin (0.76 on the ratio scale for CDAI 70) does preserve 39% of the historical effect of adalimumab over placebo (based on a meta-analysis of GAIN and CLASSIC1; see Appendix 10.3 for further details).

7.3.2 Secondary endpoint analyses

7.3.2.1 Secondary efficacy endpoints

To support the primary objective, the secondary efficacy endpoints detailed in Section 5.1.2 will be analyzed descriptively based on the FAS.

For the proportions, the risk difference will be computed and presented together with its 90% and 95% CI and interpreted in a descriptive manner.

7.3.2.2 Secondary safety endpoints

The secondary safety endpoints detailed in Section 5.1.2 will be based on the SAF and presented descriptively. In addition, RR and risk difference together with 95% CIs will be presented.

7.3.4 Safety analyses

Adverse events will be coded using the MedDRA coding dictionary.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature. No hypothesis testing is planned. No formal inferential analyses are planned for safety comparison. The analyses will be based on the SAF.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment and end of the REP will be considered 'treatment-emergent'. The REP is defined as 10 weeks after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Other AEs will be assigned to the appropriate trial phases, i.e., screening or post-treatment. For patients switching from EU-approved Humira to BI 695501, AEs occurring after the first dose of BI 695501 will be assigned to BI 695501 for the overall AE analysis. AEs occurring before the first dose of BI 695501 will be assigned to the ongoing treatment.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA. In addition, RR and risk difference together with 95% CIs will be presented for the overall population (details will be specified in the TSAP).

Laboratory data will be analyzed quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data with their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared with findings before start of treatment.

7.4 INTERIM ANALYSES

No classic interim analysis will be performed. Instead, an overview of the different analysis time points is given below.

7.4.1 Primary analysis

The primary analysis will take place when all primary efficacy endpoint data are available and cleaned (i.e., approximately 4 weeks after the last patient has been randomized). The cut-off date will be the date on which the last patient completes the Week 4 visit and will be the same for all patients. A database snapshot will be taken with regard to this cut-off date; it will include all data available in the database up to and including the cut-off date and will be used for performing the analysis. Only cumulative results will be presented, i.e., patient level data will be excluded. Details regarding statistical analysis will be outlined in the TSAP. Only a selected team, not involved in any other trial activities, will have access to the unblinded snapshot data and will be required to sign a confidentiality agreement. Efficacy data will be included up to the Week 4 visit only and all available data for safety and other endpoints will be included up to the data cut-off date.

To ensure that the data integrity of the continuing trial will not be violated, a charter will be prepared in advance, outlining the procedures to be followed. This document will describe the measures to be implemented by the Sponsor to protect the integrity of the trial until the final database lock. Team members involved in the conduct of the trial as well as the site personnel and patients will remain blinded until the final database lock.

7.4.2 Final analysis

A final analysis (including all endpoints) will be performed when all trial data are available, i.e., approximately 56 weeks after the last patient has been randomized. In this analysis, all analyses performed for the primary analysis will be repeated with the (partially) updated data, in particular with respect to safety and efficacy endpoints collected until Week 56. The results of the final analysis will be summarized in a CTR.

7.5 HANDLING OF MISSING DATA

7.5.1 Efficacy endpoints

No missing data for the primary analysis endpoint are expected for the FAS, because Week 4 is the first post-baseline visit for efficacy assessment and, in case of discontinuation prior to Week 4, the EoT efficacy assessments should be performed. However, all patients who

discontinue treatment, are lost-to-follow-up or have any major protocol deviation related to any therapy that may significantly impact efficacy assessment (Table 4.2.2.1: 1) prior to the primary endpoint assessment will be considered as non-responders. Patients without any available CDAI evaluation at Week 4 will also be considered as non-responders. This is referred to as 'NRI'. Patients assessed as non-responders at Week 4 will be considered non-responders for all subsequent time points (LOCF).

For secondary efficacy endpoints, rules for handling of missing data will be specified in the TSAP, if necessary.

7.5.2 Safety and other endpoints

With respect to safety evaluations, it is not planned to impute missing values. For other endpoints, rules for handling of missing data will be specified in the TSAP, if necessary.

7.6 RANDOMIZATION

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized 1:1 to either BI 695501 or EU-approved Humira over the 24-week (4-week induction and 20-week maintenance) treatment period after the screening period at Visit 2. The randomization will be stratified by prior exposure to infliximab (Yes/No) and screening SES-CD (<16 or ≥16).

Randomization will occur on Day 1 (-1/+2) through a standard randomization visit call. Patients will be randomized to each treatment in a 1:1 ratio (BI 695501: EU-approved Humira) using an IRT system.

Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Trial Supply Unit or a third party appointed by the sponsor will provide the randomization list using a validated randomization number generating system. Access to the randomization code will be controlled and documented. All persons directly involved in the conduct of the trial have no access to the treatment allocation prior to final database lock. The block sizes of the randomization will be documented in the CTR.

7.7 DETERMINATION OF SAMPLE SIZE

The sample size determination is not based on a power calculation, but assures a precise estimation of the relative risk difference. For this trial a precision (distance from observed difference to confidence limit) of 0.115 has been considered necessary and sufficient by the project team. Assuming a response rate of 80%, in both the Humira as well in the BI 695501 treatment arm, the trial will need at least 130 patients (65 per treatment arm).

Table 7.7: 1 Precision of 90% CI

Assumed true response rate		Sample size	Precision[$]	Relative risk (RR)	90% CI
Humira	**BI 695501**				
85%	85%	65	0.103	1	0.897-1.103
85%	80%	65	0.118	0.941	0.823-1.059
85%	75%	65	0.115	0.882	0.767-0.997
80%	**80%**	**65**	**0.115**	**1**	**0.885-1.115**
80%	75%	65	0.120	0.938	0.818-1.058
75%	75%	65	0.125	1	0.875-1.125

[$]Precision is defined as the distance from observed difference to confidence limit. Note that the precision is independent of the actual point estimate.
Calculations performed with nQuery Advisor® 7.0

Table 7.7: 2 Precision of 95% CI

Assumed true response rate		Sample size	Precision[$]	Relative risk (RR)	95% CI
Humira	**BI 695501**				
85%	85%	65	0.123	1	0.877-1.123
85%	80%	65	0.140	0.941	0.801-1.081
85%	75%	65	0.136	0.882	0.746-1.081
80%	**80%**	**65**	**0.138**	**1**	**0.862-1.138**
80%	75%	65	0.143	0.938	0.795-1.081
75%	75%	65	0.149	1	0.851-1.149

[$]Precision is defined as the distance from observed difference to confidence limit. Note that the precision is independent of the actual point estimate.
Calculations performed with nQuery Advisor® 7.0

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

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, relevant BI and CRO SOPs, the EU regulation 536/2014, and other relevant regulations.

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 Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. 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 general rule, no trial results should be published prior to finalization of the CTR.

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, INFORMED CONSENT

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

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

The investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

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

Case Report Forms for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the sponsor, the investigator must ensure that all patient identifiers (e.g., patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g., re-training, must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)

- 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 and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation document the reason for it)
- Prior to allocation of a patient to a treatment in 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, verbal documented feedback of the patient 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 sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology, and the degree of any deviations of the intervention from normal clinical practice.

The investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review, and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor, and regulatory inspector (e.g., FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial site(s):

The trial sites must retain the source and essential documents (including ISF) according to the national or local requirements (whichever is longer) valid at the time of the end of the trial.

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Boehringer Ingelheim is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

Data protection and data security measures are implemented for the collection, storage, and processing of patient data in accordance with principles 6 and 12 of the World Health Organization GCP handbook.

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.

8.5.1 Collection, storage, and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage, and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of GCP as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The Boehringer Ingelheim internal facilities storing and analyzing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment pf the first patient in the whole trial.

The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out"), the date that the last patient in the trial dies, or the date that the last patient in the trial is lost to follow-up (whichever occurs last).

The "**Last Patient Drug Discontinuation**" (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or

prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 10 weeks after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC/competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

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10. APPENDICES

10.1 MEDICATION BLINDING PROCEDURE FOR THIRD PARTY BLINDING

This is a double-blind trial, therefore patients, investigators, and trial personnel (except the trial personnel administering the trial medication at site) will remain blinded with regard to the randomized treatment assignments until after database lock.

The secondary packaging (boxes containing syringes) will be identical for both BI 695501 and EU-approved Humira, allowing the blinding of the site pharmacy during the first 22 weeks of treatment. Thereafter, all patients will receive BI 695501 and the drug supplies will not require blinding via secondary packaging.

A qualified unblinded designee will administer the trial medication until Week 22, as well as being responsible for preparation of unused trial medication for return to the sponsor or destruction in a blinded fashion and according to local SOPs.

Records of the product's delivery to the trial site will include dates, quantities, batch/serial numbers, expiry ('use by') dates and the unique code numbers assigned to the investigational products and trial patients. The designated unblinded or blinded person will maintain records that document doses administered to patients and reconcile all investigational product received at site. At the time of return to sponsor or local destruction, the designated unblinded or blinded person must verify that no supplies remained at the trial site.

The unblinded trial personnel administering the trial medication will not be involved in any other trial assessments or procedures.

A description of the trial medication is provided in Table 4.1.1: 1 and Table 4.1.1: 2.

Patient blinding procedure

Trial medication will be administered by unblinded trial personnel until Week 22. To ensure patient's blinding during the administration process, the following procedures are to be applied:

- Syringes unpacked and prepared for injection are to be covered by a surgical drape at the time of patient preparation for dosing. The same procedure is to be applied to used syringes after injection.
- During the dose administration, patients are to be separated from the unblinded designee who will administer the trial medication by, for example, a surgical drape or screen.
- Used syringes should be discarded in a sharp container immediately after use .

Site staff blinding procedure

Responsibilities for blinded and unblinded study site staff are defined below. At each site, a form with the name(s) of the staff members, blinded and unblinded, with their respective responsibilities will be filled in.

(NOTE: all personnel noted below will have signed the Site Personnel Signature Log, clearly outlining each individual's responsibility).

In case of non-availability of blinded or unblinded study staff, the CRO and sponsor should be informed immediately.

Blinded Personnel	**Main Responsibilities**
Principal Investigator: **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Monitors patient status • Responsible for the delegation of tasks to appropriate staff and to ensure correctness of all assessments • Provides direct patient care • Works and communicates with blinded CRA • Ensures adequate unblinded trial site personnel and facilities for administration of trial medication • Contacts IXRS® to enter screen failures, screened patients, randomizations, and obtain subsequent medication assignments
Blinded Sub-Investigator or Study Coordinator/Study Nurse: **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Contacts IXRS® to enter screen failures, screened patients, randomizations, and obtain subsequent medication assignments • Monitors patient status • Provides direct patient care, if applicable • Works and communicates with blinded CRA • Can be involved in the receipt, storage control and return of IP (since secondary package is blinded)
Blinded CRA: **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS** **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Acts as the primary point of contact for the blinded and unblinded site team • Provides ongoing site support in all areas of trial conduct and performs accountability and reconciliation of trial medication (after disposal of the syringes by the unblinded trial medication administrator) • Conducts blinded site monitoring visits and performs source document verification

CRA = clinical research associate

Unblinded Personnel	Main Responsibilities
Unblinded Trial Medication Administrator (Sub-Investigator or Study Nurse): **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS**	• Prepares trial medication for dispensing • Performs the trial medication administration and ensures patient is blinded during IP administration • Discard used syringes in a blinded fashion after administration of trial medication according to local procedures such as local SOPs • Retains used unsealed/opened boxes (secondary packaging), which contained the syringes before administration of trial medication, for reconciliation by blinded CRA prior to destruction • Works and communicates with the blinded CRA in a way that does not reveal the treatment arm • Can be involved in the receipt, storage control, and return of trial medication

Training

All professional personnel taking part in the clinical trial are trained and aware of the need to respect study blinding principles as foreseen by the protocol. Blinded and unblinded trial site staff, as well as blinded CRAs, will be trained on trial blinding procedures before the start of any trial activities at site. Unblinded trial site staff is restricted to persons handling trial medications including the injection of trial drug. Training in study blinding procedures for blinded trial CRAs will be provided during a CRA Meeting. Training in trial blinding procedures for blinded and unblinded site staff will be provided at the Investigators' Meeting. For the remaining site staff, who do not participate in an Investigators' Meeting, applicable training in trial blinding procedures will be provided by a blinded CRA during the Site Initiation Visit, based on information in the CTP, Medication Blinding Procedures, and Pharmacy Manual. Such training is a part of trial specific agenda for Site Initiation Visit, as well as the slide presentation prepared for the visit. All training will be documented.

10.2 LIST OF LABORATORY TESTS

Category	Test name
Hematology	Hematocrit Hemoglobin RBC count / erythrocytes Reticulocyte count WBC / leukocytes Platelet count
Differential automatic (relative and absolute count)	Neutrophils Eosinophils Basophils Monocytes Lymphocytes
Differential manual (relative and absolute count) (if differential automatic is abnormal)	Neutrophils, bands Neutrophils, polymorphonuclear Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Partial thromboplastin time Prothrombin time (Quick/INR) Fibrinogen
Enzymes	AST ALT Alkaline phosphatase Creatine kinase CK-MB, only if CK is elevated GGT Lactic dehydrogenase Lipase Amylase
Specific gamma-globulin quantification	IgE (only in case of allergic reaction) IgG
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate

Category	**Test name**
Substrates	Glucose Creatinine and creatinine clearance Bilirubin total Bilirubin direct Total protein Albumin Uric acid Cholesterol, total High density lipoprotein cholesterol Calculated low density lipoprotein Cholesterol Triglycerides
Hormones	TSH (Screening visit only) Free T3, Free T4 if TSH <LLN or >ULN
Pregnancy test (only for female patients of childbearing potential)	β-hCG (serum or urine)
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocyte Urine WBC/Leukocytes Urine pH
Urine sediment (microscopic examination) (if urine analysis is abnormal)	Urine Sediment Bacteria Urine Casts in Sediment Urine Squamous Epithelial Cells Urine Sediment Crystals, Unspecified Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leucocytes
Infectious serology (only at Screening)	HBsAg HBc antibody (IgM) Hepatitis C antibody HIV-1, and HIV-2 antibody (at the discretion of the investigator where clinically indicated or where mandated by local authorities)
TB screening for infections (at Screening, Visit 14 and EoT Visit)	TB test (IGRA e.g., QuantiFERON® Gold assay)

Category	Test name
Stool studies to evaluate for enteric pathogens[1] (only at Screening)	*Salmonella* *Shigella* *Yersinia* *Campylobacter* *Vibrio* *Escherichia coli* O157/H7 *Clostridium difficile* toxin Enteric parasites and their ova (including *Cryptosporidia*)

β-hCG: beta human chorionic gonadotropin; EoT: end of treatment; GGT: gamma-glutamyl transferase; HBc: hepatitis B core; HbsAg: hepatitis B surface antigen; HIV: human immunodeficiency virus; Ig: immunoglobulin; IGRA: interferon-gamma release assay; INR: International Normalized Ratio; LLN: lower limit of normal; RBC: red blood cell; TB: tuberculosis; TSH: thyroid stimulating hormone; ULN: upper limit of normal; WBC: white blood cell.
1. The tests listed in the table are mandatory. If other pathogens are identified, the results will also be provided to the sites.

10.3 DETAILS ABOUT THE STATISTICAL CONSIDERATIONS

The purpose of this appendix is to detail the meta-analysis to estimate the expected treatment effect.

The historical treatment effect of Humira was established based on a meta-analysis of studies being representative for the treatment effect of Humira in the intended 1297.4 trial population:

- CLASSIC 1 (R13-2267): a randomized, double-blind, placebo-controlled, dose-ranging trial performed to evaluate the efficacy of adalimumab induction therapies in patients with CD. In this trial, one endpoint was the percentage of patients achieving a 70-point response at Week 4.
- GAIN (R13 2264): a 4-week, randomized, double-blind, placebo-controlled trial performed to determine whether adalimumab induces remission more frequently than placebo in adult patients with CD who have symptoms. One endpoint was also the decrease in CDAI score by 70 points.

The results are detailed in Table 10.3: 1.

Table 10.3: 1 CLASSIC I and GAIN study results

	CLASSIC I		GAIN	
	Ada 160 mg/80 mg	Placebo	Ada 160 mg/80 mg	Placebo
Number and frequency of patients with 70 points CDAI decrease	45 (59.2%)	27 (36.5%)	82 (51.6%)	56 (33.7%)
Total number of patients per group	76	74	159	166

Ada: adalimumab; CDAI: Crohn's Disease Activity Index.

Response rate

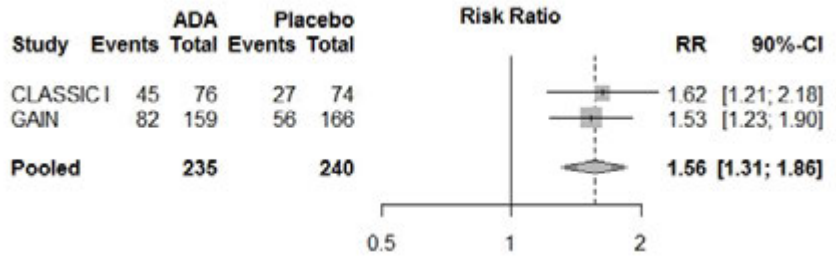
The effect size was computed using the Freeman and Tukey method which is used to normalize and variance-stabilize the sampling distribution of proportions. Then the fixed-effects method was used to pool the response rates together. When back-transforming the results and considering inverse-variance weights, the pooled response rate was 54.1% (95% CI from 47.6% to 60.4%).

Non-inferiority margin

As this is an add-on study only, the standard rules for non-inferiority margin selection will not be applied. Instead, the magnitude of preserved historical treatment effect will be used (based on the point estimate rather than confidence interval).

The RRs of the two studies were pooled to determine the non-inferiority margin of the study. Log transformation was performed and a fixed-effect method (Mantel-Haenszel) was used to pool the RRs together. Using the inverse of the lower limit of the 90% CI of the RR, M1 = 1/1.31 (=0.76) preserves about 39% of the historical treatment effect of adalimumab over placebo (calculated as [ln{1.56}-ln{1.31}]/ln[1.56]=0.3928). The results are presented below:

Figure 10.3:1 Forest plot of the meta-analysis of CLASSIC I and GAIN studies



ADA: adalimumab; CI: confidence interval; RR: risk ratio.
Note: Forest plot produced with R 3.2.3 software.

10.4 CLINICAL EVALUATION OF LIVER INJURY

10.4.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.3.6.1 (AESIs), are to be further evaluated using the following procedures.

10.4.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) within 48 to 72 hours. If it is confirmed that ALT and/or AST values ≥3 times ULN occur in conjunction with an elevation of total bilirubin of ≥2 times ULN, the laboratory parameters listed below (clinical chemistry, serology, hormones, hematology) must be determined and made available to the investigator and to Boehringer Ingelheim as soon as possible.

In addition:

- Obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the "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 ISF;

and report these via the eCRF.

Clinical chemistry

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

Serology

- Hepatitis A (anti-IgM, anti-IgG), hepatitis B (HbsAg, anti-HBs, DNA), hepatitis C (anti-HCV, RNA if anti-HCV positive), hepatitis D (anti-IgM, anti-IgG), hepatitis E (anti-HEV, anti-HEV IgM, RNA if anti-HEV IgM positive), anti-smooth muscle antibody (titer), anti-nuclear antibody (titer), anti-liver-kidney microsomes antibody, anti-mitochondrial antibody

Hormones, tumor marker

- Thyroid stimulating hormone

Hematology

- Thrombocytes, eosinophils

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 (total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then monitor further as specified in the protocol. Depending on further laboratory changes, additional parameters identified, e.g., by reflex testing, will be followed up based on medical judgment and GCP.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		15 Mar 2017
EudraCT number **EU number**		2016-000612-14
BI Trial number		1297.4
BI Investigational Product(s)		BI 695501
Title of protocol		BI 695501 versus Humira® in patients with active Crohn's disease: a randomized, double-blind, multicenter, parallel group, non-inferiority trial comparing efficacy, endoscopic improvement, safety, and immunogenicity
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		Synopsis, Trial site(s)
Description of change		Approximate number of sites and countries updated per latest information.
Rationale for change		To reflect current trial status.
Section to be changed		Synopsis, Methodology
Description of change		Inserted text: "The hematocrit value required to determine CDAI score at Week 4 will be assessed locally and confirmed via central laboratory assessment."
Rationale for change		To clarify that local hematocrit value will be used for CDAI evaluation at the Week 4 visit in order that clinical response can be determined immediately.
Section to be changed		Synopsis, Statistical methods
Description of change		Stratification factor for baseline SES-CD corrected to "<16 or ≥16" (previously ">16 or ≥ 16").
Rationale for change		To correct a typographical error.
Section to be changed		Flow Chart A, footnote 10
Description of change		Text added: "At Visit 4 (Week 4), the hematocrit value to determine CDAI score will be assessed

		locally and confirmed via central laboratory assessment. At visits where no physical examination is performed, weight must be measured for use in CDAI determination."
Rationale for change		To clarify that local hematocrit value will be used for CDAI evaluation at the Week 4 visit in order that clinical response can be determined immediately. Also, to clarify that weight must be measured at all visits where CDAI is evaluated.
Section to be changed		Flow Chart B, footnote 6
Description of change		Text added: "At Visit 8 (Week 12), the hematocrit value from the central laboratory assessment at Visit 6 (Week 8) will be used to determine CDAI score. At visits where no physical examination is performed, weight must be measured for use in CDAI determination."
Rationale for change		To clarify that hematocrit value from prior central laboratory assessment (Visit 6) will be used to determine CDAI at Visit 8, and that weight must be measured at all visits where CDAI is evaluated.
Section to be changed		3.3.2
Description of change		Inclusion criterion 1c updated to "Presence of mucosal ulcers in at least one segment of the ileum or colon and a SES-CD score ≥7 (for patients with isolated ileal disease SES-CD score ≥4), as assessed by ileocolonoscopy and confirmed by central independent reviewer(s) before randomization".
Rationale for change		To amend endoscopic eligibility to make severity of disease as defined by CDAI consistent with endoscopic evaluation (moderate to severely active Crohn's disease implemented as primary inclusion criterion: CDAI 220-450).
Section to be changed		3.3.2
Description of change		Inclusion criterion 2 updated to remove text "or any other anti TNF agent (except adalimumab)".
Rationale for change		To clarify that only infliximab is allowed as first-line anti-TNF therapy; previous treatment with other anti-TNF therapies (specifically certolizumab pegol) will not be permitted.
Section to be changed		Table 4.2.2.1: 1
Description of change		Table row #7: treatment column updated to add

		"and other biologic therapies". Table row #10: treatment column updated to "Cyclosporine, tacrolimus, and mycophenolate mofetil". Reference to "anakinra (Kineret®) and other biologic therapies" removed.
Rationale for change		To maintain consistency with restrictions presented elsewhere in the protocol.
Section to be changed		5.2.1
Description of change		Text inserted into paragraph #2: "At Week 4, the hematocrit value required to determine CDAI score will be assessed locally and confirmed via central laboratory assessment. At Visit 8 (Week 12), the hematocrit value from the central laboratory assessment at Visit 6 (Week 8) will be used to determine CDAI score. At visits where CDAI evaluation is performed and no physical examination is planned, body weight must be measured for use in CDAI determination."
Rationale for change		To clarify that local hematocrit value will be used for CDAI evaluation at the Week 4 visit in order that clinical response can be determined immediately. Also, to clarify that hematocrit value from Visit 6 will be used for Visit 8 CDAI determination and that weight must be measured at all visits where CDAI is evaluated.
Section to be changed		Table 5.2.1: 1
Description of change		CDAI scoring formula corrected for "Body Weight" variable on last row of table.
Rationale for change		To correct typographical error.
Section to be changed		5.3.3
Description of change		New paragraph added: "At Week 4, in order to assess clinical response during the visit, the hematocrit value required to determine CDAI score will be assessed locally and subsequently confirmed via central laboratory assessment."
Rationale for change		To clarify that local hematocrit value will be used for CDAI evaluation at the Week 4 visit in order that clinical response can be determined immediately.
Section to be changed		6.2.1, Screening Visit 1.1, Day -9
Description of change		In paragraph #1, specified use of weight measurement from Visit 1 in addition to

		hematocrit value. In same paragraph, also added that for patients to be eligible, evidence of mucosal ulcers must be in at least one segment of the ileum or colon. Also updated "initial isolate ileitis" to "isolated ileal disease".
Rationale for change		To clarify use of Visit 1 weight for CDAI determination and to update requirements for eligibility to be consistent with inclusion criteria.
Section to be changed		6.2.2, Visits 4 and 14 (Days 29 and 169, respectively)
Description of change		Inserted text as new bullet #5: "Local hematocrit testing (Visit 4 only; to be used for CDAI evaluation)"
Rationale for change		To clarify that local hematocrit value will be used for CDAI evaluation at the Week 4 visit in order that clinical response can be determined immediately.
Section to be changed		7.4.1
Description of change		In paragraph #1: 1. Original text "A snapshot of the database will be taken and will be used for performing the analysis." is replaced by "The cut-off date will be the date on which the last patient completes the Week 4 visit. The cut-off date will be the same for all patients. A database snapshot will be taken with regard to this cut-off date; it will include all data available in the database up to and including the cut-off date and will be used for performing the analysis." 2. New text inserted at end of paragraph: "Efficacy data will be included up to the Week 4 visit only and all available data for safety and other endpoints will be included up to the data cut-off date."
Rationale for change		To add further clarification of the process to be used for primary analysis.
Section to be changed		Appendix 10.1
Description of change		In paragraph #4, added clarification that designated person may be unblinded or blinded and that unused trial medication may be returned to sponsor as an alternative to local destruction.
Rationale for change		To bring protocol in line with instructions included

		in trial Pharmacy Manual.
Section to be changed		Appendix 10.1, Patient blinding procedure
Description of change		Text added as new bullet #3: "Used syringes should be destroyed immediately at the local site after use and this should be documented in the related investigational product forms."
Rationale for change		To bring protocol in line with instructions included in trial Pharmacy Manual.
Section to be changed		Appendix 10.1, Site staff blinding procedure
Description of change		In table listing blinded personnel, for Blinded Sub-Investigator or Study Coordinator/Study Nurse, text inserted as new bullet #6: "Can be involved in the receipt, storage control and return of IP (since secondary package is blinded)"
Rationale for change		To bring protocol in line with instructions included in trial Pharmacy Manual.
Section to be changed		Appendix 10.1, Site staff blinding procedure
Description of change		In table listing blinded personnel, for Blinded CRA, in bullet #2 added that blinded and unblinded site teams will be supported.
Rationale for change		To bring protocol in line with instructions included in trial Pharmacy Manual.
Section to be changed		Appendix 10.1, Site staff blinding procedure
Description of change		In table of unblinded personnel for Unblinded Trial Medication Administrator, bullet list updated as follows: 1. New bullet #2 added: "Destroys used syringes in a blinded fashion after administration of trial medication according to local procedures such as local SOPs" 2. New bullet #3 added: Retains used unsealed/opened boxes (secondary packaging), which contained the syringes before administration of trial medication, for reconciliation by blinded CRA prior to destruction" 3. Original bullet #3 updated to: "Works and communicates with the unblinded CRA in a way that does not reveal the treatment arm" 4. Original bullet #4 replaced by: "Can be

		involved in the receipt, storage control, and return of trial medication"
Rationale for change		To bring protocol in line with instructions included in trial Pharmacy Manual.

11.2 GLOBAL AMENDMENT 2

Date of amendment		12 Dec 2017
EudraCT number **EU number**		2016-000612-14
BI Trial number		1297.4
BI Investigational Product(s)		BI 695501
Title of protocol		BI 695501 versus Humira® in patients with active Crohn's disease: a randomized, double-blind, multicenter, parallel group, exploratory trial comparing efficacy, endoscopic improvement, safety, and immunogenicity
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, Synopsis (Title of trial, Methodology, No. of patients, Statistical methods), Sections 2.1, 3.1, 3.2, 7.1, 7.2, 7.3.1, 7.3.2.1, 7.7.
Description of change		The study methodology as well as related statistical method and sample size calculations have been updated
Rationale for change		Based on the fact that BI 695501 was already approved by the authorities for all Humira indications and an additional confirmatory trial is not necessary. Additionally, the patients with moderately to severely active CD (CDAI 220-450), confirmed by endoscopy or radiologic evaluation represent a relatively small proportion in a Crohn's disease population. This fact causes enormous difficulties to find the patients for the study participation within a reasonable timeframe and therefore the trial was redesigned to an exploratory trial. Implementation of the updated statistical considerations will allow achieving the study objectives for the efficacy, as well as the

		assessments of safety with the number of evaluable subjects decreased to 65 in each group and the total sample size of approximately 130.
Section to be changed		Flow Chart A, footnote 4
Description of change		Text added: "….TB test will be performed at Week 24 before switch from EU-approved Humira to BI 695501, at EoT visit and may be performed….." Flow Chart B: TB testing (IGRA) added on Visit 14, Week 24.
Rationale for change		Additional TB testing added on Week 24, before switching from Humira to BI 695501, to clarify whether the incidence of possible positive TB tests is linked to the reference or investigational product.
Section to be changed		3.3.3, 4.2.2.1:1
Description of change		Exclusion criterion 8 updated to "Patients who have received any biological treatment (other than TNF inhibitors), or investigational biological agent with the exception of infliximab within 6 months prior to Screening". 4.2.2.1:1 Line 6 and 7 updated accordingly
Rationale for change		To emphasize that TNF inhibitors use is not allowed.
Section to be changed		3.3.3
Description of change		Exclusion criterion 10 updated to remove text "or are positive for anti-adalimumab antibodies at baseline"
Rationale for change		To clarify that the results of the ADA are not available at the time of inclusion.
Section to be changed		5.2.1
Description of change		Text updated in paragraph #3: "The patient is required to keep a symptom diary for 4 of these 8 variables (number of liquid stools, abdominal pain, general well-being, and use of antidiarrheal drugs) for 7 *consecutive* days before each CDAI evaluation." Paragraph #4: The day of bowel preparation for colonoscopy *and the day of colonoscopy* will be

		excluded from the CDAI assessment.
Rationale for change		To emphasize on which days the parameters for the CDAI score are to be captured.
Section to be changed		5.3.5.1,
Description of change		Paragraph 2, TB testing included at Visit 14 Week 24 (before switch from EU- approved Humira to BI 695501. New paragraph 3 added: "In the event of an indeterminate or positive result during the study, the test should be repeated and if a result is positive then the patient will discontinue receiving the study treatment and followed up for safety. The patient will be referred to the specialist as required by local regulations."
Rationale for change		To clarify the TB testing procedure, evaluation and follow up.
Section to be changed		6.2.2, Visits 4 and 14 (Days 29 and 169), 10.2
Description of change		New bullet point added: TB test (IGRA e.g., QuantiFERON® Gold assay; at Visit 14 only)
Rationale for change		To clarify the TB testing procedure
Section to be changed		6.2.2, End of Treatment Visit
Description of change		Inserted new text added: "The patient who early discontinued from the trial will receive treatment as deemed appropriate by the investigator and in accordance with the applicable guidance".
Rationale for change		To give a guidance how to proceed in case of early discontinuation.
Section to be changed		Appendix 10.1
Description of change		Patient blinding procedure: Text in the bullet #3 updated: "Used syringes should be *discarded in a sharp container* immediately after use. The following sentence was removed: "at the local site after use and this should be documented in the related investigational product forms." Site staff blinding procedure (Unblinded personnel): 3rd bullet point updated to: "*Discard* used syringes

		in a blinded fashion after administration of trial medication according to local procedures such as local SOPs.
Rationale for change		To correct the misleading wording on how to handle used syringes in accordance with medical requirements and to bring the protocol in line with instructions included in trial Pharmacy Manual.
Section to be changed		Appendix 10.2, List of laboratory tests, Stool studies
Description of change		Foot note 1 was added: "1. The tests listed in the table are mandatory. If other pathogens are identified, the results will also be provided to the sites."
Rationale for change		To clarify that other pathogens might also be identified.
Section to be changed		Appendix 10.3, Non-inferiority margin
Description of change		Following paragraph was added: As this is an add-on study only, the standard rules for non-inferiority margin selection will not be applied. Instead, the magnitude of preserved historical treatment effect will be used (based on the point estimate rather than confidence interval).
Rationale for change		To emphasize that the study design and methodology was changed.

APPROVAL / SIGNATURE PAGE

Document Number: c09542349 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-revision-02

Title: BI 695501 versus Humira in patients with active Crohn's disease: a randomized, double-blind, multicenter, parallel group, exploratory trial comparing efficacy, endoscopic improvement, safety, and immunogenicity

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		13 Dec 2017 11:42 CET
Approval-Translational Medicine Expert		13 Dec 2017 11:44 CET
Author-Trial Statistician		13 Dec 2017 11:50 CET
Author-Trial Clinical Pharmacokineticist		13 Dec 2017 12:31 CET
Approval-Team Member Medicine		13 Dec 2017 12:46 CET
Verification-Paper Signature Completion		13 Dec 2017 13:37 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed