Clinical Trial Protocol

	Document Number:	**c10710598-04**
EudraCT No.: **EU Trial No:**	2017-000100-20	
BI Trial No.:	1368-0004	
BI Investigational Product(s):	BI 655130	
Title:	Exploratory Trial to Assess Mechanism of Action, Clinical Effect, Safety and Tolerability of 12 Weeks of Treatment with BI 655130 in Patients with Active Ulcerative Colitis (UC)	
Lay Title:	This study tests how BI 655130 works in patients with active ulcerative colitis. The study also tests how well BI 655130 is tolerated and whether it helps the patients.	
Clinical Phase:	IIa	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	Phone: Fax:	
Status:	Final Protocol (Revised Protocol (based on global amendment 3))	
Version and Date:	**Version: 4.0**	**Date: 03 Apr 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 655130	
Protocol date: 13 Feb 2017	**Trial number:** 1368-0004		**Revision date:** **03 Apr 2019**

Trial site(s):	Multi-centre, multi-national
Clinical phase:	IIa
Objective(s):	The primary objective of this study is to understand the mode of action of BI 655130 in patients with active ulcerative colitis (UC)
Methodology:	This is an open-label, single-arm, phase IIa exploratory trial in patients with moderately to severely active UC. The trial includes a screening period, a 12-week treatment period and a safety follow-up period of 16 weeks (~5 half-lives of BI 655130, after the last dose of BI 655130, which is at Week 8). Patients are required to be on conventional, non-biologic treatment for UC, with stable treatment doses throughout the trial. Cf. Section 4.2.1 for more details.
No. of patients:	
total entered:	10
each treatment:	10 (single-arm)
Diagnosis :	Moderately to severely active ulcerative colitis (UC)
Main criteria for inclusion:	• 18 – 75 years at screening • Body weight ≤ 100 kg (at screening and at Day 1 of treatment) • Diagnosis of UC ≥3 months prior to screening. • Moderately to severely active UC as confirmed by Mayo Score ≥6 (with rectal bleeding ≥ 1 and modified endoscopy score ≥2) and elevated CRP or calprotectin at pre-baseline visit • Receiving conventional, non-biologic therapy for UC.

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 655130	
Protocol date: 13 Feb 2017	**Trial number:** 1368-0004		**Revision date:** **03 Apr 2019**

	Treatment could consist of one of the following: • Oral 5-ASA compound, with stable dose for at least 4 weeks prior to screening • 6-MP, MTX or AZA, with stable dose for at least 8 weeks prior to screening • Oral corticosteroids (≤ 20mg/day per day of prednisone or equivalent), with stable dose for at least 4 weeks prior to screening • Negative colon cancer screening by full colonoscopy with serial biopsies (or according to local standard of care) performed and documented within the past 12 months prior to screening (otherwise to be done at pre-baseline visit) • Patients who are naïve or experienced to TNF antagonists (including infliximab, adalimumab, or golimumab) but have not failed that treatment due to primary non-response or loss of response (previous anti-TNF treatment outcome and reason for discontinuation must be documented in source data)
Test product(s):	BI 655130 (infusion solution)
dose:	1200mg every four weeks
mode of administration:	i.v.
Duration of treatment:	12 weeks (i.v. infusions at Day 1, Week 4, Week 8)
Primary and Secondary Endpoints	**Primary endpoint:** The total number of deregulated genes comparing baseline to post-treatment, analysed by gene expression of mucosal biopsies via RNA sequencing, per time point up to week 12. **Secondary endpoints:** • Drug related adverse events • Percent change in CRP from baseline to Week 12

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 655130	
Protocol date: 13 Feb 2017	**Trial number:** 1368-0004		**Revision date:** **03 Apr 2019**

	• Percent change in faecal calprotectin from baseline to Week 12 • Percent change in faecal lactoferrin from baseline to Week 12 • Clinical remission (defined as Mayo score ≤2 points, and all subscores ≤1 point) at Week 12
Safety criteria:	Physical examination, vital signs, 12-lead ECG, laboratory tests, adverse events, serious adverse events and tolerability
Pharmacokinetic criteria	Pharmacokinetic parameters of BI 655130: trough levels (for all patients), descriptive statistics and PK parameters as appropriate
Statistical methods:	Descriptive statistics for efficacy endpoints, safety and PK.

FLOW CHART

Trial periods	**Screening**		**Treatment period**								**Follow-up**	
Visit	**V1a (Screening)**	**V1b (Pre-baseline)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**EoT[13]**	**FU1**	**EoO[12]**
Week					**2**	**4**	**6**	**8**	**10**	**12**	**18**	**28**
Day	**-35 to -9**	**-8 to -6**	**1**	**4**	**15**	**29**	**43**	**57**	**71**	**85**	**V7 +70**	**V7 +141**
Visit window (days)					**±1**	**±2**	**±2**	**±2**	**±2**	**-6 to+1**	**±5**	**+5**
Informed consent	X											
In-/exclusion criteria	X	X	X									
Demographics	X											
Medical history incl smoking/alcohol	X											
Sigmoidoscopy + biopsies[1]		X[2]	X[3, 14]	X	X			X[3]		X		
Mayo score[4]		X[T]	X[T]		X[T]	X[P]	X[P]	X[T]	X[P]	X[T]	X[P]	X[P]
Physical exam[5]	X[C]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[C]	X[T]	X[C]
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X			X		X		X		X
Height	X											
12-lead ECG	X		X			X		X		X		X
Pregnancy test[7]	X		X			X		X		X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for safety lab tests[8] and infection screening	X	X	X[9]	X	X	X[9]	X	X[9]	X	X	X	X

Flow chart (cont.)

Trial periods	**Screening**		**Treatment period**								**Follow-up**	
Visit	**V1a (Screening)**	**V1b (Pre-baseline)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**EoT[13]**	**FU1**	**EoO[12]**
Week					**2**	**4**	**6**	**8**	**10**	**12**	**18**	**28**
Day	**-35 to -9**	**-8 to -6**	**1**	**4**	**15**	**29**	**43**	**57**	**71**	**85**	**V7 +70**	**V7 +141**
Visit window (days)					**±1**	**±2**	**±2**	**±2**	**±2**	**-6 to+1**	**±5**	**+5**
QuantiFERON Test for TB screening	X											
Blood sampling for gene expression and methylation pattern		X	X[9,14]	X	X	X[9]		X[9]		X		
Blood sampling for PK			X[9]	X	X	X[9]	X	X[9]	X	X	X	X
Blood sampling for ADAs			X[9]			X[9]		X[9]		X	X	X
Stool sampling for faecal BMs		X	X	X	X	X	X	X	X	X		
Stool sampling for enteric pathogens	X[10]	X[10]										
Diary dispensing[11]	X											
BI 655130 i.v. infusion			X			X		X				
Trial completion											X[13]	X[13]

1. Sigmoidoscopy (or colonoscopy at pre-baseline visit, if applicable), should be done prior to study drug administration. At each visit indicated, biopsies will be collected for gene expression and for methylation patterns. At Day 1 (pre-dose), at Week 2 and at Week 12, additional biopsies will be taken
. Refer to Section 15 of the ISF for further information on the collection of biopsies.
2. A documented negative colon cancer screening by full colonoscopy with serial biopsies (or according to local standard of care) is required from the past 12 months prior to screening. If this is not available, colon cancer screening has to be conducted at Visit 1b (pre-baseline). In that case, a full colonoscopy will be done instead of the planned sigmoidoscopy at that visit. In both cases, biopsies for the evaluation of trial endpoints will be taken. Refer to Section 15 of the ISF for further details.
3. At study visits with study drug administration, biopsy samples must be obtained prior to start of i.v. infusion. At study visit 2, additional biopsy samples must be obtained at 4 hours after start of the study drug infusion.
4. Mayo score: T=total, P=partial (without endoscopic subscore), a modified Mayo Score excluding physician's assessment will also be evaluated. Refer to Appendix 10.1.
5. Physical examination: C=complete, T=targeted. Refer to Section 5.3.1.
6. At visits with study drug administration (Visits 2, 5 and 7), vital signs will be assessed pre-dose, and at approximately 5 and 120 minutes after end of infusion. Monitor for signs and symptoms of hypersensitivity reactions for approximately 2 hours after end of infusion. Refer to Section 5.3.2.
7. Only applicable for women of childbearing potential. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all other visits indicated in the Flow Chart. In case of a positive urine pregnancy test, a serum pregnancy test will be done. Urine pregnancy testing should be done prior to administration of study drug in case there is dosing at study visits. Study drug should only be administered in case of a negative test result.
8. Includes clinical chemistry, haematology, coagulation and urinalysis assessments. Patient must be fasting for at least 8 hours prior to blood collection (except screening visit). If not fasted, mark on laboratory requisition.
9. At study visits with drug administration, blood samples must be obtained within approximately 2 hours prior to start of i.v. infusion.
10. Stool sampling will be done during screening period (Visit 1a or visit 1b, or at an unscheduled visit).
11. Diary will be used by the patient for the reporting of bowel movement frequency and rectal bleeding (blood in stool). The information will be used for the calculation of mayo score at the visits indicated in the Flow Chart. In addition, background UC medication will be recorded. Refer to Section 6.2.1 for more details.
12. Patients with early treatment discontinuation will complete EoT visit procedures and return for EoO visit 20 weeks (>5 half-lives of BI 655130) after the last dose of BI 655130.
13. Patients who complete regular treatment in study 1368-0004 will be offered to enter a long-term extension trial (1368-0017), which is currently in preparation. These patients can switch to trial 1368-0017 at EOT visit, and for these patients, their EoT visit will also be their EoO visit.
14. At Visit 2, a second sigmoidoscopy will be performed at 4 hours after start of the first study drug infusion to collect biopsy samples 4 hours post-dose. Also an additional blood sample for gene expression and methylation pattern analysis will be collected at 4 hours after start of infusion.

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
5-ASA	5-Aminosalicylate
AST	Aspartate Aminotransferase
AUC	Area under the Curve
AZA	Azathioprine
BI	Boehringer Ingelheim
BM	Biomarker
CD	Crohn's Disease
C_{max}	Maximum concentration observed
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CRS	Cytokine Release Syndrom
CRP	C-Reactive Protein
CTP	Clinical Trial Protocol
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
ELISA	Enzyme Linked Immunosorbent Assay
EoO	End of Observation (End of Trial)
EoT	End of Treatment
EudraCT	European Clinical Trials Database
FcR	Fc Receptor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPP	Generalized Pustular Psoriasis
GPV	Global Pharmacovigilance
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry

IL-36R	Interleukin-36 Receptor
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	intravenous
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Drug Regulatory Activities
MoA	Mode of Action
MTX	Methotrexate
6-MP	6-Mercaptopurine
PBMC	Peripheral Blood Mononuclear Cells
PBO	Placebo
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
PPP	Palmoplantar pustulosis
PT	Preferred Term
qw	Once a week
rDNA	Ribosomal DNA
RBS	Rectal Bleeding Subscore
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RNA	Ribonucleic Acid
RNAseq	RNA sequencing
RRBS	Reduced Representation Bisulfite sequencing
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TCM	Trial Clinical Monitor
TGF-β	Transforming Growth Factor beta
TNF	Tumour Necrosis Factor
TSAP	Trial Statistical Analysis Plan
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
V	Visit
VEGF	Vascular Endothelial Growth Factor
w	Week
WBC	White Blood Count
WHO	World Health Organization

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Ulcerative Colitis (UC) has an estimated incidence of 24.3 and 19.2 cases per 100,000 persons per year in Europe and the USA, respectively, resulting in a continuously rising prevalence (R15-0886). UC is characterized clinically by abdominal pain, fever, and blood or mucosa-containing diarrhea, and pathologically by inflammatory lesions in the gastrointestinal mucosa. Inflammatory lesions characteristically occur distal to the terminal ileum, and by confinement of lesions to the mucosa and submucosa without transmural inflammation. UC typically follows a relapsing and remitting course, and is associated with substantial acute and long-term morbidity and increased mortality. The mainstays of drug therapy for UC are: orally administered aminosalicylates, glucocorticoids, oral immunomodulatory agents azathioprine (AZA) and 6-mercaptopurine (6-MP), and Tumour Necrosis Factor (TNF) antagonists. In patients with mild UC, 5-Aminosalicylate (5-ASAs) are safe and effective for induction and maintenance treatment. Glucocorticoids, immunomodulators, TNF antagonists, and more recently vedolizumab, are reserved for patients with moderate to severe disease, in whom the primary goals of drug therapy are to induce and subsequently to maintain remission from signs and symptoms of active disease. Current biologic treatment of UC is associated with approximately one third of patients each failing with primary or secondary non-response. In addition, treatment may be limited due to safety and tolerability issues. Therefore, despite therapeutic progress, there remains a significant unmet medical need for new treatment options with an improved safety and efficacy profile compared to the current therapeutic standard.

1.2 DRUG PROFILE

BI 655130 is a humanized antagonistic monoclonal Immunoglobulin G (IgG)1 antibody that blocks human Interleukin-36 (IL-36R) signalling. Binding of BI 655130 to IL-36R is anticipated to prevent the subsequent activation of IL-36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways with the aim to reduce epithelial cell/ fibroblast/ immune cell-mediated inflammation and interrupt the inflammatory response that drives pathogenic cytokine production in inflammatory diseases including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP) and inflammatory bowel disease (IBD).

Preclinical studies
BI 655130 binds to human IL-36R with high binding avidity. BI 655130 effectively inhibits IL36 ligand-stimulated NF-κB activation, IL8 release and IFNγ secretion in human cell cultures or Peripheral Blood Mononuclear Cells (PBMC) stimulated with IL36α, IL36β, or IL36γ combined with IL12.

Mutations BI 655130`s Fc receptor (FcR) were introduced to abrogate FcR binding activity and function. Direct assessment of the impact of these mutations in the IgG1 FcR binding sites revealed that the mutations abrogate both antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effector functions and indicate that BI 655130 will be a non-depleting therapy in vivo.

Toxicology studies
BI 655130 does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with BI 655130. However, hazard identification studies of the mode-of-action (MoA) of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (mAb) (BI 674304), a mouse IgG2a mAb with rat variable regions. In a 13-week intravenous (i.v.) toxicity study of BI 674304 in mice, no adverse effects of IL-36R antagonism were seen at a dose (50 mg/kg, twice weekly) that was 5 fold higher than the dose that was protective in an experimental mouse colonic inflammation model. The in vitro cytokine release and tissue cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, BI 655130 stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1 mL injections of the subcutaneous formulation in rabbits.

These preclinical data suggest that BI 655130 can be safely administered to humans for up to 13 weeks.

Clinical PK/PD studies
BI 655130 or placebo (PBO) was administered to 78 healthy volunteers at single ascending IV doses from 0.001 mg/kg to 10 mg/kg body weight (1368.1). Safety and tolerability of all tested IV doses was good. There were no drug-related serious adverse events (SAEs). Adverse events (AEs) categorized as related to treatment were observed in 3/19 (15.8%) subjects in the PBO group and in 7/59 (11.9%) subjects treated with BI 655130. The most frequent treatment-emergent AEs were nasopharyngitis (BI 655130: 21%; PBO: 15%), headache (BI 655130: 9%; PBO: 15%), influenza like illness (BI 655130: 7%; PBO: 10%), and diarrhoea (BI 655130: 3%; PBO: 10%). There were two AEs of moderate intensity (injection site haematoma, headache), all remaining AEs were of mild intensity. There was no apparent relationship between the frequency of AEs and the dose. There were no relevant changes compared to PBO for laboratory safety, including clinical chemistry, haematology, coagulation parameters, and urinalysis. No clinically relevant changes were observed in 12 lead ECGs, vital signs, and cardio-monitoring.

Pharmacokinetics (PK) analysis showed that exposure ($AUC_{0\text{-tz and Cmax}}$) to BI 655130 seems to increase with increasing dose in a greater than dose-proportional manner from 0.01 to 0.3 mg/kg while exposure increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. The effective half-life of BI 655130 is approximately 4 weeks in the linear dose range. Overall, PK data so far suggests target-mediated drug disposition kinetics for BI 655130. The saturation of the non-linear elimination pathway is likely occurring after 0.3 mg/kg and BI 655130 seems to exhibit linear kinetics from the next dose-level onwards. Anti-drug antibodies (ADA) were detected in 8 patients, 3 of those had pre-existing levels. However, caution should be taken in interpreting the ADA results because the drug concentrations in many ADA samples exceeded the drug tolerance level of the ADA assay (100 µg/mL). Pharmacodynamic (PD) effects in this first in human Single Rising Dose trial (c03320877) were assessed by indirect target engagement of IL-36R by BI 655130 using an ex-vivo whole blood stimulation assay. Preliminary analyses indicate that >94% peripheral IL-36R receptor occupancy is achieved with doses ≥3 mg/kg from 30 minutes post infusion to Week 10.

In the multiple rising dose trial (1368.2), BI 655130 or PBO have been administered to healthy male volunteers at multiple ascending i.v. doses of 3, 6 and 10 mg/kg given once a week (qw) for 4 weeks (i.e. 4 administrations), as well as a single dose cohort of 20 mg/kg. All dose groups (8 patients each, 3:1 on active or PBO) have completed dosing and 4 weeks of follow-up. Overall, BI 655130 was well tolerated. There were no AEs considered to be dose limiting and no SAEs. In all cases the AEs were of mild or moderate intensity. Furthermore, there were no clinically relevant abnormalities on treatment with BI 655130 with respect to safety laboratory, vital signs, or ECGs as assessed by a central reader.

Based on population pharmacokinetic modelling informed by both studies, the exposures of BI 655130 in this trial 1368.10 are not predicted to exceed the exposures tested and found safe with the highest tested dose regimen in 1368.2 (20 mg/kg qw for 4 weeks). Specifically, body weight was included as a covariate in the PK model which accounted for a small portion of inter-individual variability in exposure. This model was then used to simulate with variability the pharmacokinetic profile for a typical 30 kg individual dosed 1200 mg every 4 weeks and compared to a 60 kg individual receiving 20 mg/kg weekly as shown in the plot below:

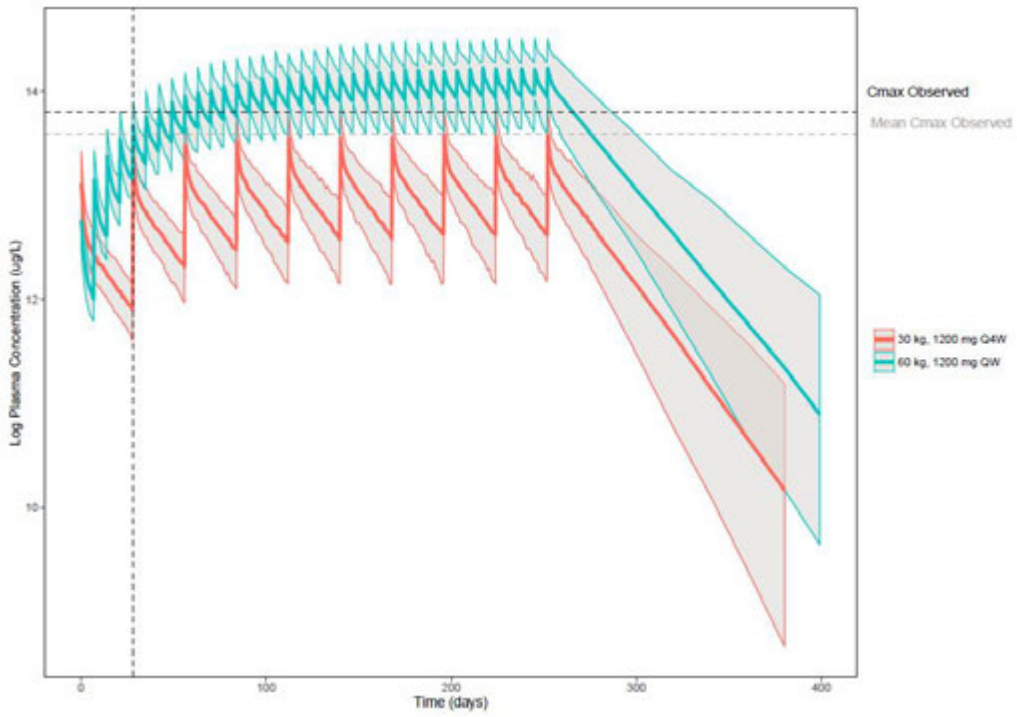

Figure 1.2: 1 Population pharmacokinetic modelling comparing the 1200 mg q4w dosing regimens of a 30 kg individual in 1368.10 to the 1200 mg qw dosing regimen of a 60 kg subject in 1368.2.

The shaded region in the plot represents the 90 % prediction/confidence interval of the simulated PK profiles for the respective dosing regimens. As can be seen from the plot, the 30 kg predictions do not exceed the maximum observed C_{max} from the 1368.2 trial for the planned 1368.10 trial duration. Additionally, the AUC and C_{max} predicted at steady state for the 30 kg individual do not exceed the steady state exposures predicted after weekly dosing

of 20 mg/kg. Assuming no differences in drug clearance between healthy volunteers and patients with UC, for patients with a body weight of 30 kg, the median AUC at steady state is predicted to be 2.88 fold lower (35,595 ug/mL*day vs 12,344 ug/mL*day) in the 30 kg subject dosed 1200 mg q 4 weeks compared to the 20 mg/kg dosing regimen given weekly. Similarly, the median C_{max} (log transformed) at steady state is predicted to be lower at 13.58 ug/L (13.4 – 13.9 (90% CI)) for the 30 kg individual compared to 14.3 ug/L (13.98 – 14.53 (90% CI)).

Summary
BI 655130 is an anti IL-36R antibody with a high potential to block IL-36R signaling. BI 655130 has been tested in healthy volunteers with single and multiple doses up to 20 mg/kg i.v. (single dose) or 20 mg/kg (multiple doses), which were all safe and well tolerated. In addition, IL-36R inhibition shows a favorable nonclinical safety profile. Therefore, BI 655130 might be a promising drug to treat patients suffering from UC.

For a more detailed description of the BI 655130 profile, please refer to the current "Investigator`s Brochure" (c03320877).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

BI 655130 is currently under development for the treatment of UC. Its unique dual mode of action (MoA) includes anti-inflammatory effects as well as tissue remodeling effects and thus may provide a clear advantage over current drugs and investigational compounds, which target inflammatory pathways. The potential BI655130 effects on remodeling may turn into increased mucosal healing and reduced stricturing and fistulizing complications of IBD.

The link between IL-36R driven inflammation and epithelial inflammation has led to the hypothesis that IL-36R signalling may play an important role in IBDs such as UC:

- IL-36R and its ligands are expressed in intestinal biopsies from patients with chronic IBD;
- IL36-induced genes are upregulated in human intestinal myofibroblasts and correlate with gene signatures observed in UC and Crohn's disease (CD) patients;
- Human IL-36 ligands in cell culture enhance epithelial intestinal barrier permeability, a hallmark of IBD pathogenesis;
- IL-36R signalling induces in human intestinal myofibroblasts and macrophages not only pro-inflammatory but also tissue remodelling related mediators (e.g., tissue growth factor TGF-β, matrix metalloproteinase), which differentiates this mechanism from TNF alpha and IL23 pathways;
- IL-36R signalling in disease relevant cells such as intestinal myofibroblasts and macrophages induce not only pro-inflammatory but also tissue remodelling related mediators (e.g., tissue growth factor TGF-β, matrix metalloproteinase)
- An antagonist anti-mouse IL-36R antibody ameliorates intestinal inflammation in various acute and chronic murine colitis models.

Altogether these findings support a prominent role of IL-36R in driving intestinal inflammation.

In the present trial, an exploratory systems biology approach will be used to investigate genomic changes in the patient, in response to the cytokine blockade induced by systemic (i.v.) exposure to BI 655130.

The collected data from this trial will enable the determination of the mechanism of action of BI 655130 and the characterization of pathophysiology events following BI 655130 exposure in UC patients.

In addition, first data on clinical effect, safety and PK of 12 weeks of BI 655130 treatment in UC patients will be gained and compared to the BI 655130 exposure achieved with equivalent doses in healthy volunteers. These data will help to understand the pharmacokinetic characteristics of BI655130 in UC, which may differ from those in healthy volunteers and patients with other diseases due to the expected intestinal protein loss subsequent to mucosal inflammation and ulceration in the colon.

These findings will support planning and conduct of later stage proof-of-concept dose-finding and pivotal trials.

Furthermore, the collected data may assist in identifying potential biomarkers (BMs) for the development of targeted therapies and for clinical monitoring of therapeutic effect of treatment.

The most recent and more detailed information is available in the current IB (c03320877).

2.2 TRIAL OBJECTIVES

The primary objective of this trial is:
- To understand the mechanism of action of BI 655130 in patients with UC

Secondary and further objectives are:
- To explore clinical effect, safety and tolerability (including immunogenicity) of BI 655130 treatment
- To identify specific BMs with potential usefulness to predict clinical efficacy or safety outcome or to help understand BI 655130's MoA
- To evaluate PK during treatment with BI 655130 in UC as compared to healthy volunteers and other disease states (e.g. PPP and GPP)

2.3 BENEFIT-RISK ASSESSMENT

Preclinical profiles of BI 655130 and clinical data from trials in healthy volunteers suggest that BI 6555130 is safe and may address an unmet medical need in UC patients by a dual bimodal anti-inflammatory and anti-fibrotic mechanism of action (cf. Section 2.1).

No relevant animal species is available for toxicology testing of the highly human specific antibody BI 655130. However, preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of IL-36R inhibition in mice (for details cf. IB (c03320877)).

The clinical safety and tolerability profile of BI 655130 has been tested and found favourable in male healthy subjects treated with i.v. single doses up to 20mg/kg or multiple doses up to 20 mg/kg body weight qw for up to 4 weeks: BI 655130 was safe and well tolerated in both completed Phase I trials at all dose groups with no reporting of any dose dependent, severe or serious AE (for details cf. Section 1.2 and Investigator's Brochure (IB) (c03320877)). In addition, further phase I studies in healthy volunteers (1368.3, 1368.9) and clinical proof-of-concept studies are ongoing in different indications (1368.11 – GPP; 1368.15 – PPP, 1368.10 – UC) under regular surveillance by an independent DMC. None of these studies has so far

generated any specific safety signal (see IB c03320877). In summary, as of September 2017, more than 170 subjects have been exposed to active drug without observation of any dose limiting safety or tolerability issue.

Importantly, based on population pharmacokinetic modelling informed by1368.1 and 1368.2, the exposures of BI 655130 in this trial are predicted to not exceed the exposures tested and found safe with the highest tested dose regimen in 1368.2 even in subjects with a body weight as low as 30 kg (see section 1.2). As can be seen from the plot in figure 1.2: 1, the predictions for a 30 kg individual do not exceed the maximum observed C_{max} from the 1368.2 trial for the planned 1368.10 trial duration. However, the expected difference in drug clearance between healthy volunteers and patients with UC will further increase the differences in exposures between 1368.2 and 1368.10 and thus increase the safety margin. Therefore, there is no need to restrict enrolment in patients with a low body weight.

As BI 655130 is a first-in class compound, no clinical patient data of compounds with a related MoA have been disclosed. Trial 1368-0004 is the first trial to include evaluations for efficacy with BI 655130 in UC patients. Therefore, it is difficult to estimate the chance of a direct benefit for the individual patient in this phase II trial. However, as remissions under induction treatment in active UC can typically be seen after 4-8 weeks of treatment with biologics, 12 weeks treatment duration in this trial are expected to be sufficient in principle to observe a clinical and/or endoscopic remission, which would represent an individual benefit. Also, patients who complete 12 weeks treatment duration will be offered to continue treatment in a long-term extension trial.

For patients experiencing treatment failure or relapse after End of Treatment (EoT), four approved biologics with two different MoAs will be available for treatment, as all patients are naïve to previous biologics treatments.

In addition to a potential individual benefit, this trial may also contribute to generate a group benefit for this and other patient populations, as the main aim of this trial is to investigate the mode of mechanism of BI 655130 by collection of various BMs in mucosal biopsies, blood and stool.

Thus, the exposure range expected with the selected dose regimen in study participants will be covered by safety data from healthy volunteer studies, even if the subject's body weight is as low as 30 kg. However, these predictions are made based upon comparable exposures between healthy volunteers and IBD patients, while in fact lower systemic exposures are typically found in UC patients compared to healthy subjects due to higher drug clearance of monoclonal antibodies resulting from: (i) intestinal protein loss caused by exsudative enteropathy (R16-5741; R16-5706), (ii) higher degree of systemic inflammatory burden (R13-3046) and (iii) higher expression of the target molecule (IL-36R) in diseased tissues as compared to peripheral blood of healthy subjects, which may increase the effect of target-mediated drug disposition on clearance of BI 655130.

Such lower exposure found with many biologics in IBD patients represents the basis for requiring higher doses in IBD compared to other indications (e.g. infliximab, adalimumab, ustekinumab) (R13-5226; R15-4915; R16-0692; R16-0573).

Also, in contrast to new chemical entities, the safety and tolerability profile of biologics is generally driven by the downstream effects of target molecule binding, and is not directly dose dependent at exposures approaching full receptor occupancy, which has been achieved for BI 655130 in the healthy volunteer trials. The only exception might be infusion reactions, which have not been reported in phase I and will be closely monitored during extended monitoring after each study drug administration.

As with any immune modulating agent, BI 655130 has the theoretical potential to impair immune function resulting in an increased risk of infection or lymphoma. In line with IL-36 being a member of the pro-inflammatory IL-1 cytokine family, IL-36 has been shown *in vitro* to stimulate various pro-inflammatory cytokines and activate NFκB.

The potential risk of immunosuppression will be mitigated by thorough safety measures: (i) exclusion of patients with history or increased risk of malignancies or infections; (ii) close clinical monitoring for AEs, including Rheumatology Common Toxicity Criteria (RCTC) criteria for intensity grading as project standard; (iii) selection of sites experienced in treatment of IBD patients with biologics; and (iv) implementation of an independent data-monitoring committee (DMC).

Other risks of participating in this study include risks related to the trial specific procedures blood sampling, i.v. infusion of study medication, and sigmoidoscopy (or colonoscopy) with biopsy. Blood sampling and i.v. infusions can cause local bruising, inflammation, nerve damage and pain. Colonoscopy or sigmoidoscopy with biopsy, although generally well tolerated, can be associated with diarrhoea, abdominal pain, perforation, bleeding, effects from anaesthetic medications, and infection. Most of the endoscopies in this trial will be limited to sigmoidoscopies, which do not require a complete bowel preparation and are better tolerated by the patients. Investigators are highly experienced and UC patients are familiar with the burden and risks of endoscopies from their own disease history.

Due to its antagonistic effect it is considered highly unlikely that BI 655130 may lead to a clinical cytokine release syndrome. In addition, preclinical and clinical phase I evaluation did not suggest cytokine release induced by BI 655130. However, occurrence of such a syndrome will be carefully monitored for as an AESI.

Manifestations of local and systemic hypersensitivity reactions are readily detectable, transient in nature, and in general manageable with standard medical treatment. Specific safety measures will be taken during the trial. Following the i.v. infusion, the patients will be monitored for infusion reactions at the site for two hours after infusion.

Although rare, a potential for drug induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.5.1.

Based on the findings in the nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of women of childbearing potential in this

study is justified (c03320877). To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, women of childbearing potential must agree to the requirements for pregnancy testing at the visits indicated in the Flow Chart and contraceptive methods described in the patient information. Male patients will be asked to use effective methods of birth control to prevent their partner from becoming pregnant if she is of childbearing potential. Birth control methods must be used for 20 weeks after the last infusion (corresponding to five BI 655130 half-lives).

Summary of benefit-risk assessment

Due to the lack of mechanism- or compound-related safety signals and the antagonistic MoA action of BI 655130 it is considered likely that UC patients will not be exposed to undue risks and AEs in relation to the information that is expected to be gained from this trial. Considering the medical need of the development of an effective and well tolerated drug for the therapy of UC, the benefit of this trial is considered to outweigh the potential risks for individual UC patients participating in this trial.

The benefit-risk profile is thus considered appropriate for an experimental therapy at this stage of clinical development.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is an open-label, single-arm, phase IIa exploratory trial to assess the genomic and epigenetic changes in both the patient and the microbiome, in response to the IL-36 *signalling* blockade induced by i.v. treatment with BI 655130 in patients with moderate to severe active UC. 10 patients will be investigated.

The trial includes a screening period, a 12-week treatment period and a safety follow-up period of 16 weeks. This allows safety monitoring for 20 weeks (~5 half-lives of BI 655130) after the last dose of BI 655130, which is administered at Week 8.

Patients should be on stable doses of conventional treatment for their disease.

Patients found suitable for trial participation based on in-/exclusion criteria during screening period can enter the treatment phase. Administration of 1200mg BI 655130 intravenously will take place every four weeks (Day 1, Week 4 and Week 8).

A schematic overview of trial design is shown in Figure 3.1: 1.

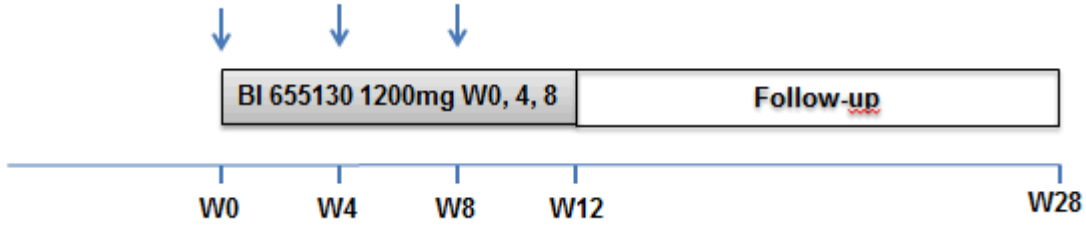

Figure 3.1: 1 Trial Design

Abbreviations: W0: Week 0, W4: Week 4, W8: Week 8, W12: Week 12, W28: Week 28, ↓ : i.v. infusion

During treatment phase, sequential sigmoidoscopies will be conducted to collect biopsies for evaluation of endpoint variables. Also, blood and stool samples will be collected at various visits, and data will be correlated with the results from biopsies.

Endoscopic as well as histologic evaluations of mucosal biopsies will be performed by a central expert who is independent from the investigator.

Patients who terminate study drug early in trial 1368-0004 will complete EoT visit procedures and return for an End of Observation (EoO) visit 20 weeks (>5 half-lives of BI 655130) after the last dose of BI 655130.

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedules and details of trial procedures at selected visits, refer to Section 6.1 and Section 6.2, respectively.

Patients who complete the full treatment period of study 1368-0004 will be offered to roll over into a long-term extension trial (1368-0017).

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at different centres participating in this multi-centre trial. Tasks and responsibilities are defined in a contract.

A project-independent, partially-external data monitoring committee (DMC), will be established to assess the progress of the clinical trial, including a safety and efficacy assessment at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop the trial due to safety or ethical concerns. Measures will be put in place to ensure blinding of the project team and all other trial participants. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

Relevant documentation on the participating (principal) investigators and other important participants, including their curricula vitae, will be filed in Investigator Site File (ISF).

BI has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CMLs), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit) in accordance with applicable regulations and internal SOPs, or by a Clinical Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs. Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service will be used in this trial. Details will be provided in a Central Laboratory Manual, available in Section 10 of the ISF. Central reading of endoscopies and central evaluation of histopathology will be done. Details will be provided in Section 15 of the ISF.

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

This trial is designed as an open-label, single-arm, phase IIa exploratory trial of BI 655130 in patients with active UC.

The present trial is of exploratory nature and aims to explore the mechanism of action of the 1st in class IL-36R inhibitor in UC. The primary aim of the trial is to evaluate changes in various genetic and epigenetic markers under conditions of IL-36 pathway inhibition and will be compared to the individual baseline values rather than a control group. The comparison between two baseline visits will describe the spontaneous variability in expression of the target genes and markers. The nature of the regulated genes and BMs will shape the subsequent development of BI 655130 in IBD to define potential new endpoints, target indications and BMs to identify responder patient populations. In addition, this trial will include clinical and endoscopic activity evaluations of BI 655130 which may support subsequent trials in achieving clinical proof of concept (PoC) of this potential UC treatment. As shown in the recent proof of concept trial with etrolizumab (R17-0373) in a similar UC population as the one proposed here with BI 655130, the clinical response and remission rates on PBO were very low, probably due to endoscopic screening of patients. Since the patient population in this trial will be similar and endoscopic eligibility criteria have to be met as well, a potential clinical effect is likely to be caused by treatment rather than representing a PBO effect. However, clinical effects are not the primary objective and a clinical PoC study will be conducted in a different properly designed trial. Therefore, a control group is not required for this mechanistic trial comparing gene and BM expression after treatment with baseline, and a single-arm open-label design is appropriate to answer this question.

Since a PoC for BI 655130 is not yet available in UC, the chance of an individual benefit for study participants is difficult to estimate, and thus the sample size and treatment duration was limited to a minimum to achieve the study objectives. The sample size of 10 treated subjects is not based on a power calculation but on coordinating investigator's experience with regard to similar mechanistic studies.
The treatment duration of 12 weeks of BI 655130 was selected to cover a longer induction period compared to currently approved biologic treatment and is covered by currently available preclinical Good Laboratory Practice (GLP) toxicology studies.
As clinical remissions under induction treatment in active UC are typically detected after 6-8 weeks of treatment with biologics, the duration of 12 weeks will allow observation of clinical and/or endoscopic remissions, provided BI 655130 is clinically active in UC. It may also determine the kinetics of response and optimal duration of induction treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that a total of 10 patients will be treated in the current trial. A sufficient number of patients will be screened to meet this goal. Recruitment will be competitive.
Patients who fulfil all the inclusion criteria (Section 3.3.2) and none of the exclusion criteria (Section 3.3.3) are eligible for inclusion in the trial. The selection of biologics naïve patients will maximize the chance to detect biologic activity not confounded by previous treatments, and at the same time offer approved rescue treatment in case of insufficient responses.

Women of childbearing potential or men able to father a child with a level of acceptable contraception, in alignment with the Clinical Trials Facilitation Group guideline on "Recommendations related to contraception and pregnancy testing in clinical trials" will be allowed to participate, as supported by results from pre-clinical toxicology and teratology studies with BI 655130. Please refer to the IB for more details.

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 with moderately or severely active UC who have not been satisfactorily controlled on conventional treatments, are naïve or experienced to TNF antagonist treatment but have not failed that treatment due primary non-response or lack of response, and have not received any other biologic agent in the past.

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. 18 – 75 years at screening

2. Body weight ≤ 100 kg (at screening and at Day 1 of treatment)

3. Diagnosis of UC ≥3 months prior to screening.

4. Moderately to severely active UC as confirmed by Mayo Score ≥6 (with rectal bleeding ≥ 1 and modified endoscopy score ≥2) and elevated C-Reactive protein (CRP) or faecal calprotectin at pre-baseline visit.

5. Receiving conventional, non-biologic therapy for UC.

   This therapy could consist of one or more of the following:

   - Oral 5-ASA compound, with stable dose for at least 4 weeks prior to screening
   - 6-MP, Methotrexate (MTX) or AZA, with stable dose for at least 8 weeks prior to screening
   - Oral corticosteroids (≤ 20mg/day per day of prednisone or equivalent), with stable dose for at least 4 weeks prior to screening

6. Negative colon cancer screening by full colonoscopy with serial biopsies (or according to local standard of care) performed and documented within the past 12 months prior to screening (otherwise to be done at pre-baseline visit)

7. Patients who are naïve or experienced to TNF antagonists (including infliximab, adalimumab, or golimumab) but have not failed that treatment due to primary non-

response or loss of response (previous anti-TNF treatment outcome and reason for discontinuation must be documented in source data).

8. Women of childbearing potential and men able to father a child must use highly effective methods of birth control per International Conference on Harmonisation (ICH) M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

Note: A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

9. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

The exclusion criteria are divided into 3 categories: gastrointestinal exclusion criteria, infectious disease exclusion criteria, and general exclusion criteria. Patients meeting any of the following exclusion criteria are not eligible for trial participation.

3.3.3.1 Gastrointestinal Exclusion Criteria

1. Patients who have previously failed treatment with any TNF antagonist (including infliximab, adalimumab, golimumab) due to primary non-response or loss of response

2. Patients who were treated with a TNF antagonist within 8 weeks prior to screening, or 3 half-lives of agent from screening, whichever is longer

3. Prior use of any other biological treatment in the past (e.g. integrin inhibitors, IL12/23 or IL23 inhibitors, any other investigational biological drugs)

4. Extensive colonic resection, subtotal or total colectomy

5. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine

6. Patients who must or wish to continue the intake of restricted medications (see Table 4.2.2: 1) or any drug considered likely to interfere with the safe conduct of the trial

7. Evidence of infection with C. difficile or other intestinal pathogen <30 days prior to screening

8. Currently require or are anticipated to require surgical intervention for UC

9. Colonic moderate or severe mucosal dysplasia

10. Colonic adenomas (unless properly removed)

11. Primary sclerosing cholangitis

12. Faecal transplant ≤ 6 months before screening

13. Disease limited to the rectum, extending <15 cm past the anal verge (ulcerative proctitis).

3.3.3.2 Infectious Disease Exclusion Criteria

14. Increased risk of infectious complications (e.g., recent pyogenic infection, any congenital or acquired immunodeficiency (e.g., HIV), live vaccination within 6 weeks prior to screening, past organ or stem cell transplantation)

15. Active or latent tuberculosis (TB) (Note: Patients with a positive QuantiFERON TB test are excluded. Patients with suspected false positive or undeterminable QuantiFERON TB result may be re-tested.)

16. Any severe infection within 30 days prior to screening, including chronic or acute hepatitis B or C infection

3.3.3.3 General Exclusion Criteria

17. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than UC, surgical procedure, medical examination finding (including vital signs and electrocardiogram (ECG)), or laboratory value at the screening visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data

18. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix

19. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned during the trial, e.g., hip replacement

20. Pathological safety lab parameters: haemoglobin <8.5g/dL, total white blood count (WBC) <3.500 cells/µl, neutrophils <1.000 cells/µl, thrombocytes <75.000/µl, albumin <30g/L, serum creatinine ≥ 2mg/dL, AST >2xULN, ALT>2xULN, total bilirubin > 1.5x ULN (patients with Gilbert's syndrome are not excluded), alkaline phosphatase >3x ULN

21. Currently enrolled in another investigational device or drug study, or less than 30 days or 5 half-lives, whichever is longer, since ending another investigational device or drug study(s), or receiving other investigational treatment(s)

22. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

23. Known hypersensitivity to any component of BI 655130

3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see Section 3.3.4.1 and Section 3.3.4.2 below.
Every effort should be made to keep the patients in the trial, at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, as well as the explanation of the consequences of withdrawal.
The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and Electronic Case Report Form (eCRF).

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication. Please refer to Section 4.2.2 for restricted medication during this trial.
- The patient requires additional medical therapy or dose increase in patient's baseline medication, as deemed by the investigator, to treat the underlying UC due to disease worsening.
- 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 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.

Exclusion criteria occurring after randomization will not necessarily be a reason for withdrawal of a patient.

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

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

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision. This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation.

3.3.4.3 Discontinuation of the trial by the sponsor

BI 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 trial protocol, or the contract impairing 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

Multiple doses of BI 655130 will be administered intravenously. BI 655130 will be supplied by BI.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Description of test product BI 655130 12 weeks

Substance:	BI 655130
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Chemical form:	Anti-human IL-36 Receptor mAb
Molecular weight:	146 kDa
Unit strength:	150mg/vial (20mg/mL)
Posology	1200mg at Day 1, at Week 4 and at Week 8
Route of administration:	intravenous infusions
Duration of Use	12 weeks

4.1.2 Selection of doses in the trial

The aim of this small exploratory study is to provide the highest likelihood to study the mechanism of BI 655130 in UC analysing various BMs in sequential biopsies. Based on other effective anti-cytokine drugs in IBD and pre-clinical assays for IL36 inhibition, a linear or logistic rather than a bell-shaped dose-response curve is expected for these BMs. Thus, the highest tolerated dose should provide the highest likelihood to achieve this objective. This dose is also expected to provide the best chance to induce clinical remissions in UC patients.

The fixed rather than weight-based dose regimen of 1200mg given at weeks 0, 4 and 8 has been selected for the following reasons:

- Early trials of therapeutic monoclonal antibodies often investigate body weight based regimens to reduce the inter-subject variability in drug exposure. However, there is generally only modest contribution of body weight to overall PK and PD variability of monoclonal antibodies. Furthermore, monoclonal antibodies are highly target-specific and offer a relatively large therapeutic window as compared to new chemical entities. Therefore, most monoclonal antibodies are approved at fixed doses in antibody/target excess in order to cover target turnover and maximize efficacy. (R13-4749, R10-6267, R13-4753, R13-4750, R13-4754).

- Body weight has been included in the current PK model as a covariate indicating decreased exposure with increasing body weight. The current model indicates that body weight explains less than 15% of between-subject variability in PK of BI 655130 when comparing a model with and without body-weight as a covariate of exposure.

- A fixed dose regimen will minimize the potential for dosing errors due to less complex dose calculation, study drug preparation and administration as compared with weight based dosing. It will also facilitate dose finding and PK-PD analyses due to covering a wider weight/exposure range (R10-6267).

- This dose regimen is the highest covered by current healthy volunteer PK and safety data irrespective of body weight.

Currently approved or investigational biologics (e.g. TNFi, vedolizumab, ustekinumab) have established 4-8 weeks duration of induction treatment in UC; a longer induction period of 12 weeks was selected to allow assessment of the response kinetics for BI 655130, which represents a new and clinically non-validated mode-of-action (MoA). The dosing interval of once every 4 weeks is supported by the long half-life of BI 655130 of approximately four weeks. The discontinuation of BI 655130 treatment after 12 weeks is supported by preclinical GLP toxicology studies with the surrogate antibody and will allow study of the PK and PD wash-out profile (clinical effect and BM) of BI 655130.

4.1.3 Method of assigning patients to treatment groups

There is only one treatment group in this trial.

4.1.4 Drug assignment and administration of doses for each patient

In this trial, a dose of 1200mg of BI 655130 will be administered intravenously at Day 1, Week 4 and Week 8. The concentration of the application solution in the infusion bag will be 20mg/mL.

Detailed instructions for the preparation of the infusion solution, the volume to be administered and the infusion rate are provided in Section 4 of the ISF.

In case of safety concerns, e.g., due to infusion reactions, it is at the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited to slowing down the infusion rate, stopping of the infusion and provided no further safety

concern exists restarting at a slower rate. In any case, the total duration of infusion should not exceed 240 minutes (4 hours) provided that the maximum time between the start of preparation and completion of administration of the solution to the patient does not exceed 300 minutes (5 hours). For further instructions on how to proceed in case of an infusion reaction, please refer to Section 4.2.1.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open-label, single-arm trial. Therefore, no blinding will be necessary.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

For details of packaging and the description of the label, refer to Section 4 of the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the sponsor must be contacted immediately. Refer to the Section 4 of the ISF for contact information.

For further user information and in-use stability, refer to Section 4 of the ISF.

4.1.8 Drug accountability

The Investigator and/or Pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol (CTP)

Only authorised personnel as documented in the form "Trial Staff List" may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. The Investigator and/or Pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates and the unique code numbers assigned to trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor< and/or >appointed CRO, the Investigator / Pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial staff and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Patients in this trial are required to be on conventional, non-biologic treatment for UC.

Conventional treatment may consist of one or more of the following drugs (cf. Section 3.3.2, inclusion criteria), which are therefore permitted concomitant medications:

- Oral 5-ASA compound, with stable dose for at least 4 weeks prior to screening and throughout the trial
- 6-MP, MTX or AZA, with stable dose for at least 8 weeks prior to screening and throughout the trial
- Oral corticosteroids (≤ 20mg/day per day of prednisone or equivalent), with stable dose for at least 4 weeks prior to screening and throughout the trial. For equivalent doses of corticosteroids, please cf. Appendix 10.3.

Dose has to be stable throughout the trial. In the event that a patient experiences an intolerable increase of UC, as deemed by the investigator, during the course of the trial, the decision whether or not to discontinue treatment (if applicable) and start rescue treatment should be taken in the discretion of the investigator and in discussion with the CML. Rescue treatment may be any new medication or any increase in dose of a baseline medication.

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation (cf. Section 3.3.3) are permissible. All concomitant medications should be carefully evaluated by the investigator, and the CML should be contacted when there are questions regarding concomitant medications.

Details of all concomitant medication will be recorded in the eCRF, along with the main reason for prescription. In addition, all prior treatment for UC within 12 months of Visit 1a will be recorded.

Infusion reactions including anaphylactic reactions:

In case of infusion reactions including anaphylactic reactions emerging during or after infusion of BI 655130, the investigator should consider in accordance with severity of the reaction and local standard of care to

- Immediately interrupt the infusion
- Treat with systemic anti-histamines and i.v. steroids and in case of a severe allergic reaction (eg, anaphylactic reaction) epinephrine

Also draw a plasma sample for IgE and ADA as detailed in the Lab Manual (Section 10 of the ISF).

Based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate infusion reactions (according to RCTC grading in Section 5 of the ISF) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of BI 655130 in the Investigator Site File.

In any case, the total duration of infusion should not exceed 240 minutes (4 hours) provided that the maximum time between the start of preparation and completion of administration of the solution to the patient does not exceed 300 minutes (5 hours).

In case of anaphylactic reaction, the investigator should discontinue treatment with BI 655130.

Cytokine release syndrome (CRS)

This syndrome manifests when a large number of immune cells becomes activated and releases inflammatory cytokines. It is clinically characterized by fever, chills, rigor and rash, possibly with nausea, dyspnoea, tachycardia and hypotension.
Potentially life-threatening complications of a cytokine release syndrome include cardiac dysfunction, respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. In case of suspicion of a cytokine release syndrome, it is recommended to measure IL-6 levels in the local laboratory if the assay is available.
The investigator should discontinue treatment with BI 655130. Aggressive supportive care is essential for patients experiencing CRS, with early intervention for hypotension and treatment of concurrent infections. IL-6 receptor blockade with tocilizumab remains the mainstay pharmacologic therapy for CRS, though indications for administration vary among centres. Corticosteroids should be reserved for neurologic toxicities and CRS not responsive to tocilizumab (R16-5751).

Opportunistic infections or mycobacterium tuberculosis infections or serious infections

The investigator should discontinue treatment with BI 655130. Treatment of the infection has to be initiated according to local standard of care.

4.2.2 Restrictions

Restrictions regarding previous and concomitant treatment are summarized in Table 4.2.2: 1.

Table 4.2.2: 1 Restrictions regarding previous and concomitant treatment

Medication or class of medications	**Restriction**
Biologics	TNF inhibitors are only allowed in the past, if stopped for other reasons than primary non-response or lack of response Other biologics are excluded. Not allowed from 8 weeks prior to screening or 3 half-lives of agent from screening, whichever is longer, up to the end of the trial.
Cyclosporine, tacrolimus, mycophenolate mofetile and other immunomodulators not listed below	Not allowed from 8 weeks prior to screening or 5 half-lives of agent from screening, whichever is longer, up to end of the trial
AZA, 6-MP, MTX	Only allowed during the trial, if dose is stable for at least 8 weeks prior to screening and throughout the trial. For use of any of these drugs as concomitant medication, refer to Section 4.2.1.

Table 4.2.2: 1 Restrictions regarding previous and concomitant treatment (cont.)

5-ASA	*Oral administration:* Only allowed during the trial, if dose is stable for at least 4 weeks prior to screening and throughout the trial. For use as concomitant medication, refer to Section 4.2.1. *Rectal route of administration (5-ASA):* Not allowed from 2 weeks prior to screening up to end of the trial
Corticosteroids	*Oral administration:* Only allowed at a dose of ≤ 20mg/day per day of prednisone or equivalent and with stable dose for at least 4 weeks prior to screening and throughout the trial. For use of oral corticosteroids as concomitant medication, refer to Section 4.2.1. *Parenteral administration:* Not allowed from 2 weeks prior to screening up to end of the trial *Rectal administration:* Not allowed from 2 weeks prior to screening up to end of the trial
NSAID	Chronic use (Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc., and daily use of baby or low dose (81-162.5mg) aspirin for cardiovascular prophylaxis are permitted.)
Probiotics	Not allowed from 2 weeks prior to screening up to end of the trial
Antidiarrheals	Not allowed from screening up to end of the trial
Life-attenuated vaccines	Not allowed from 6 weeks prior to screening up to end of the trial
Antibiotics for IBD	Not allowed from 4 weeks prior to screening up to end of the trial

4.2.2.1 Restrictions on diet and life style

Patient should be fasted for at least 8 hours prior to collection of the safety laboratory samples, starting from Visit 2 and as indicated in the Flow Chart.

4.2.2.2 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods as described in the patient information.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre by the authorised personnel (e.g., study nurse). The measured plasma concentration will provide additional confirmation of compliance.

Subjects who are not compliant (e.g., who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the eCRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

Any missed dose has to be documented and reported to the CML.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The total number of deregulated genes comparing baseline to post-treatment, analysed by gene expression of mucosal biopsies via RNA sequencing (RNAseq), per time point up to week 12.

The total number of deregulated genes per time point will be reported.
Further details on the planned analyses will be given in Section 7.3.

5.1.2 Secondary Endpoints

- Drug related AEs
- Percent change in CRP from baseline to Week 12
- Percent change in faecal calprotectin from baseline to Week 12
- Percent change in faecal lactoferrin from baseline to Week 12
- Clinical remission at Week 12 based on Mayo Score (Mayo Score ≤2 with all subscores ≤1)

For a definition of (modified) Mayo Score please refer to Appendix 10.1

5.2 ASSESSMENT OF EFFICACY

The changes in UC activity during the trial will be assessed using the Mayo score (disease activity score) as indicated in the Flow Chart. Please refer to Appendix 10.1 (Mayo Score) for further details.

The change in CRP as well as in faecal calprotectin and faecal lactoferrin during the trial will be assessed as a measure for UC activity, as indicated in the Flow Chart. The normal ranges will be provided by the lab.

5.3 ASSESSMENT OF SAFETY

The secondary safety endpoint to assess safety and tolerability of BI 655130 is specified as drug related AEs.

In general, safety will be assessed descriptively based on:

- AEs
- SAEs
- Clinical laboratory values (haematology, clinical chemistry, coagulation and urinalysis)
- Physical examination
- Vital signs
- 12-lead ECG

5.3.1 Physical examination

A complete physical examination will include general appearance as well as evaluation of all organ systems and will be performed by the investigator or a delegated sub-investigator at Visit 1a, at EoT visit and at EoO visit. Height (cm) and weight (kg, without shoes) will be measured at Visit 1a. Weight will also be measured (prior to dosing, if applicable) at Day 1 of treatment, at Week 4 (Visit 5), Week 8 (Visit 7) and EoT Visit.

A targeted physical examination will include evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities and will take place at all other visits.

Preferably, the same individual should perform the physical examinations for a patient during the course of the trial. The investigator will evaluate the clinical significance.

Clinically relevant abnormal findings will be reported as baseline conditions or AEs.

5.3.2 Vital Signs

Vital signs will be assessed at all study visits. Vital signs assessment will include temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate and blood pressure will be measured after the patient has been sitting comfortably for at least five minutes. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

At visits with study drug administration (Visits 2, 5 and 7) vital signs will be assessed pre-dose, and additional evaluations will be taken at approximately 5 and 120 minutes after end of study drug administration.

The investigator should evaluate the clinical significance of the results. Clinically abnormal findings will be reported as baseline conditions or AEs.

5.3.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.3.3:1. For the sampling time points please see the Flow Chart.

Table 5.3.3: 1 Safety laboratory parameters

Functional lab group	Test name
Haematology	Haematocrit (Hct)
	Haemoglobin (Hb) Mean cellular haemoglobin (MCH) Mean cellular haemoglobin concentration (MCHC)
	Mean cellular volume (MCV)

Table 5.3.3: 1 Safety laboratory parameters (cont.)

	Reticulocyte count Platelet count Red blood cell (RBC) count / Erythrocytes White blood cell (WBC) count / Leucocytes
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 (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin Time (Quick / INR) Fibrinogen
Enzymes	Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Alkaline Phosphatase (AP) Gamma Glutamyl Transferase (GGT) Lactic Dehydrogenase (LDH) Creatine Kinase (CK) CK-MB (if CK >ULN)
	Amylase Lipase
Electrolytes	Calcium Sodium Potassium

Table 5.3.3: 1 Safety laboratory parameters (cont.)

	Bicarbonate Chloride
Substrates	Creatinine C-Reactive protein (CRP) Albumin Glucose eGFR (estimated by CKD-EPI formula) (only at screening) Bilirubin Total Bilirubin Direct (only if total bilirubin outside the normal range) Bilirubin Indirect (only if total bilirubin outside the normal range) Total Cholesterol, High density Lipoprotein (HDL) Cholesterol, Calculated Low Density Lipoprotein (LDL) Cholesterol Triglycerides Protein, Total Urea nitrogen Uric acid Troponin (only in case of elevated CK) Protein electrophoresis (only at Visit 1a)
Hormones	Thyroid stimulating hormone (only at Visit 1a) fT3 and fT4 (only if TSH is outside normal range)
Urinalysis (dipstick)	Urine Glucose Urine Bilirubin
	Urine Ketone Specific Gravity Urine RBC / Erythrocytes Urine WBC / Leucocytes
	pH

Table 5.3.3: 1 Safety laboratory parameters (cont.)

	Urine Protein
	Urine Urobilinogen Urine Nitrite
Urine sediment (microscopic examination if urine analysis abnormal)	Only positive findings will be reported (e.g., the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)
Infection screening	Hepatitis B Surface Antigen (only at Visit 1a) Hepatitis C Antibody (only at Visit 1a) HIV –and HIV-2 Antibody (only at Visit 1a) QuantiFERON®-TB (only at Visit 1a)
Specific gamma-globulin quantification	IgE (only in case of allergic reaction), IgG
Stool sample (for enteric pathogens)	Salmonella (only at Visit 1a) Shigella (only at Visit 1a) Yersinia (only at Visit 1a) Campylobacter (only at Visit 1a) Vibrio (only at Visit 1) E. coli O157/H7 (only at Visit 1a) Clostridium difficile toxin (only at Visit 1a) Enteric parasites and their ova including Cryptosporidia (only at Visit 1a)
Urine pregnancy test (only for female patients of childbearing potential) at randomization and continued as indicated in the Flow Chart	Human Chorionic Gonadotropin in urine
Serum Pregnancy test (only for female patients of childbearing potential) at Visit 1a and if urine pregnancy test is positive	Human Serum Chorionic Gonadotropin

With the exception of urine pregnancy test, all analyses will be performed by a central laboratory, the respective reference ranges will be provided in Section 10 of the ISF.

Patients will need to be fasted for all visits (except Visit 1a) as several parameters in the safety lab require fastened conditions.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in Section 10 of the ISF.
Laboratory results (i.e. all safety laboratory and clinical laboratory data relevant for current clinical practice) of the patients will be available in real time to the respective investigator (via laboratory reports) and to the sponsor (via the central laboratory website) and selected abnormal laboratory alerts will be flagged to the site and sent to sponsor in real time.

Clinically relevant abnormal findings will be reported as baseline conditions or AE's. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results should be confirmed using an unscheduled visit laboratory kit and should be repeated until normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria (R13-3515).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.3.5.1 and the DILI Checklist provided in Section 5 of the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

5.3.4 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow Chart.

ECGs will be recorded after the patients have rested for at least 5 minutes in a supine position and will always precede blood sampling to avoid impact of sampling on results. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six pre-cordial leads (V1–V6), according to Wilson, will be used.

ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation).

Additional ECGs may be collected for safety reasons. Clinically relevant, abnormal findings will be reported as AEs.

The electronic version, if applicable, or dated and signed printouts of the ECG will be regarded as source data and stored in the patient's medical file.

5.3.5 Assessment of adverse events

5.3.5.1 Definitions of adverse events

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 unfavourable 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.

Serious adverse event

An SAE is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- 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 on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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 hospitalisation or development of dependency or abuse.

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in 5.3.5.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".
In accordance with the European Medicines Agency initiative on Important Medical Events, BI 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 defined above.
The latest list of "Always Serious AEs" can be found in the Electronic Data Capture (eDC) system. 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, i.e., AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see above.

The following is considered an AESI:

Infusion reactions including anaphylactic reaction

Any suspicion of severe infusion reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (R11-4890).

Cytokine release syndrome

May manifest when a large number of immune cells becomes activated and releases inflammatory cytokines. Potentially life-threatening complications include cardiac dysfunction, respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.

Opportunistic and mycobacterium tuberculosis infections

These include pneumocystis pneumonia, toxoplasmosa gondii encephalitis, cryptosporidiosis, microsporidiosis, mycobacterium tuberculosis, mycobacterium avium, bacterial respiratory disease, bacterial enteric infection, mucocutaneous candidiasis, invasive mycoses, CMV, EBV, herpes simplex, varicella zoster, human herpesvirus 8, JC virus infection (adapted from http://aidsinfo.nih.gov/guidelines).

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 lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in Section 5 of the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, 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.

Intensity of adverse events
The intensity of AE will be classified and recorded in the eCRF according to the RCTC Version 2.0. For these criteria, please refer to Section 5 of the ISF.

Causal relationship of adverse events
Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:
- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.

- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. 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.

5.3.5.2 Adverse event collection and reporting

AE Collection
The investigator shall maintain and keep detailed records of all AEs in the patient files.

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

- From signing the informed consent onwards until the individual patient's end of trial: all AEs (serious and non-serious) and all 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 related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

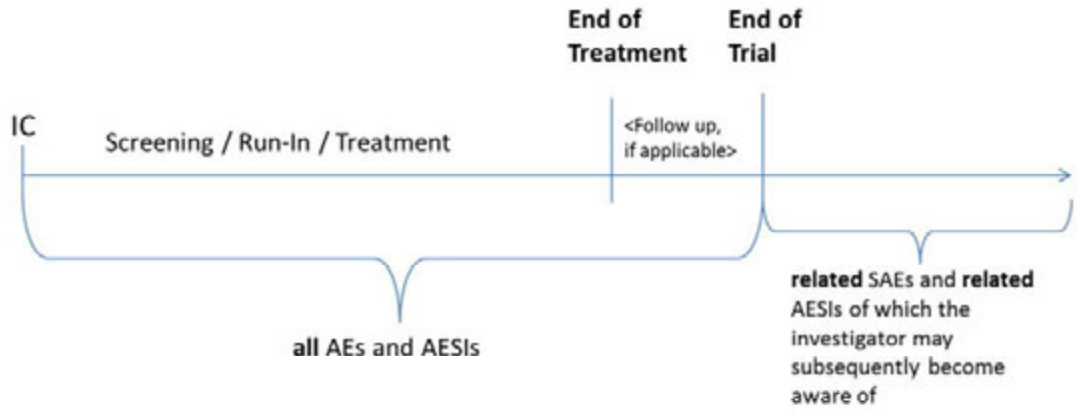

Figure 5.3.5.2: 1 AE reporting

The residual effect period (REP) for BI 655130, i.e., when measurable drug levels or PD effects are still likely to be present after the last administration, is 140 days (20 weeks). Therefore, all AEs reported through the REP will be considered on-treatment, cf. Section 7.3.4.

As end of REP coincides with EoO visit (last per protocol (PP) visit) in this trial, all AEs reported from first dose until end of the trial will be considered on-treatment.

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 unique entry point (country specific contact details will be provided in Section 1 of the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor 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 timelines 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, if applicable. The investigator should determine the causal relationship to the trial medication and any possible interactions between the trial medication and a Non-Investigational Medicinal Product / Auxiliary Medicinal Product

The following should also be recorded as an (S)AE in the CRF and BI 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 to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

Pregnancy
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

BI 655130 concentrations will be reported descriptively. The relationship between PK and selected endpoints, BMs and AEs may be assessed. Also, ADAs will be measured, as the clearance of BI 655130 can potentially be affected by the presence of anti-BI 655130 antibodies similar to the cases seen in anti- TNFs.

Refer to Flow Chart for the time points of PK and ADA sample collection. Data and exact time of drug administration and PK and ADA sampling will be recorded on eCRFs. These actual administration and sampling times will be used for determination of PK parameters. On visits with study medication dosing, PK and ADA samples should be collected prior to administration of study drug.

5.4.2 Analytical determinations

BI 655130 concentrations will be determined by a validated immunoassay.

The presence of ADA to BI 655130 will be assessed via a tiered approach using a validated electrochemiluminescence assay (screening, confirmatory, and titration analysis, as appropriate). Samples that are confirmed positive may be further characterized using a validated neutralizing antibody (Nab) assay.

5.4.3 Methods of sample collection

5.4.3.1 Plasma sampling for PK analysis

For quantification of BI 655130 plasma concentrations, blood will be taken from a forearm vein into a K2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flow Chart under plasma PK. Handling procedures can be found in the lab manual (Section 10 of the ISF).

After completion of the trial, the plasma samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the analyte will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.4.3.2 Plasma sampling for ADA assessment

For ADA assessment, blood will be taken from a forearm vein into a K2EDTA anticoagulant blood-drawing tube at the time points listed in the Flow Chart under plasma ADA. Handling procedures can be found in the lab manual (Section 10 of the ISF).

After completion of the trial, the plasma samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the ADAs will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

The PK and PD data from this study may be used for an exploratory investigation of PK/PD relationship of BI 655130, however, it is not planned to report the results of this investigation into the clinical trial report of this study.

5.5 ASSESSMENT OF BIOMARKER(S)

BMs associated with UC and the IL-36 pathway will be assessed in biopsies, peripheral blood (including serum and plasma) and stools from patients pre and post treatment with BI 655130.

Samples will be collected at time points indicated in the Flow Chart for the analysis of BMs. For further information on sample handling, please refer to the lab manual (Section 10 of the ISF).

All the BMs, other than the ones defined as formal endpoints (see Section 5.1.3), may be reported in a separate BM report.

5.5.1 RNA sequencing

During visits at time points specified in the Flow Chart, colon biopsies and blood will be collected for RNAseq.

Please refer to the ISF for further details on the collection and the processing of the biopsies and the handling of the blood samples.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. Each visit data (with its window) up to EoT is to be counted from Day 1 (Visit 2). If any of these visits has to be rescheduled, subsequent visits should follow the original visit date schedule from Day 1. Follow-up visits (after EoT) refer to the last dose administration of BI 655130 at Visit 7 (Week 8). Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and the respective protocol sections. Refer to Section 5 and Section 10 (Appendix) for explanations of procedures. Additional details on procedures at selected visits are provided below.

Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits.

6.2.1 Screening and run-in period(s)

After patients have been informed about the trial, written informed consent in accordance with GCP and the local legislation must be obtained prior to performing any study related procedures.

Once they have consented, the patient is considered to be enrolled in the trial. The patient should be recorded on the subject enrolment log. Patient will be assigned a patient number and enrolment must be recorded in the eCRF pages.

Screening visit (Visit 1a):

The Screening visit (Visit 1a) should normally take place no more than 35 days before Visit 2 and be complete no less than 9 days prior to Visit 2. At this visit, information will be collected for evaluation of trial eligibility as indicated in the Flow Chart.

Baseline Conditions
Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy (excluding UC) will be reported on the baseline condition eCRF page.

Patients who have a laboratory test value outside the range specified by the inclusion criteria may have the test repeated to determine eligibility. The result must be available prior to Visit 2 (Day 1).

Demography
Informed consent date, gender, age, race and ethnic origin will be collected in the eCRF page. Also, the patient's smoking and alcohol history will also be assessed. Information concerning race/ethnicity will be collected as it has been suggested that there might be race/ethnicity variations in the incidence, phenotypic manifestations and outcome of UC. Note: In some countries, race may not be collected.

Medical and Surgical History
Information on clinically significant previous and concomitant illnesses, other than UC, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical and surgical history at screening. For planned procedures/hospitalisations during the trial, documentation should be completed at the time of the screening. Regarding the UC, a detailed history of the disease, including date of diagnosis, disease severity, hospitalizations, and extraintestinal manifestations will be collected. Also, previous and concomitant treatment for UC will be recorded.

Blood sampling
Blood samples will be taken for safety lab and infection screening (HIV, HBV, HCV, TBC). For women of childbearing potential, a serum pregnancy test will be performed.

Stool sampling
A stool sample will be collected to exclude existence of enteric pathogens. If collection is not possible at Visit 1a, stool sample has to be collected at (or prior to) Visit 1 or at an unscheduled visit. For further details, please refer to the lab manual (Section 10 of the ISF).

Patient diary
Patients who are eligible at Visit 1a will receive a patient diary to be used for
1) daily reporting of stool frequency and rectal bleeding (blood in stool) during the week prior to visits which include assessment of Mayo score, as well as
2) confirming regular intake of concomitant UC medication over the whole treatment period.
Patients will be instructed on the use of the diary during screening and treatment phase. The diary will be returned at EoO visit.

Visit 1b:
The Visit 1b should take place no more than 8 days and no less than 6 day prior to Visit 2.

A full colonoscopy with serial mucosal biopsies will be performed at this visit to exclude malignancy, if no fully documented procedure is available ≤ 12 months prior to screening. If a full colonoscopy is available from the past 12 months prior to Visit 1, a sigmoidoscopy incl. biopsy will be performed instead. Images will be centrally read by an external independent assessor.

Based on the results from sigmoidoscopy (or colonoscopy, if applicable) and clinical symptoms of the patient, a baseline Mayo score will be determined.

Results from the mucosal biopsies will be used as first baseline value for endpoint parameters. Refer to Section 15 of the ISF for details.

Blood samples will be collected to evaluate baseline gene expression, methylation pattern, immunophenotyping, metabolomics profiling and inflammatory BMs.

For a detailed description of the trial procedures at Visits 1a and 1b, please refer to the Flow Chart.

The time window for Visit 1a and 1b may be extended at the discretion of the CML in conjunction with the TCM on a case by case basis or re-screening is performed.

Re-screening will be allowed once.

6.2.2 Treatment period(s)

The treatment period is from Visit 2 to End of Treatment (EoT) Visit.

Study related procedures will be performed as specified in the Flow Chart.

Pregnancy testing
Urine pregnancy testing for all women of child-bearing potential will be conducted on-site approximately every four weeks and must be negative to continue treatment. The pregnancy testing should be done **prior to** study drug administration. A positive urine test must be confirmed with a serum pregnancy test.

Blood sampling
Blood sampling (e.g., for safety lab, BMs) should be done **prior to** study drug administration and **prior to** sigmoidoscopy, if applicable. Patients should come in a fasted condition. If a patient comes in a non-fasted condition, where a fasting condition is required, the visit should be performed, the non-fasted condition documented on the laboratory requisition, and the patient reminded about the expected conditions.
At Visit 2, an additional blood sample for gene expression and methylation pattern will be collected at 4 hours after start of i.v. infusion.

Sigmoidoscopies
Sigmoidoscopies will be done after blood sampling and **prior to** study drug administration. During sigmoidoscopies, biopsies will be taken for endpoint evaluation at time points as indicated in the Flow Chart. Please refer to Section 5 of the ISF for further information on the collection and the processing of biopsies.
At Visit 2, an additional sigmoidoscopy will be done at 4 hours after start of i.v. infusion to collect additional biopsy samples.

PK and ADA sampling
At visits with study drug administration, blood sampling for PK assessments should be done within 2 hours **prior to** study drug administration**.**

Clinical monitoring after study drug administration:
The patient will be monitored for infusion reactions at the site for approximately 2 hours after end of infusion. At all visits with study drug administration, vital signs will be assessed pre-dose, and at approximately 5 and 120 minutes after end of infusion.
Unscheduled visits
The patient may be called in for additional unscheduled visits due to safety reason at the discretion of the investigator or the sponsor, unless the patient has withdrawn his/her consent. The patient may also contact the site due to safety reason for an unscheduled visit. The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the investigator such as laboratory samples, ECGs, or other procedures which were missed at a previous visit. All unscheduled visits should be described (including the reason for the visit) and documented in the medical/source record, and in the eCRF.

Concomitant medication review
Data concerning concomitant medications and procedures will be collected throughout the trial, as specified in the Flow Chart. These data will be obtained at scheduled or unscheduled trial visits based on information provided in the patient diaries, provided spontaneously by the patient or as a result of questioning the patient.

6.2.3 Follow Up Period and Trial Completion

For all patients, termination of trial medication and trial completion must be recorded on the corresponding eCRF.

For patients completing the trial regularly, two safety follow-up visits will be scheduled: 10 weeks (FU1 visit) and 20 weeks (EoO visit) after the last dose of study drug (which is at Week 8, Visit 7).

Early treatment discontinuation
Patients who discontinue treatment prior to the regular EoT visit, EoT procedures should be completed as soon as possible after termination of study drug. These patients should return to the clinic for an EoO visit 20 weeks after their last administered dose of BI 655130.

Further treatment after the end of the trial
At the end of the trial, patients will be treated for their UC at the discretion of the investigator, according to local UC guidelines (e.g. ECCO guideline R17-0243).

Trial completion:
Trial completion is defined as a patient having reached the EoO visit (Week 28).

Patients who complete regular treatment in study 1368-0004 will be offered to enter a long-term extension trial (1368-0017), which is currently in preparation. These patients can switch to trial 1368-0017 at EoT visit, and for these patients, their EoT visit will also be their EoO visit.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial is designed as an open-label, single-arm, Phase IIa exploratory trial of BI 655130 in patients with active moderate or severe UC. For each patient, two pre-treatment blood and biopsy samples (pre-baseline at V1b and baseline at Visit 2) will serve as an internal control for the change in relevant endpoint variables. Patients should be on stable conventional treatment for their disease.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in a confirmatory sense. Instead, the endpoints will be described in their entirety and evaluated by descriptive statistical methods.

For efficacy endpoints 95% confidence intervals may be presented in addition. They have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

Due to the exploratory nature of this trial, all statistical descriptions of clinical results will be descriptive and no formal testing for significance of differentiation will be provided.

Gene expression of mucosal biopsies as assessed by RNAseq will be analysed to identify the total number of deregulated genes over time. Deregulated genes are those genes that react to the drug administration over time (compared to baseline) in a significant manner. Quantitative criteria for the selection of deregulated genes are given below in Section 7.3.1 after the required details of the gene expression analyses including pre-processing of raw read count values are described.

The gene expression analysis includes initially all genes and all determined read counts. This means, if no gene expression values have to be excluded due to technical or other reasons, there is one read count value per person, per gene and per time point (pre-baseline, baseline, and during treatment period at time points indicated in the Flow Chart).

Based on these raw read count values (refer to Section 5.5.1) the DESeq2 method, one of the standard methods to analyse RNAseq data, is used for the gene expression analysis and for the identification of deregulated genes. In the following key properties and special characteristics of this method with regard to the considered analysis will be delineated. For a detailed description of this method and further statistical details please refer to Love et al. (R16-5384).

Starting with the raw read counts the DESeq2 method models these counts following a negative binomial distribution with a certain mean and dispersion parameter. In more detail, the read count K_{ij} for gene i in sample j is described by

$$K_{ij} \sim NB(\text{mean} = \mu_{ij}, \text{dispersion} = \alpha_i).$$

The mean consists of a design specific quantity q_{ij} scaled by a normalization factor s_{ij}. The basic idea of the DESeq2 method is now to fit a generalized linear model of the negative binomial family with a logarithmic link. Thereby the quantity q_{ij} of each gene is described by $\log_2 q_{ij} = \sum_r x_{jr}\beta_{ir}$ with design matrix elements x_{jr} and coefficients β_{ir}

To get interpretable results several pre-processing steps are needed to correct e.g. for different sequencing depth. For most of these steps the default approach (option) in the DESeq2 software package is used. In detail for the actual study design the following steps are conducted:

- Genes for which the sum of all counts is less than or equal to 1 are excluded.

- Genes with a high pre-treatment variability are excluded from the analysis:
  A gene is excluded if it meets the regular criteria (>1.5 fold deregulation, FDR adjusted p value <0.01) of being differentially expressed between the two consecutive pre-treatment time points. Hereby, the adjusted P-value is based on the Wald test including only the two pre-treatment time points (i.e. pre-baseline and baseline).

- Read Counts are normalized using the median-of-ratios method of Anders and Huber (R17-0129):
  The normalization constants s_{ij} are considered constant within a sample, i.e. $s_{ij} = s_j$. The value s_j is calculated by
  $s_j = \text{median}_{i:K_i^R \neq 0} \frac{K_{ij}}{K_i^R}$ with $K_i^R = \left(\prod_{j=1}^m K_{ij}\right)^{1/m}$.

- Estimation of the dispersion parameter α_i:
  For each gene, an estimate of the dispersion is found which maximizes the Cox Reid-adjusted profile likelihood (R17-0128).

- Handling of outlier using Cook's distance (using the default option *cooksCutoff = 0.99* in the DESeq2 package): Cook's distance (R17-0126) quantifies how much a single sample is influencing the fitted coefficients for a gene, and a large value of Cook's distance is intended to indicate an outlier count. No changes to the default setting are conducted.

After these pre-processing steps the actual expression analysis can be conducted (see Section 7.3.1)

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations (IPVs) will be identified in the Trial Statistical Analysis Plan (TSAP).

The patient set for the primary evaluation of gene expression will include all patients who completed trial medication and trial through EoT visit and who provide at least one evaluable baseline and one evaluable post-baseline biopsy RNA measurement. The patient set for the safety analyses will include all patients who received at least one dose during the trial. Details on the analysis sets and further analysis sets e.g. for the BM assessments, will be defined in the TSAP.

7.3.1 Primary endpoint analyses

For all genes, which are not excluded in the pre-processing step the Wald test (included as the default test for significance testing in the DESeq2 package) is conducted to identify whether this gene is deregulated or not for a certain time point.

Only one baseline value is included in the model, namely the last value before first drug administration, but all post-treatment values. The generalized linear model includes time as additional covariable (and also subject as covariable). So every time point is an additional design matrix element x_{jr} and the model fit leads (for every gene i) to β_{ir} estimates for each time point. To test changes from baseline the contrasts of these β coefficients (or more precisely the difference between post-treatment estimate and baseline) are divided by their estimated standard error, resulting in a z-statistic, which is compared to a standard normal distribution. Hereby the default option *lfcThreshold = 0* is utilized, meaning a null hypothesis of no difference.
The Wald test results in a P-value and an FDR adjusted P-value for each gene and each post-treatment time point. A gene has a small P-value at a certain time point if there is a significant difference to the pre-treatment estimate, meaning an adjusted mean value clearly lower or higher compared to baseline. The calculation of the FDR adjusted P-value is (by default in the DESeq2 package) based on the Benjamini and Hochberg (P05-11198) approach (*pAdjustMethod = "BH"*) combined with independent filtering (*independentFiltering = TRUE*). The independent filtering is based on the mean of normalized counts as a filtering statistic (R17-0127). A threshold on the filter statistic is found which optimizes the number of FDR adjusted P-values lower than a significance level of *alpha=0.1* (default setting). In doing so, genes with very low counts at all time points are excluded and no FDR adjusted P-value is reported for these genes.

Beside the FDR adjusted P-value the Wald test calculates for every gene and every time point the difference in fold change compared to the baseline estimate. To get a conservative and stringent approach for the identification of deregulated genes both of these measurements, the FDR adjusted P-value based on the Wald test and the-fold change, are used to identify deregulated genes.

Definition of deregulated genes
A gene is defined as deregulated at time point i if the FDR adjusted P-value of the Wald test is below 0.01 and if |fold change (time point i vs. baseline)| ≥ 1.3.

The total number of deregulated genes per time point will be reported.

Sensitivity analyses for example evaluation of alternative thresholds for the classification of genes (deregulated vs. not deregulated) will be provided in the TSAP. In particular if e.g. the number of identified deregulated genes is very large a smaller threshold for the FDR adjusted P-value might be considered.

7.3.2 Secondary endpoint analyses

The efficacy endpoints, such as percent change in CRP, will be evaluated descriptively, along with exact 95% confidence intervals, if feasible. Additionally the original as well as change from baseline values for all time points from baseline up to Week 12 will be presented. If the data appears to be very skewed then a log transformation and a summary statistic on the log scale will also be presented. Summary plots will also be produced if necessary.

The binary efficacy endpoint patient with clinical remission based on Mayo score at Week 12 will be described using patient frequencies and percentages. Exact 95% confidence intervals will additionally be provided for the proportion of patients, if feasible. Furthermore shift tables from baseline up to Week 12 will be produced for the Mayo score.

Analysis of safety and tolerability is described in Section 7.3.4.

7.3.4 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.3. All treated patients (that is all patients who received at least one dose of the study drug) will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

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 residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 140 days after the last dose of trial medication. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Drug related AEs, as a secondary endpoint of this trial, will be tabulated by system organ class and preferred term (PT) after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

In addition, the frequency, severity, and causal relationship of AEs will be tabulated by system organ class and PT after coding according to the current version of the MedDRA.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings.

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 to findings before start of treatment.

For vital signs, the differences from baseline will be evaluated.
Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

In order to ensure the patient's safety during the trial, a partially external DMC, independent of the trial and project teams, will be set-up to review all available safety data as well as selected efficacy data at regular intervals following first-patient-in. A DMC Statistical Analysis Plan (SAP) which describes the analyses required for assessment by the DMC will be produced and finalized prior to first patient screened into the trial. Further details will be provided in a DMC charter.

No formal interim analysis is planned. However a first exploratory analysis of BM data (e.g. RNAseq and inflammatory BMs) may be performed if the period for recruiting of the entire patient population exceeds approximately 6 months. The purpose will be to facilitate further substance development and project planning. The results of these evaluations will be preliminary and may be subject to change, as these do not involve a formal database lock. No interim report will be written. There will be no changes to the design of the trial as a result of the performance of this optional exploratory analysis. If performed, the exploratory analysis of BM data will be done once the first 50% of the total required number of patients has completed 12 weeks of study. Further details of this optional exploratory analysis of BM data will be described in the TSAP.

7.5 HANDLING OF MISSING DATA

Every effort should be made to collect complete data at all visits.

With respect to safety evaluations, it is not planned to impute missing values.

No imputations for the primary endpoint and for any missing BM data are planned.

7.6 RANDOMISATION

No randomisation is planned in this trial, as it is an open-label trial with one treatment arm. All patients will receive the same treatment. A randomisation list will only be provided for logistical reasons with a block size of 1, i.e., a list of consecutive numbers is provided with separate number ranges for each site (starting with number and so on for the different sites).

7.7 DETERMINATION OF SAMPLE SIZE

In line with the exploratory nature of the trial, 10 patients with active UC will be enrolled. The planned sample size is not based on a power calculation but on feasibility, coordinating investigator's experience with regard to recruitment and practical considerations.

If patients withdraw early from treatment prior to Week 12, they may be replaced. Up to 4 patient replacements is considered adequate to ensure that the required number of patients provide data through Week 12.

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 Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (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 BI 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 rule, no trial results should be published prior to finalization of the Clinical Trial Report.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Independent Ethics Committee (IEC) and competent authority 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 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."

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 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 (CRF) for individual patients will be provided by the sponsor. 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 subject 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.
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 eCRF, 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 surgeries, history of UC 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 into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, 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, Institutional Review Board (IRB) / IEC review and regulatory inspections. Direct access must be provided to the eCRF 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 eCRFs 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 site(s) must retain the source and essential documents (including ISF) according to the national or local requirements (whatever 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

BI 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 and in 5.5.1. 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 the principles 6 and 12 of the WHO 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 or delegates, by the IRB / IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of 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 "**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 PP or prematurely). Individual Investigators will be notified of Suspected Unexpected Serious Adverse Reactions
(SUSARs) occurring with the trial medication until 6 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).

9. REFERENCES

9.1 PUBLISHED REFERENCES

P05-11198 Benjamini Y, Hochberg Y, Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc 1995; (B) 57 (1), 289 – 300

R10-6267 Wang DD, Zhang S, Zhao H, Men AY, Parivar K, Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009; 49, 1012 – 1024

R11-4890 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW. Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 117 (2), 391 - 397 (2006)

R13-3046 Ordas I, Mould DR, Feagan BG, Sandborn WJ, Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms; Clin Pharmacol Ther 2012; 91 (4), 635 – 646

R13-3515 Woodworth T, Furst DE, Alten R, Bingham C, Yocum D, Sloan V, Tsuji W, Stevens R, Fries J, Witter J, Johnson K, Lassere M, Brooks P, Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0, J Rheumatol 2007; 34 (6), 1401 – 1414

R13-4749 Bai S, Jorga K, Xin Y, Jin D, Zheng Y, Damico-Beyer LA, Gupta M, Tang M, Allison DE, Lu D, Zhang Y, Joshi A, Dresser MJ, A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012; 51 (2), 119 – 135

R13-4750 Joos B, Trkola A, Kuster H, Aceto L, Fischer M, Stiegler G, Armbruster C, Vcelar B, Katinger H, Guenthard HF, Long-term multiple-dose pharmacokinetics of human monoclonal antibodies (MAbs) against human immunodeficiency virus type 1 envelope gp120 (MAb 2G12) and gp41 (MAbs 4E10 and 2F5). Antimicrob Agents Chemother 2006; 50 (5), 1773 – 1779

R13-4753 Deng R, Iyer S, Theil FP, Mortensen DL, Fielder PJ, Prabhu S, Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned? MAbs 2011; 3 (1), 61 – 66

R13-4754 Xin y, Gordon MS, Jin D, Wakshull E, Chen DS, Rosen LS, Munster PN, Naumovski L, Bai S, Population pharmacokinetic (PK) analysis supports fixed dosing for the humanized monoclonal antibody (huMAb) anti-EGFL7 (MEGF0444A) administered intravenously in patients with advanced solid tumors. 47th Ann Mtg of the American Society of Clinical Oncology (ASCO), Chicago, 3 - 7 Jun 2011. J Clin Oncol 2011; 29 (15) (Suppl), Abstr 2586

R16-5751 Brudno JN, Kochenderfer JN, Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 127 (26), 3321-3330 (2016)

R13-5226 Remicade 100 mg powder for concentrate for solution for infusion (EPAR - product information: summary of product characteristics, manufacturer(s) of the biological active substance(s) and manufacturer(s) responsible for batch release, conditions or restrictions regarding supply and use, other conditions and requirements of the marketing authorisation, conditions or restrictions with regard to the safe and effective use of the medicinal product, labelling and package leaflet, last updated: 06/08/2013), webpage: ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/ human/000240/WC500050888.pdf (access date: 2 Feb 2017)

R15-0886 Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG, Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012; 142 (1), 46 – 54

R15-4915 Humira 40 mg/0.8 ml solution for injection for paediatric use, 40 mg solution for injection in pre-filled syringe, 40 mg solution for injection in pre-filled syringe with needleguard, 40 mg solution for injection in pre-filled pen, 40 mg solution for injection in pre-filled syringe (summary of product characteristics, manufacturer(s) of the biological active substance and manufacturer(s) responsible for batch release, conditions or restrictions regarding supply and use, other conditions and requirements of the marketing authorisation, conditions or restrictions with regard to the safe and effective use of the medicinal product, labelling and package leaflet, 20150728).
webpage: ec.europa.eu/health/documents/community-register/2015/20150728132555/anx_132555_en.pdf (access date: 2 Feb 2017)

R16-0573 Sandborn W, Gasink C, Blank M, Lang Y, Johanns J, Gao LL, Sands B, Hanauer S, Feagan B, Targan S, Ghosh S, Villiers W de, Colombel J F, Lee S, Desreumaux P, Loftus E, Vermeire S, Rutgeerts P, A multicenter, double-blind, placebo-controlled phase3 study of ustekinumab, a human IL-12/23P40 mAB, in moderate-service Crohn's disease refractory to anti-TFNalpha: UNITI-1. AIBD 2015; Advances in Inflammatory Bowel Diseases National Clinical and Research Conf of the Crohn's and Colitis Foundation of America, Orlando, 10 - 12 Dec 2015. Inflamm Bowel Dis 2016; 22 (Suppl 1), Abstr O-001

R16-0692 Feagan B, Gasink C, Lang Y, Friedman JR, Johanns J, Gao LL, Sands B, Hanauer S, Rutgeerts P, Targan S, Ghosh S, Villiers W de, Colombel JF, Tulassay Z, Seidler U, Sandborn WJ, A multicenter, double-blind, placebo-controlled Ph3 study of ustekinumab, a human monoclonal antibody to IL-12/23P40, in patients with moderately-severely active Crohn's disease who are naive or not refractory to anti-TNFa: UNITI-2. 23rd United European Gastroenterology Week (UEGW), Barcelona, 24 - 28 Oct 2015, United Eur Gastroenterol J (2015); 3 (6), 563 - 564, Abstr OP054-LB4

R16-4416 Schroeder KW, Tremaine WJ, Ilstrup DM, Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis: a randomized study. N Engl J Med 317 (26), 1625 - 1629 (1987)

R16-5384 Love MI, Huber W, Anders S, Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol 2014; 15, 550

R16-5706 Brandse JF, Brink GR van den, Wildenberg ME, Kleij D van der, Rispens T, Jansen JM, et al, Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology 2015; 49 (2), 350 – 355

R16-5741 Kapel N, Meillet D, Favennec L, Magne D, Raichvarg D, Gobert JG, Evaluation of intestinal clearance and faecal excretion of alpha1-antiproteinase and immunoglobulins during Crohn's disease and ulcerative colitis, Eur J Clin Chem Clin Biochem 1992; 30 (4), 197 - 202

R17-0038 Ulcerative Colitis: Clinical Trial Endpoints. Guidance for Industry. Draft Guidance. August 2016; website: http://www.fda.gov/downloads/Drugs/Guidances/UCM515143.pdf: (assess date: 2 Feb 2017)

R17-0126 Cook RD, Detection of influential observation in linear regression, Technometrics 1977; 19 (1), 15 – 18

R17-0127 Bourgon R, Gentleman R, Huber W, Independent filtering increases detection power for high-throughput experiments, Proc Natl Acad Sci USA 2010; 107 (21), 9546 – 9551

R17-0128 McCarthy DJ, Chen Y, Smyth GK, Differential expression analysis of multifactor RNA-Seq experiments with respect to biological variation, Nucleic Acids Res 2012; 40 (10), 4288 – 4297

R17-0129 Anders S, Huber W Differential expression analysis for sequence count data. Genome Biol 2010; 11, R106

R17-0243 Dignass A, Van ASsche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP, European Crohn's and Colitis Organisation (ECCO), Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management, J Crohns Colitis 2010; 4(1) 28-62

R17-0373 Vermeire S, O'Byrne S, Keir M, Williams M, Lu TT, Mansfield JC, Lamb CA, Feagan BG, Panes J, Salas A, Baumgart DC, Schreiber S, Dotan I; Sandborn WJ, Tew GW, Luca D, Tang MT, Diehl L, Eastham-Andersen J, De Hertogh G, Perrier C, Egen JG, Kirby JA, van Assche G, Rutgeerts P, Etrolizumab as induction therapy for ulcerative colitis: a randomized, controlled, phase 2 trial 2014; 384: 309-18

9.2 UNPUBLISHED REFERENCES

c03320877 Investigator's Brochure BI 655130

10. APPENDICES

10.1 MAYO SCORE

The Mayo score (R16-4416) is a composite disease activity score consisting of four items or subscores: stool frequency (relative to normal), rectal bleeding, physician's global assessment, and endoscopic appearance. As proposed by FDA draft guidance (R17-0038), the endoscopic subscore is modified so that a value of 1 does not include friability. The overall range of the Mayo score is 0-12 (higher scores being worse) and each subscore has a range of 0-3 (Table 10.1: 1). At visits without sigmoidoscopy, a partial Mayo score without endoscopy subscore will be assessed. The overall range of this partial Mayo score is 0-9.

In addition, based on FDA's recommendation (R17-0038), a modified Mayo score will be assessed, which excludes physician's assessment. The overall range of the modified Mayo score is 0-9.

The scores for stool frequency and rectal bleeding will be calculated as an average of the last 3 non-missing entries (from the patient daily diary) within the week prior to each applicable visit. If the patient undergoes bowel preparation for endoscopy on any of the days before a visit, the stool frequency and RBS for that day(s) should be considered missing. In addition, the stool frequency and RBS will be considered missing for the day of and the day after all endoscopies.

The endoscopic appearance score will be assessed by a central reader, who is independent from the investigator.

Table 10.1: 1 Mayo score (adapted from Schroeder et al, 1987 (R16-4416))

Subscore	Severity	Score
Stool Frequency[a] (daily)	Normal number of stools for patient	0
	1 to 2 stools more than normal	1
	3 to 4 stools more than normal	2
	≥5 stools more than normal	3
Rectal Bleeding[b] (daily)	No blood seen	0
	Streaks of blood with stool	1
	Obvious blood with stool	2
	Blood alone passes	3
Physician's Global Assessment[c]	Normal	0
	Mild disease	1
	Moderate disease	2
	Severe disease	3
Endoscopic Appearance[d]	Normal	0
	Mild disease	1
	Moderate disease	2
	Severe disease	3

[a] Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
[b] The daily bleeding score represents the most severe bleeding of the day.
[c] The physician's assessment acknowledged the three other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.
[d] Modified endoscopic appearance: 0 (normal), Mild (erythema, decreased vascular pattern), Moderate (marked erythema, loss of vascular pattern, any friability, erosions), Severe (spontaneous bleeding, ulceration).

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		16 Jan 2018
EudraCT number		2017-000100-20
BI Trial number		1368-0004
BI Investigational Product(s)		BI 655130
Title of protocol		Exploratory Trial to Assess Mechanism of Action, Clinical Effect, Safety and Tolerability of 12 Weeks of Treatment with BI 655130 in Patients with Active Ulcerative Colitis (UC)
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
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		Across whole protocol
Description of change		Trial number 1368.4 was changed to 1368-0004
Rationale for change		To implement new format of trial number across trial documents for consistency reason
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		The lower body weight limit of 60 kg was deleted.
Rationale for change		A lower body weight limit is not needed any more.
Section to be changed		FLOW CHART
Description of change		For some visits, total Mayo Score (“^{T}”) was replaced by partial Mayo Score (“^{P}”).
Rationale for change		To correct a typographical error.
Section to be changed		FLOW CHART
Description of change		Sigmoidoscopy at 4 hours after the first i.v. infusion was deleted. All biopsy samples should be obtained prior to IMP administration.

Rationale for change		To reduce the overall number of sigmoidoscopies in this trial.
Section to be changed		FLOW CHART
Description of change		The time-point of EoO visit was corrected.
Rationale for change		To ensure that EoO visit will take place after the end of the residual effect period of the IMP.
Section to be changed		FLOW CHART
Description of change		It was added that patients who completed regular treatment in trial 1368-0004 would be offered to enter the long-term extension trial 1368-0017.
Rationale for change		To add option for long-term treatment for patients who completed regular treatment.
Section to be changed		1.2 DRUG PROFILE
Description of change		Information from study 1368.1 and 1368.2 and from population pharmacokinetic modelling was updated.
Rationale for change		To update safety information on BI 655130 and provide rationale why the lower body weight limit is not needed anymore.
Section to be changed		2.3 BENEFIT-RISK ASSESSMENT
Description of change		Information from study 1368.1 and 1368.2 and from population pharmacokinetic modelling was updated.
Rationale for change		To update safety information on BI 655130 and provide rationale why the lower body weight limit is not needed anymore.
Section to be changed		2.3 BENEFIT-RISK ASSESSMENT
Description of change		It was added that patients who completed 12 weeks treatment duration would be offered long-term treatment in trial 1368-0017.
Rationale for change		To include the option for long-term treatment for patients who completed regular treatment in the risk-benefit assessment, as long-term treatment for these patients is considered an individual benefit.
Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		It was added that patients who complete regular treatment can receive long-term treatment in trial 1368-0017.
Rationale for change		To update the trial design regarding the option for long-term treatment for patients who complete regular treatment in trial 1368-0004.
Section to be changed		3.3.1 Main diagnosis for trial entry
Description of change		The trial population was extended to patients who were treated with TNF antagonist(s) previously but did not stop that treatment due to primary non-

		response or loss of response
Rationale for change		To update trial population with the aim to facilitate recruitment
Section to be changed		3.3.2 Inclusion criteria
Description of change		The lower body weight limit of 60 kg was deleted.
Rationale for change		A lower body weight limit is not needed any more.
Section to be changed		3.3.2 Inclusion criteria
Description of change		The trial population was extended to patients who were treated with TNF antagonist(s) previously but who stopped treatment for other reasons than primary non- response or lack of response. The reason for stopping treatment has to be documented in the source data.
Rationale of change		To update trial population with the aim to facilitate recruitment.
Section to be changed		3.3.3 Exclusion criteria
Description of change		The trial population was extended to patients who were treated with TNF antagonist(s) previously but did not stop that treatment due to primary non-response or loss of response
Rationale for change		To update trial population with the aim to facilitate recruitment.
Section to be changed		3.3.3.3 General exclusion criteria
Description of change		Unit for haemoglobin was corrected to g/dL.
Rationale for change		To correct error.
Section to be changed		3.3.3 Exclusion criteria
Description of change		The numbering of exclusion criteria was changed so that it is continuous.
Rationale for change		To update numbering of exclusion criteria so that it is consistent with the numbering in the BRAVE system.
Section to be changed		4.1.2 Selection of doses in this trial
Description of change		The lower body weight limit of 60kg was deleted.
Rationale for change		A lower body weight limit is not needed anymore.
Section to be changed		Section 4.2.1 Other treatments and emergency procedures
Description of change		Further guidance has been added regarding infusion reactions, cytokine release syndrome and infections.
Rationale for change		To provide guidance to the investigator for infusion reactions, cytokine release syndrome and infections.
Section to be changed		Section 4.2.2 Restrictions

Description of change		The information regarding biologics treatment was updated to allow previous TNF antagonist(s) treatment, if stopped for other reasons than primary non- response or lack of response. Also, it was added, that the last dose of TNF antagonist(s) treatment has to be at least 8 weeks or 3 half-lives, whichever is longer, from screening.
Rationale for change		To update restrictions regarding the previous use of biologics.
Section to be changed		Section 5.3.5.1 Definitions of adverse events
Description of change		Infusion reactions including anaphylactic reactions, cytokine release syndrome and opportunistic and mycobacterium tuberculosis infections were added to adverse events of special interest (AESIs).
Rationale for change		To update section on AESIs so that it is consistent across the BI 655130 project.
Section to be changed		Section 6.2.1 Screening and run-in period
Description of change		The information regarding the patient diary was changed, as daily reporting of CMs is not included in the current diaries, but the patients have to confirm regular intake of CMs before each visit.
Rationale for change		To change description of the diaries to clarify that daily reporting of CM intake is not included.
Section to be changed		6.2.3 Follow up period and Trial Completion
Description of change		It was added that patients who complete regular treatment can receive long-term treatment in trial 1368-0017. EoO visit would be on the same day as EoT visit.
Rationale for change		To clarify the time-point of trial completion for patients who enter long-term extension trial 1368-0017.
Section to be changed		Section 7.3 PLANNED ANALYSES
Description of change		It was clarified that the set for the primary evaluation of gene expression includes all patients who completed trial medication and trial throughout EOT visit and who provide at least one evaluable baseline and one evaluable post-baseline biopsy RNA measurement.
Rationale for change		To clarify description of the patient set for the primary evaluation of gene expression.
Section to be changed		Section 7.3.1 Primary endpoint analyses
Description of change		“log2” was removed.
Rationale for change		To correct an error.
Section to be changed		

Description of change		
Rationale for change		
Section to be changed		Section 9.1 PUBLISHED REFERENCES
Description of change		To add two additional references.
Rationale for change		To update Section 9.1 regarding two additional references.
Section to be changed		Section 10.2 MAYO SCORE
Description of change		In Table 10.2: 1, “granularity” was deleted from footnote d.
Rationale for change		To correct assessment of modified endoscopic response, according to established criteria for Mayo Score.
Section to be changed		Section 10.3 EQUIVALENT DOSES OF CORTICOSTEROIDS
Description of change		“16-Methylprednisolone” was deleted from the table.
Rationale for change		To correct typographical error.
Section to be changed		10.3 EQUIVALENT DOSES OF CORTICOSTEROIDS
Description of change		To add equivalent doses of budenoside.
Rationale for change		To update table with information for budesonide.

Number of global amendment		2
Date of CTP revision		18 May 2018
EudraCT number		2017-000100-20
BI Trial number		1368-0004
BI Investigational Product(s)		BI 655130
Title of protocol		Exploratory Trial to Assess Mechanism of Action, Clinical Effect, Safety and Tolerability of 12 Weeks of Treatment with BI 655130 in Patients with Active Ulcerative Colitis (UC)
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard –		

IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		FLOW CHART
Description of change		The time-point of FU1 visit was corrected.
Rationale for change		To correct an error.
Section to be changed		FLOW CHART
Description of change		Sigmoidoscopy with biopsy sample collection and blood sampling for gene expression and methylation pattern analysis at 4 hours after the first i.v. infusion was re-included.
Rationale for change		Based on expert PI feedback.
Section to be changed		Section 3.3.3
Description of change		The numbering of the exclusion criteria was corrected.
Rational for change		To correct an error.
Section to be changed		Section 6.2.2
Description of change		It was clarified that an additional sigmoidoscopy will take place at 4 hours after first i.v. infusion to collect biopsy samples. Also, it was clarified that an additional blood sample will be collected at 4 hours after first i.v. infusion for gene expression and methylation pattern analysis.
Rationale for change		Based on expert PI feedback.
Section to be changed		Section 7.3.1
Description of change		A typographical error was corrected.
Rationale for change		To correct an error.
Section to be changed		Section 7.6
Description of change		The description of the number ranges per site was updated.
Rationale for change		Additional study sites are planned to be included.
Section to be changed		Section 11
Description of change		The word “biologics” was replaced by “TNF antagonist(s)” in the description of changes related to sections 3.3.1, 3.3.2, 3.3.3 and 4.2.2.

Rationale for change		To correct an inconsistency.

Number of global amendment		3
Date of CTP revision		03 Apr 2019
EudraCT number		2017-000100-20
BI Trial number		1368-0004
BI Investigational Product(s)		BI 655130
Title of protocol		Exploratory Trial to Assess Mechanism of Action, Clinical Effect, Safety and Tolerability of 12 Weeks of Treatment with BI 655130 in Patients with Active Ulcerative Colitis (UC)
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
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		
Sections to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS, Section 3.3.2 Inclusion criteria
Description of change		Inclusion criterion 1: Change upper age limit from 65 years to 75 years.
Rationale for change		Upper age limit is changed to 75 years in order to facilitate recruitment into the study. 75 years as upper age limit is also consistent with more recently started trials in this project. No safety issues detected in program so far (see IB)

APPROVAL / SIGNATURE PAGE

Document Number: c10710598 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-revision-03

Title: Exploratory Trial to Assess Mechanism of Action, Clinical Effect, Safety and Tolerability of 12 Weeks of Treatment with BI 655130 in Patients with Active Ulcerative Colitis (UC)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		04 Apr 2019 16:55 CEST
Author-Trial Clinical Pharmacokineticist		04 Apr 2019 17:06 CEST
Approval-Team Member Medicine		04 Apr 2019 17:08 CEST
Author-Clinical Trial Leader		04 Apr 2019 17:21 CEST
Approval-Therapeutic Area		05 Apr 2019 09:43 CEST
Verification-Paper Signature Completion		05 Apr 2019 10:06 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**