Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c18806983-08**
EudraCT No.: **EU Trial No:**	2018-000334-35	
BI Trial No.:	1368-0017	
BI Investigational Product(s):	BI 655130	
Title:	An open label, long term safety trial of BI 655130(SPESOLIMAB) treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 trials	
Lay Title:	BI 655130 long-term treatment in patients with moderate-to-severe ulcerative colitis	
Clinical Phase:	II	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator:	[redacted] Telephone: [redacted] Fax: [redacted]	
Status:	Final Protocol (Revised protocol (based on Global Amendment 7))	
Version and Date:	**Version: 8.0**	**Date: 23 May 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name:	BI 655130 (SPESOLIMAB)
Protocol date	20 Mar 2018
Revision date	23 May 2022
Trial number	1368-0017
Title of trial:	An open label, long term safety trial of BI 655130 (SPESOLIMAB) treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 trials
Coordinating Investigator:	[redacted] Telephone: [redacted] Fax: [redacted]
Trial site(s):	Multi-centre trial
Clinical phase:	II
Objective(s):	1. To evaluate the long-term safety of BI 655130 (SPESOLIMAB) in patients with moderate to severely active ulcerative colitis, who have completed treatment in previous trials 2. To evaluate the long-term efficacy of BI 655130 (SPESOLIMAB) in patients with moderate to severely active ulcerative colitis, who have completed treatment in previous trials
Methodology:	Open label (OL), 7 year, single group, long-term extension study Patients will be treated in this study according to their clinical outcome achieved in the previous trial.
Number of patients entered:	Approximately 160
Number of patients on each treatment:	IV re-induction: N~80 SC maintenance: N~80 Number of patients in each group depends on number of patients achieving a clinical response following induction/re-induction

Diagnosis :	Moderate to severe ulcerative colitis
Main in- and exclusion criteria	• Male or female patients , aged ≥18 years • Have completed treatment with study drug in the previous trials and agree to continue treatment in 1368-0017 • Women of childbearing potential (WOCBP) must be ready to use highly effective methods of birth control • Have not experienced dose limiting adverse events during induction treatment with study drug • Have not developed any of the exclusion criteria from the original induction study
Test product(s):	BI 655130
dose:	Maintenance: 300mg q4w s.c., 600mg q6w s.c. OR Re-induction: 1200mg q4w i.v.
mode of administration:	See above ; s.c. as a maintenance treatment and i.v. as re-induction
Comparator products:	Not applicable
dose:	Not applicable
mode of administration:	Not applicable
Duration of treatment:	Maintenance treatment : 336 weeks Re-induction: 12 weeks
Endpoints	**Primary endpoint:** Primary endpoint is the exposure adjusted rate of patients reporting a treatment emergent adverse event (TEAE) up to week 336 of maintenance treatment **Secondary endpoint:** Proportion of patients with clinical remission at week 336 of maintenance treatment
Safety criteria:	Physical examination, vital signs, 12-lead ECG, laboratory tests, adverse events, serious adverse events and tolerability. The intensity grading of AEs and abnormal laboratory values will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0.
Statistical methods:	Descriptive statistics only.

FLOW CHART 1A: INDUCTION RESPONDERS V1, V1A, M1-M5B

Trial periods	**Screening**		**Maintenance Treatment s.c.**														
Visit	**V1[1]**	**V1a[2]**	**M1[12, 16]**	**M1a**	**M1b**	**M2**	**M2a**	**M2b**	**M3**	**M3a**	**M3b**	**M4**	**M4a**	**M4b**	**M5**	**M5a**	**M5b**
Week	-1 to 0	-1 to 0	**0**	4	8	12	16	20	24	28	32	36	40	44	48	52	56
Day	-7 to -2	-2 to -1	1	29	57	85	113	141	169	197	225	253	281	309	337	365	393
Visit Window (days)	N.A.	N.A.	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed consent	x																
Eligibility criteria	x	x	x														
Demographics	x																
Medical and surgical history	x																
Sigmoidoscopy + biopsy, mESS recording[3]	x														x		
Physical exam (including vital signs) and weight[4]	x^C		x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^C	x^T	x^T
12-lead ECG	x		x						x						x		
Pregnancy test[5]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	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	x	x	x	x	x
Safety laboratory tests[6]	x		x			x			x			x			x		
QuantiFERON-TB test[20]	x														x		
[redacted]	[redacted]		[redacted]						[redacted]						[redacted]		
[redacted]	[redacted]		[redacted]						[redacted]						[redacted]		
IBDQ; EQ-5D(-5L)[10]	x		x						x						x		
Diary review, incl PGA (Physician Global Assessment)[11]	x	x	x			x			x			x			x		
Contact IRT	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug administration[12]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Local tolerability assessment			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study completion																	

FLOW CHART 1B: INDUCTION RESPONDERS M6-EOS

Trial periods	Maintenance Treatment s.c.												Follow-up
Visit	**M6**	**M6a**	**M6b**	**M7**	**M7a**	**M7b**	**M8**	**M8a**	**M8b**	**M9**	**M9a**	**M9b, M10 -> M28b**	**M29/EOT**	**EOS[14]**
Week	60	64	68	72	76	80	84	88	92	96	100	Follow visit schedule/visit procedure every 4 wks	336	352
Day	421	449	477	505	533	561	589	617	645	673	701		2353	2466
Visit Window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±7	+7
Informed consent														
Eligibility criteria														
Demographics														
Medical and surgical history														
Sigmoidoscopy + biopsy, mESS recording[3]										x			x	
Physical exam (including vital signs), weight[4]	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^T	x^C	x^T		x^C	x^C
12-lead ECG				x						x			x	x
Pregnancy test[5]	x	x	x	x	x	x	x	x	x	x	x		x	x
Concomitant therapy	x	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	x
Safety laboratory tests[6]	x			x			x			x			x	x
QuantiFERON-TB test[20]										x			x	x
[redacted]				[redacted]						[redacted]			[redacted]	[redacted]
[redacted]				[redacted]						[redacted]			[redacted]	[redacted]
IBDQ; EQ-5D(-5L)[10]				x						x			x	x
Diary review, incl PGA (Physician Global Assessment)[11]	x			x			x			x			x	x
Contact IRT	x	x	x	x	x	x	x	x	x	x	x		x	
Study drug administration[12]	x	x	x	x	x	x	x	x	x	x	x		x	
Local tolerability assessment	x	x	x	x	x	x	x	x	x	x	x		x	
Study completion														x

FLOW CHART 2: INDUCTION NON-RESPONDERS

Trial periods	**Screening**		**i.v. re-induction**				…	**For patients not responding to i.v. re-induction:**	
Visit	**V1[1]**	**V1a[2]**	**R1 (I01)**	**R2 (I02)**	**R3 (I03)**	**R4 (I04)[15]**		**EOT**	**EOS[14]**
Week	-1 to 0	-1 to 0	0	4	8	12		n/a	16 wks after R3
Day	-7 to -2	-2 to -1	1	29	57	85		n/a	113 days after R3
Visit Window (days)	N.A.	N.A.	0	±3	±3	±3		n/a	+7
Informed consent	x						for patients responding to treatment: continue with visit M1 of flowchart 1 (inductions responders) 5-7 days after R4 (after results of sigmoidoscopy are obtained) for patients who did not respond to re-induction treatment continue with early EOT visit as soon as possible after R4 and EOS visit 16 weeks after R3		
Eligibility criteria	x	x	x			x			
Demographics	x								
Medical and surgical history	x								
Sigmoidoscopy + biopsy, mESS recording[3]	x					x			
Physical exam (including vital signs),weight[4]	x^C		x^T	x^T	x^T			x^C	x^C
12-lead ECG	x		x					x	x
Pregnancy test[5]	x		x	x	x			x	x
Concomitant therapy	x	x	x	x	x	x		x	x
Adverse events	x	x	x	x	x	x		x	x
Safety laboratory tests[6]	x		x	x	x			x	x
QuantiFERON-TB test[20]	x								
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
IBDQ; EQ-5D(-5L)[10]	x		x					x	x
Diary review, incl PGA (Physician Global Assessment)[11]	x	x	x	x	x	x		x	x
Contact IRT	x		x	x	x			x	
Study drug administration[12]			x	x	x				
Local tolerability assessment									
Study completion									x

FLOW CHART 3: PATIENTS WITH DISEASE FLARE

Trial periods	**Flare confirmation**	**i.v. re-induction**	**Flare Maintenance Treatment s.c.[19]**						**Follow-up**
Visit	**F0y**	**R0y**	**F1-x**	**F2-x**	**F3-x**	**F4-x**		**EOT**	**EOS[14]**
Week	0	0	6	12	18	24	...	336 wks from initial M1	16 wks after EOT
Day	-5 to -0	1	43	85	127	169		2353 days after initial M1	113 days after EOT
Visit Window (days)	N.A.	±2	±7	±7	±7	±7		±7	+7
Eligibility criteria		x					Restart at F1-x until EOT visit at same intervals		
Sigmoidoscopy + biopsy, mESS recording[3]	x		first sigmoidoscopy 12 weeks from i.v. re-induction (R0y), then every 48 weeks from R0y	x				x[17]	
Physical exam (including vital signs), weight[4]		x^T	x^T	x^T	x^T	x^C		x^C	x^C
12-lead ECG		x				x		x	x
Pregnancy test[5]		x	x	x	x	x		x	x
Concomitant therapy	x	x	x	x	x	x		x	x
Adverse events	x	x	x	x	x	x		x	x
Safety laboratory tests[6]		x		x		x		x	x
QuantiFERON-TB test[20]									
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Stool [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Stool sampling for enteric pathogens[7]	x								
IBDQ; EQ-5D(-5L)[10]		x				x		x	x
Diary review, incl PGA (Physician Global Assessment)[11]	x	x	x	x	x	x		x	x
Contact IRT		x	x	x	x	x		x	
Study drug administration[18]		x	x	x	x	x		x	
Local tolerability assessment			x	x	x	x		x	
Study completion									x

Footnotes for all Flow Charts:

1. Visit V1 of this long-term extension study should be performed during the last visit (V6/EOT) of the preceding trial 1368-0005 Part 1 or 1368-0004. Assessments performed at last visit (V6/EOT) in the previous trial do not have to be repeated at visit 1 in this trial. Patients not eligible to take part in trial 1368-0017 shall complete follow-up visit 16 weeks after last dose given in trial 1368-0004 or 1368-0005 Part I.
2. Visit V1a can be performed via telephone. Main reason for this visit is to check eligibility based on sigmoidoscopy and patient diary results in order to plan the next visit.
3. Sigmoidoscopies have to be performed every 48 weeks during maintenance treatment period. Additional sigmoidoscopies are to be done: a) at screening (EOT of previous trial); b) at W12 of re-induction period to check response to i.v. re-induction (Flowchart 2); c) In case of disease flare, an unscheduled confirmatory sigmoidoscopy has to be performed, followed in12 weeks after i.v. re-induction to check response to disease flare treatment. Two sets of mucosal biopsies will be taken; 1 set for gene expression analyses and 1 set for histopathology/IHC analyses at each visit indicated. Sigmoidoscopy images will be centrally read by an external independent assessor(s); management of images will be performed by an external vendor. Colonoscopy instead of sigmoidoscopy can be performed if required as colon cancer screening per local guidelines.
4. Physical examination: C=complete, T=targeted. Refer to Section 5.2.1 and 5.2.2. Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits and at screening. In addition, at visits with s.c. study drug administration, vital signs will be assessed at approx. 10 minutes after study drug administration. At visits with i.v. study drug administration, vital signs will be assessed at approximately 5 and 60 minutes after study drug administration. Monitor for signs and symptoms of hypersensitivity reactions for 1h following i.v. study drug administration.
5. 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. Study drug should only be administered in case of a negative test result. More frequent testing should be done if required by the local regulation or per investigator judgment.
6. Includes clinical chemistry, hematology, coagulation and urinalysis assessments. Patient is not required to be fasting prior to blood collection. If fasted mark it on laboratory requisition form. At visits with study drug administration blood sampling should be done prior to the study drug administration. For details of laboratory tests see Section 5.2.3, Table 5.2.3:1and Table 5.2.3:2. TSH and Glycosylated Hbc (HbA1c) tests have to be done every 48 wks, starting from W36 of maintenance treatment period.
7. Absence of enteric pathogens in stool shall be confirmed as a part of disease flare confirmation using central laboratory.

[redacted]

10. Inflammatory Bowel Disease Questionnaire (IBDQ) and EQ-5D(-5L) must be completed by the patient on his/her own in a pre-specified order in a quiet area/room before any other visit assessments or treatments and, as much as possible, before any interaction with the investigator or other members of the study team. Refer to Section 6.2. IBDQ and EQ-5D(-5L) will be collected at every 24 weeks until visit M13 (Week 144 or equivalent for flare patients), afterwards only at visits with sigmoidoscopy, EOT and EOS visit as indicated in the Flowchart.
11. An e-diary will be used by the patient for the reporting of bowel movement frequency and rectal bleeding (blood in stool) for a period of 14 days prior to visits and when a patient perceives a worsening of UC symptoms at any time between visits as a precursor to disease flare assessment. This information will be used for the calculation of Mayo score. PGA (Physician Global Assessment) should be completed according to flowchart Refer to Section 6.2.1.
12. First study drug administration will be administered at M1/R1 after response status check is completed
13. For patients who discontinue study medication before scheduled end of treatment, an early EOT visit has to be scheduled.subsequently EOS visit 16 weeks after last dose of study medication has to be performed.
14. At visit R4 patient response status to i.v. re-induction has to be checked. Sigmoidoscopy and eDiary data review are part of eligibility check to continue into maintenance treatment. Patients who did not respond to i.v. re-induction will be discontinued from study medication and early EOT visit has to be performed. EOS visit has to be performed 16 weeks after last dose of study medication (16 weeks after R3 visit). Sigmoidoscopy does not need to be done at EOT visit for these patients.
15. Visit M1 (flowchart for re-induction non-responders) has to be performed after results of sigmoidoscopy performed at visit R4 are received (usually 5-7 days)
16. For patients with disease flares only, sigmoidoscopy does not need to be repeated if done within 6 weeks prior to EOT visit.
17. Patients who develop a disease flare during maintenance study treatment period confirmed by sigmoidoscopy will receive a single infusion of 1200mg BI 655130 (SPESOLIMAB) i.v. followed 6 weeks later by intensified maintenance treatment with 600mg BI 655130 s.c. q6w until the originally scheduled EOT visit (i.e. at week 336 after start of first sc. maintenance treatment)
18. Cycle of visits F1-x to F4-x (visits every 6 weeks) is repeated until originally scheduled EOT, 336 weeks after initial visit M1, is reached.
19. QuantiFERON-TB test should be done every 48 wks.

TABLE OF CONTENTS

ABBREVIATIONS

[redacted]	[redacted]
ADCC	antibody-dependent cellular cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine transaminase
AST	Aspartate transaminase
[redacted]	[redacted]
BI	Boehringer Ingelheim
b.i.d.	bis in die (twice daily dosing)
BIO	Biologics
BL	Base Line
c	complete
CCDS	Company Core Data Sheet
CD	Crohn's disease
CDC	complement-dependent cytotoxicity
cf.	confer
CI	Confidence Interval
CML	Clinical Monitor Local
CR	Clinical Remission
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRP	C-Reactive Protein
CS	Systemic corticosteroids
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eDC	electronic Data Capturing
EOS	End of Study
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome

EQ-5D(-5L)	Questionnaire developed by EuroQoL Group
ESS	Mayo Endoscopy Score
EU	European Union
EudraCT	European Clinical Trials Database
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FC	Flow Chart
FCP	Faecal calprotectin
FcR	Fc receptor - a protein found on the surface of certain cells
FDA	Food and Drug Administration
FIH	First in human
GCP	Good Clinical Practice
GPP	generalized pustular psoriasis
H	hour
HbA1c	Hemoglobin A1c
Hbc	Hemoglobin C
HCRU	Healthcare resource utilisation
HPC	Human Pharmacology Centre
HT29	a human colorectal adenocarcinoma cell line with epithelial morphology
i.v.	intravenous
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IC90	inhibitory concentration of 90 (mg/mL)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IgE	Immunglobulin E
IgG1	Immunglobulin G1
IHC	immunohistochemistry
IL36R	Interleukin 36R
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITE	indirect target engagement
LoEE	List of Essential Element
LPDD	Last Patient Drug Discontinuation

MCID	minimal clinically important difference
MCS	Mayo Clinical Score
MedDRA	Medical Dictionary for Drug Regulatory Activities
mESS	modified Endoscopic Subscore
mMCS	modified Mayo Clinical Score
MoA	Mode of action
MST	Medical Sub Team
NF-kB	nuclear factor 'kappa-light-chain-enhancer' of activated B-cells
NOAEL	no-observed-adverse-effect level
OL	Open-label
OPU	Operative Unit
p.o.	per os (oral)
PBMC	Peripheral Blood Mononuclear Cell
PBO	placebo
pCR	partial Clinical Remission
PD	Pharmacodynamics
PGA	Physician's global assessment
[redacted]	[redacted]
PMR	Partial Mayo Clinical Score remission
PRO	Patient reported outcome
PoC	proof of concept
PoCC	proof of clinical concept
PPP	palmoplantar pustulosis
Pts.	Patients
q.d.	quaque die (once a day)
q.w.	quatery week (every 4th week)
RBS	rectal bleeding score
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
RHI	Robarts Histology Index
RS	Randomized Set
SAE	Serious Adverse Event
s.c.	subcutaneous
SCR	Screening
SD	Single dose
SF-36	36 question instrument to measure health-related quality of life
SFS	stool frequency score
SMC	Safety Monitoring Committee

SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
t.i.d.	ter in die (3 times a day)
t	targeted
TB test	blood test that aids in the detection of *Mycobacterium tuberculosis*, the bacteria which causes tuberculosis (TB)
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TGF-β	tissue growth factor
TMDD	target-mediated drug disposition
TMF	Trial Master File
TNF	Tumor necrosis factor
TNFi	TNFa inhibitor
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid-stimulating hormone
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
v	visit
w	week
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WPAI-UC	Work Productivity and Activity Impairment Questionnaire, Ulcerative Colitis -specific version

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Ulcerative Colitis (UC) is a chronic inflammatory bowel disease characterized by the key symptoms of chronic diarrhea, bloody stools and abdominal pain. It 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 immunosuppressive agents azathioprine and 6-mercaptopurine, and TNF antagonists. In patients with mild UC, 5-ASAs are safe and effective for induction and maintenance treatment. Glucocorticoids, immunosuppressives, 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.

Biologic treatment of moderate/severe 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 of 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 (SPESOLIMAB) is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signaling. Binding of BI 655130 (SPESOLIMAB) to IL36R is anticipated to prevent the subsequent activation of IL36R 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 (SPESOLIMAB) binds to human IL36R with a binding avidity of less than 1 pM. BI 655130 inhibits IL36 ligand-stimulated NF-κB activation in HT29 and transformed epithelial cells and in primary human dermal fibroblasts or intestinal myofibroblasts with IC90 values in a consistent range of 0.7 to 3.7 nM. BI 655130 (SPESOLIMAB) also inhibits IL8 release in primary human intestinal myofibroblasts and IFNγ secretion in human PBMC stimulated with IL36α, IL36β, or IL36γ combined with IL12.

Mutations of two key residues (L234 and L235) to alanine were made to BI 655130 (SPESOLIMAB) to abrogate FcR binding activity and function. Direct assessment of the impact of the mutations in the IgG1 FcR binding sites on both antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity CDC effector functions revealed that the mutations abrogate both ADCC and CDC effector functions and indicate that BI 655130 will be a non-depleting therapy in vivo.

Toxicology studies
BI 655130 (SPESOLIMAB) 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 (SPESOLIMAB). 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 (BI 674304), which is a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous 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. In the 26-week toxicity study, male and female mice (20-30/sex/group at 0, 10 and 50 mg/kg/day) were administered BI 674304 twice weekly for 26 weeks by intravenous injection via the caudal vein. There were no BI 674304-related changes in clinical observations, body weights, food consumption, ophthalmology, clinical pathology parameters (hematology, clinical chemistry), organ weights, macroscopic or microscopic examinations. The no-observed-adverse-effect level (NOAEL) was considered to be 50 mg/kg/day.
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 (SPESOLIMAB) 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 toxicology data support chronic BI 655130 (SPESOLIMAB) dosing in humans.

[redacted]

Summary
BI 655130 (SPESOLIMAB) is an anti IL36R antibody with a high clinical activity to block IL36R signaling, as demonstrated in patients with Generalized Pustular Psoriasis, a severe inflammatory skin disease driven by uncontrolled IL36 activity. BI 655130 (SPESOLIMAB) has been tested in healthy volunteers with multiple dosing up to four weeks of 20 mg/kg i.v. q.w. which were all safe and well tolerated. In addition, IL36R inhibition shows a favorable nonclinical safety profile. Therefore, BI 655130 (SPESOLIMAB) might be a promising drug to treat patients suffering from ulcerative colitis.

For further details and most recent results refer to the current IB [c03320877].

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 655130 is currently under development for the treatment of ulcerative colitis (UC). It`s unique dual mode of action targets pro-inflammatory cytokines as well as tissue remodeling effects and thus may provide a clear advantage over current drugs and investigational compounds, which target inflammation only. The potential BI 655130 (SPESOLIMAB) effects on remodeling may directly increase mucosal healing, induce deeper tissue healing (histologic remission) and reduce stricturing and fistulizing complications of IBD which will provide patients who derived an individual benefit from induction or re-induction treatment with a long-term treatment option.

The link between IL36R driven inflammation and epithelial inflammation has led to the hypothesis that IL36R signalling may play an important role in inflammatory bowel diseases such as UC. This hypothesis was tested using a suite of in vitro and in vivo assays.

Immunostaining studies demonstrated that both IL-36R and its ligands are expressed in intestinal biopsies from patients with chronic IBD. Human IL36 ligands enhanced epithelial intestinal barrier permeability, a hallmark of IBD pathogenesis, based on a study using primary human intestinal epithelial cells co-cultured with intestinal myofibroblasts. The link between IL36R signalling and IBD was further strengthened by demonstrating that antagonist anti-mouse IL36R antibodies ameliorated intestinal inflammation in both acute chemically induced and chronic T cell driven murine colitis models. The therapeutic rationale for an IL36R antagonist in IBD is further based on the correlation of a set of IL36-induced genes upregulated in primary human intestinal myofibroblasts, a disease relevant cell type, with gene signatures observed in ulcerative colitis and Crohn's disease (CD) patients. Finally, IL36R 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), which differentiates this mechanism from TNF alpha, integrin and IL23 targeting pathways. Altogether these findings indicate that IL36 is a key regulatory cytokine upstream of various pro-inflammatory and tissue-remodelling cytokines including TGF-β, TNFα and IL23, and support a prominent role of IL36R in driving intestinal inflammation and fibrosis.

The most recent and more detailed information is available in the current IB [c03320877]

1.4 BENEFIT - RISK ASSESSMENT

Preclinical profiles of BI 655130 (SPESOLIMAB) and clinical data from healthy volunteers trials suggest that BI 655130 (SPESOLIMAB) is safe, tolerable and may address an unmet medical need in UC patients by a dual anti-inflammatory and anti-fibrotic mechanism of action, cf. Section 1.3 and the IB [c03320877].
Results of the PoC trial 1368-0011 in acute GPP demonstrate that BI655130 (SPESOLIMAB) treatment rapidly clears pustules, the primary lesions in GPP, a disease closely linked to loss-of-function mutations in the natural IL36R antagonist. A different pustular inflammatory epithelial disease is PPP, which does not show the clear genetic association to the IL36 signalling pathway as GPP. Although the small pilot study of BI655130 (SPESOLIMAB) in 59 patients with this disease (1368.15) failed to achieve the primary endpoint, a subgroup analysis has shown a strong dose dependent effect on pustule severity, the primary and most burdensome lesion of this disease. These data indicate that BI655130 (SPESOLIMAB) indeed inhibits IL36 in human disease and thus has the potential to also treat other neutrophil granulocyte related inflammatory epithelial diseases such as IBD. The most recent and more detailed information is available in section 6 of the current IB [c03320877].

No relevant animal species is available for toxicology testing of the highly human specific antibody BI 655130 (SPESOLIMAB). However, preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of chronic IL-36R inhibition in mice (IB [c03320877] Section 5.2.1).

A total of more than 212 subjects have been exposed to single or multiple i.v. doses of BI 655130 (SPESOLIMAB) as of September 2018 (see IB). BI 655130 (SPESOLIMAB) was safe and well tolerated in four healthy volunteers trials evaluating the i.v. and s.c. formulation (for details cf. Section 1.1 and IB c03320877).

Moreover, two trials exploring efficacy and safety of single (1368-0011) or multiple (1368-0015) doses of BI655130 (SPESOLIMAB) in patients with Generalized Pustular Psoriasis (GPP, n=7) or Palmoplantar Pustulosis (PPP; n=59) demonstrated the favourable safety profile of BI655130 (SPESOLIMAB) in these severe inflammatory skin diseases. Finally, two (1368 - 0004, 1368-0010) clinical trials exploring efficacy and safety of BI655130 (SPESOLIMAB) in patients with Ulcerative Colitis (UC; target n=10 and 30) are currently ongoing and have not yet indicated a BI655130 (SPESOLIMAB) related safety concern.

Although no direct benefit for individual patients can be assumed, based on the PoC achieved in GPP and the strong preclinical rationale, there is a reasonable chance that BI 655130 (SPESOLIMAB) may not only alleviate signs and symptoms of active ulcerative colitis but even directly promote mucosal and histological healing, which is associated with improved clinical outcomes (reductions in immunosuppressive treatments, hospitalizations, colectomy and colorectal cancer [R16-0572]. Participation in this study may thus help to generate future benefit for larger groups of patients with UC, if BI 655130 (SPESOLIMAB) proves to be successful in treating this disease.

The outcome-guided open label treatment with active drug will maximize the patient`s chance for individual benefit. Patients not benefitting from up to 24 weeks of BI 655130 (SPESOLIMAB) induction treatment will discontinue the trial and switch to individualized commercial treatment at the investigator`s discretion, which will limit the duration of BI 655130 (SPESOLIMAB) exposure in patients not individually benefitting from such treatment. In contrast, patients achieving a clinical response or remission on induction or re-induction treatment, and thus benefitting individually from BI 655130 (SPESOLIMAB), will have the option to receive long-term treatment to maintain their treatment outcome.

There are no identified or potential risks for-BI655130 (SPESOLIMAB), based on the toxicology programme or any clinical trials conducted for this product to date (see also Section 1.1). No other IL-36 receptor antagonist is currently approved, providing information on identified risks in molecules of this class.

The risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs.

In order to protect the patient's safety during conduct of this trial, an independent Data Monitoring Committee has been established for the periodic review of clinical trial safety data.

Table 1.4:1 Benefit – Risk Assessment

Hypothetical risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product		
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. See also Section 5.2.6, adverse events of special interest
Systemic hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of adverse immune reactions which can be local (e.g redness, pruritus, and or swelling at the injection site) or systemic (e.g. anaphylactic reactions).	Patients with a history of allergy/ hypersensitivity to the systemically administered trial medication agent or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to interrupt and treat the condition. Systemic hypersensitivity reaction is defined as AESI. It is subject to close monitoring and investigators are requested assess these conditions using the criteria discussed in the statement paper from Sampson HA[R11-4890].

Table 1.4:1 Benefit – Risk Assessment (cont.)

Investigational Medicinal Product		
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections. A recent characterization of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signalingpathway inhibition does not compromise host defences [R11-4890].	Screening procedures for infections are established for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Severe infections and opportunistic infections are considered AESI for this trial.These conditions and serious infections are subject to close monitoring.
Malignancies	Inhibition of the immune response with an immune-modulating biologic may increase the risk of a decreased immune defense against malignancies A recent characterization of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defences R17-3632	Patients with a recent history of malignancy will be excluded from participation in this trial. In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with BI655130 (SPESOLIMAB). Diagnostics and treatment have to be initiated according to local standard of care. Malignancies represent always serious adverse events and are subject to close monitoring.

Table 1.4:1 Benefit – Risk Assessment (cont.)

Trial procedures		
Blood Sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs; (b) selection of experienced sites and site staff; (c) training.
Colonoscopy or sigmoidoscopy with biopsy	Can be associated with diarrhea, abdominal pain, perforation, bleeding, effects from anaesthetic medications, and infection	These risks will be addressed by careful monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs; (b) selection of sites with experienced site staff; (c) colonoscopy/sigmoidoscopy will be done according to the standard local care procedure including local clinic/hospital consent authorizing this procedure (d) training

Table 1.4:1 Benefit – Risk Assessment (cont.)

Trial procedures		
SARS CoV-2 infection	Trial conduct and protocol-defined procedures do not impose more risk to trial participants. To address potential risks associated with operational aspects related to the participation in clinical trials in the context of the COVID-19 pandemic, different risk mitigation measures are considered, based on local requirements and development of the pandemic.	The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the planned trials. BI as the sponsor, where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing, and/or is in the best interest of the patient.

Table 1.4:1 Benefit – Risk Assessment (cont.)

Trial procedures		
Peripheral Neuropathy	Three cases reported by the investigator as Guillain-Barré syndrome (GBS) were received in ongoing clinical trials with spesolimab. A panel of independent neurologists and experts in the study of neuropathies assessed the 3 cases. Only 1 met level 4 diagnostic certainty for the diagnosis of GBS (lowest level on Brighton scale of 1 to 4). In that case, there was a coincident infection with SARS-CoV-2. The other 2 cases were assessed as not GBS. Observed cases showed a heterogenous pattern. As per assessment by the panel of external neurologists the nonspecific symptoms and findings in all three cases may best be referred to as peripheral neuropathy.	Timely detection, evaluation, and follow-up of suspected peripheral neuropathies to ensure patients´ safety. Use of dedicated questions to elicit neurologic history during screening and exclusion criteria to avoid selection of patients with acute demyelinating neuropathy. Targeted Follow up questions to gather detailed information in case of any event during trial to ensure proper decision making. Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.

Based on the findings in the nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of Women of Child Bearing Potential (WOCBP) in this study is justified. To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing and contraceptive methods described in Section 4.2.2.2

The preceding trial 1368-0004 has already been completed; last patient last visit occurred on 24 October 2019.

The preceding induction trial 1368-0005 was prematurely discontinued on 04 Feb 2020 due to failure to meet expected enrollment goals. An unblinded analysis was conducted including 90 patients who have either completed or discontinued through week 12. At time of trial discontinuation, 8 additional patients were ongoing and therefore not included in the interim analysis. Last patient last visit occurred on 18 May 2020.

The main results the interim analysis of trial 1368-0005, are summarized in the tables and figures below.

Table 1.4:2 Interim Analysis trial 1358-0005 Primary endpoint: Clinical Remission at week 12 (RS, NRI)

	Placebo IV	**Spesolimab 300 IV SD**	**Spesolimab 450 IV q4w**	**Spesolimab 1200 IV q4w**
Subjects N (%)	23 (100%)	22 (100%)	21 (100%)	24 (100%)
Subjects with Remission N (%)	0	0	2 (9.5)	2 (8.3)
95% CI	(0, 14.3)	(0, 14.9)	(2.7, 28.9)	(2.3, 25.8)
Risk Difference vs placebo (95% CI)			9.5 (−6.4, 28.9)	8.3 (−7.2, 25.8)

Table 1.4:3 Interim Analysis trial 1358-0005 Secondary endpoint: Mucosal Healing (Endoscopic Improvement) at week 12 (RS, NRI)

	Placebo IV	**Spesolimab 300 IV SD**	**Spesolimab 450 IV q4w**	**Spesolimab 1200 IV q4w**
Subjects N (%)	23 (100%)	22 (100%)	21(100%)	24 (100%)
Subjects with Endpoint N (%)	0	0	2 (9.5)	2 (8.3)
95% CI	(0, 14.3)	(0, 14.9)	(2.7, 28.9)	(2.3, 25.8)
Risk Difference vs placebo (95% CI)			9.5 (−6.4, 28.9)	8.3 (−7.2, 25.8)

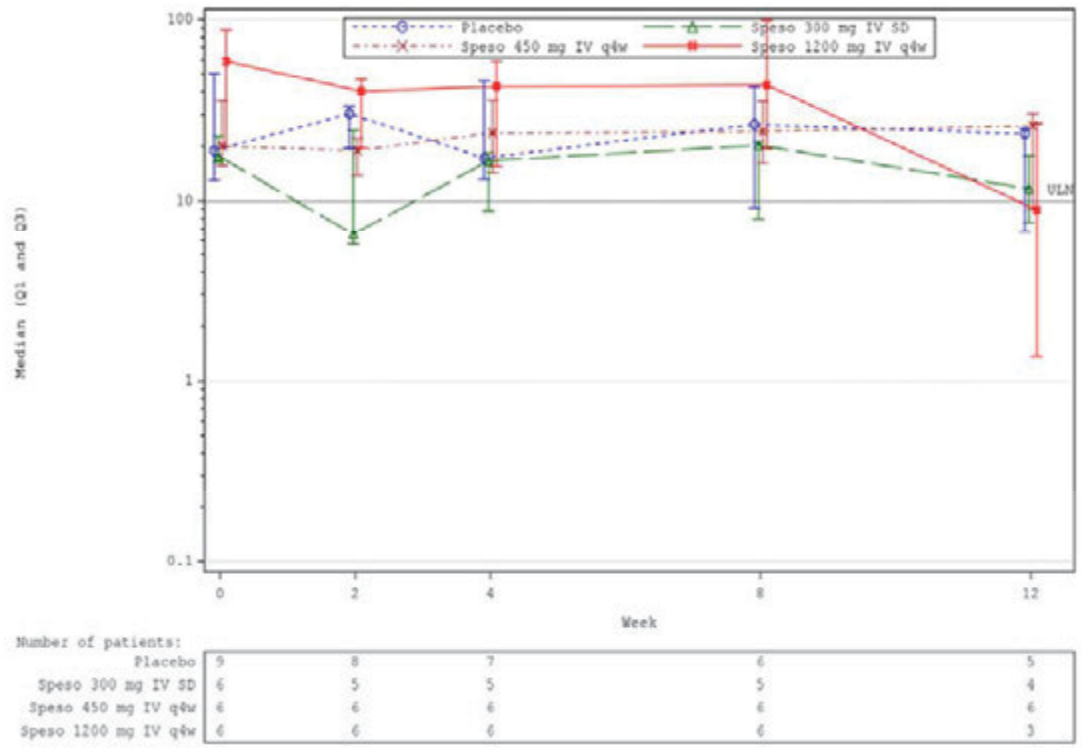
SD: Single dose; RS: Randomized Set; NRI: No response imputation.
Mucosal healing (endoscopic improvement): defined as modified endoscopic Subscore (mESS) ≤ 1.

Table 1.4:4 Interim Analysis trial 1358-0005 Secondary endpoint: Clinical Response at week 12 (RS, NRI)

	Placebo IV	**Spesolimab 300 IV SD**	**Spesolimab 450 IV q4w**	**Spesolimab 1200 IV q4w**
Subjects N (%)	23 (100%)	22 (100%)	21 (100%)	24 (100%)
Subjects with Endpoint N (%)	5 (21.7)	2 (9.1)	5 (23.8)	6 (25.0)
95% CI	(9.7, 41.9)	(2.5, 27.8)	(10.6, 45.1)	(12.0, 44.9)
Risk Difference vs placebo (95% CI)		-12.6 (-33.9, 9.6)	2.1 (-22.0, 26.5)	3.3 (-20.7, 26.5)

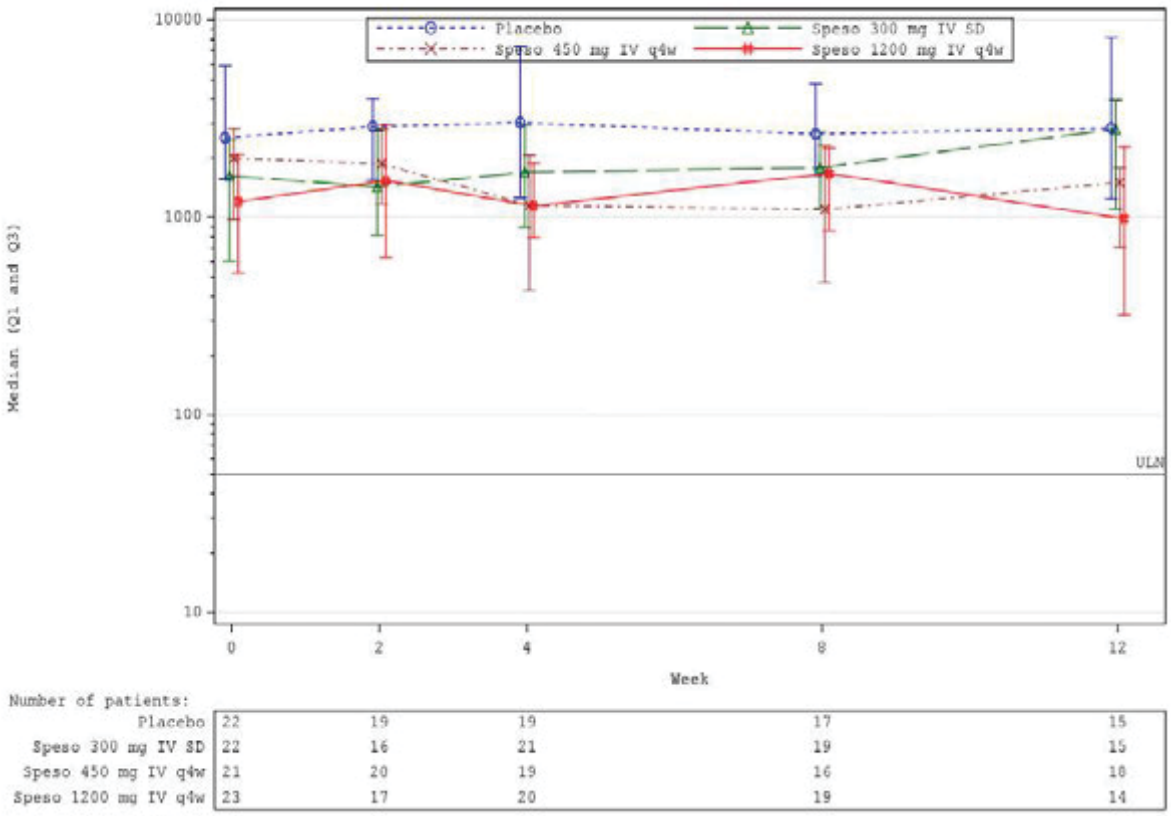
SD: Single dose; RS: Randomized Set; NRI: No response imputation.
Clinical Response: defined as defined as total MCS reduction ≥3 pts. and ≥30% from BL; AND RBS drop from baseline by ≥1pt., or absolute RBS ≤1 pt

Figure 1.4:1 Interim Analysis trial 1368-0005 Further endpoint: Median (with Q1 and Q3) of absolute values in C-Reactive Protein (CRP) over time for patients with baseline values above upper limit of normal (SAF,OC)



SD: Single dose; SAF: Safety Analysis Set, OC: Observed case.

Figure 1.4:2 Interim Analysis trial 1358-0005 Further endpoint: Median (with Q1 and Q3) of absolute values in faecal calprotectine (FCP) over time for patients with baseline values above upper limit of normal (SAF, OC)



Number of patients:

Placebo	22	19	19	17	15
Speso 300 mg IV SD	22	16	21	19	15
Speso 450 mg IV q4w	21	20	19	16	10
Speso 1200 mg IV q4w	23	17	20	19	14

SAF: Safety Analysis Set, OC: Observed case.

In summary, the results of the interim analysis of trial 1368-0005, show:

- No clear efficacy of Spesolimab over placebo on clinical endpoints across studies and UC populations.
- Effect in the most strict endpoints (clinical remission, mucosal healing) in few patients treated with higher doses of Spesolimab (450mg q4w and 1200mg q4w), although sample size is too low to show statistical significance.
- No dose response effect in primary and secondary clinical endpoints and in secondary inflammatory biomarkers.
- Spesolimab was safe and well tolerated with no evidence of previously unrecognized safety risks.

An analysis of all patients randomized in trial 1368-0005 (total of 98 patients) will be conducted after cleaning all data of these patients and subsequent data base lock.

An interim analysis was also conducted on data from patients in trial 1368-0017 who rolled over from trial 1368-0005. At time of this interim analysis, 69 patients rolled-over from trial 1368-0005 to trial 1368-0017; of those, 51 patients who did not achieve clinical response in

trial 1368-0005 received re-induction treatment of Spesolimab 1200 mg IV q4w and 18 patients who achieved clinical response in study 1368-0005 received maintenance treatment with Spesolimab 300 mg s.c. q12w. The main clinical results for patients who completed 12 weeks re-induction treatment or 12 weeks maintenance treatment in trial 1368-0017 are summarized in the table below by previous treatment in trial 1368-0005:

Table 1.4:5 Interim Analysis trial 1358-0017 Clinical endpoints for patients who completed 12 weeks re-induction treatment (TS-RT, NRI) or 12 weeks maintenance treatment (TS-MT, NRI) in trial 1368-0017 by previous treatment in trial 1368-0005

Data cut-off: 19 Feb 2020	**Placebo IV**	**Spesolimab 300 IV SD**	**Spesolimab 450 IV q4w**	**Spesolimab 1200 IV q4w**
Rolled-over from 1368-0005 to 1368-0017	**16**	**18**	**20**	**15**
Treated with re-induction (1200mg IV q4w)	**10 (100%)**	**16 (100%)**	**14 (100%)**	**10 (100%)**
Clinical remission week 12	0	0	0	0
Endoscopic Improvement week 12	0	0	0	0
Clinical response n (%) week 12	1 (10.0)	2 (12.5)	4 (28.6)	2 (20.0)
Treated in maintenance (300mg sc q12w)	**5 (100%)**	**2 (100%)**	**6 (100%)***	**5 (100%)***
Symptomatic remission week 12	0	1 (50.0)	1 (16.7)	2 (40.0)

TS-RT: Treated Set for Re-induction Treatment; TS-MT: Treated Set for Maintenance Treatment; NRI: No response imputation

Patients randomized to placebo in trial 1368-0005 who rolled-over to trial 1368-0017 and received re-induction treatment in trial 1368-0017, received in total 12 weeks of induction treatment with Spesolimab. Patients randomized to Spesolimab in trial 1368-0005 who rolled-over to trial 1368-0017 and received re-induction treatment in trial 1368-0017, received in total 24 weeks of induction treatment with Spesolimab. None of these patients achieved Clinical remission or Endoscopic improvement at week 12 and only few patients achieved Clinical response. Few patients who rolled-over from trial 1368-0005 to trial 1368-0017 and treated with maintenance treatment achieved Symptomatic remission.

Based on the results of the interim analyses of trials 1368-0005 and 1368-0017, the general benefit-risk assessment for patients currently treated in trial 1368-0017 cannot be evaluated. Therefore for these patients, the benefit-risk should be assessed by the investigator on an individual basis to evaluate patient continuation in the trial.

As recruitment of patients has been completed and no patients are ongoing in the preceding trials 1368-0004 and 1368-0005, no more patients can be enrolled in trial 1368-0017.

Summary of benefit-risk assessment

Due to the lack of mechanism- or compound-related safety signals as well as the antagonistic mode of action of BI 655130 (SPESOLIMAB) it is considered unlikely that UC patients be exposed to any undue risks in this trial. Considering the medical need of the development of an effective and well tolerated drug specifically and directly treating the structural aspects of UC, the benefit of this trial is considered to outweigh the potential risks for individual UC patients participating in this trial.

Based on the results of the above mentioned interim analysis of the preceding induction trial 1368-0005 and of trial 1368-0017, a benefit-risk assessment should be done by the investigator together on an individual basis to evaluate patient continuation in trial 1368-0017.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

Table 2.1:1 Definitions of Study Outcomes

Outcome	MCS subscore				*Total* MCS	*Mod.* MCS	*Partial* MCS	Additional Requirements
	RBS	mESS	SFS	PGA				
Clinical remission	0	≤1	0 or 1, if drop vs BL[1] ≥1	-		≤2		
CS-free remission (in pts on CS at BL)	0	≤1	0 or 1, if drop vs BL[1] ≥1	-		≤2		CS-free ≥12 wk and PMR for ≥12 wk
Clinical response	≤1, or drop vs BL[1] ≥1	Not missing	Not missing	Not missing	Drop vs BL[1] ≥3 and ≥30%			
Partial MCS response	≤1, or drop vs BL[1] ≥1	-	Not missing	Not missing			↓ ≥2 vs BL[1]	
Partial MCS remission	≤1	-	≤1	≤1			≤2	
Endoscopic remission	-	0	-	-				
Endoscopic improvement	-	≤1	-	-				
Complete remission	-	0	-	-				Robarts Histology Index (RHI) ≤6
Disease flare (after clinical response/remission, i.e. applicable on maintenance treatment only)	↑ ≥1 vs BL[2]	≥2, AND ↑ ≥1 vs BL[2]					↑ ≥2 vs BL[2]	pMCS ↑ and RBS ↑ from BL[2], conf. in 2nd indep. Visit, with mESS ↑, and neg. enteric pathogens in stool

[1] BL of preceding induction study (1368-0005 Part 1)
[2] BL of current maintenance study (1368-0017)

Table 2.1:1 Definitions of Study Outcomes (cont.)

Outcome	Definition
***Maintained* remission**	CR wk1+48, AND PMR at ≥75% of intervening visits w/o flare
***Durable* remission**	CR wk48, and PMR w/o flare in preceding 24 wks
Disease worsening	Worsening of clinical status or UC symptoms, in the investigator's opinion, requiring: 1) [during steroid taper] a suspension of tapering, or, a reversion of the steroid daily dose to the preceding daily dose, or, 2) treatment with rescue medication
Treatment Failure	Disease worsening, or a drug-related AE leading to discontinuation of study drug
Rescue Medication	New or dose increase of any non-study drug or surgical intervention for new or persist. symptoms of UC
Histological remission (HR)	Robarts Histology Index (RHI ≤ 6)

All criteria have to be met to qualify for the respective outcome at the same time

- Abbreviations: CR - clinical remission; pCR - partial clinical remission; CS - systemic corticosteroids; RBS – rectal bleeding score; mESS – modified endoscopic subscore; pts. - patients; RHI - Robarts Histology Index; SFS – stool frequency score; PGA – physician's global assessment; PMR - partial MCS remission; MCS – MayoScore; BL – baseline of previous parent induction trial
- Total MCS is calculated as the sum of RBS, mESS, SFS and PGA
- Modified MCS is calculated as the sum of RBS, mESS and SFS
- Partial MCS is calculated as the sum of RBS, SFS and PGA

2.1.1 Main objectives

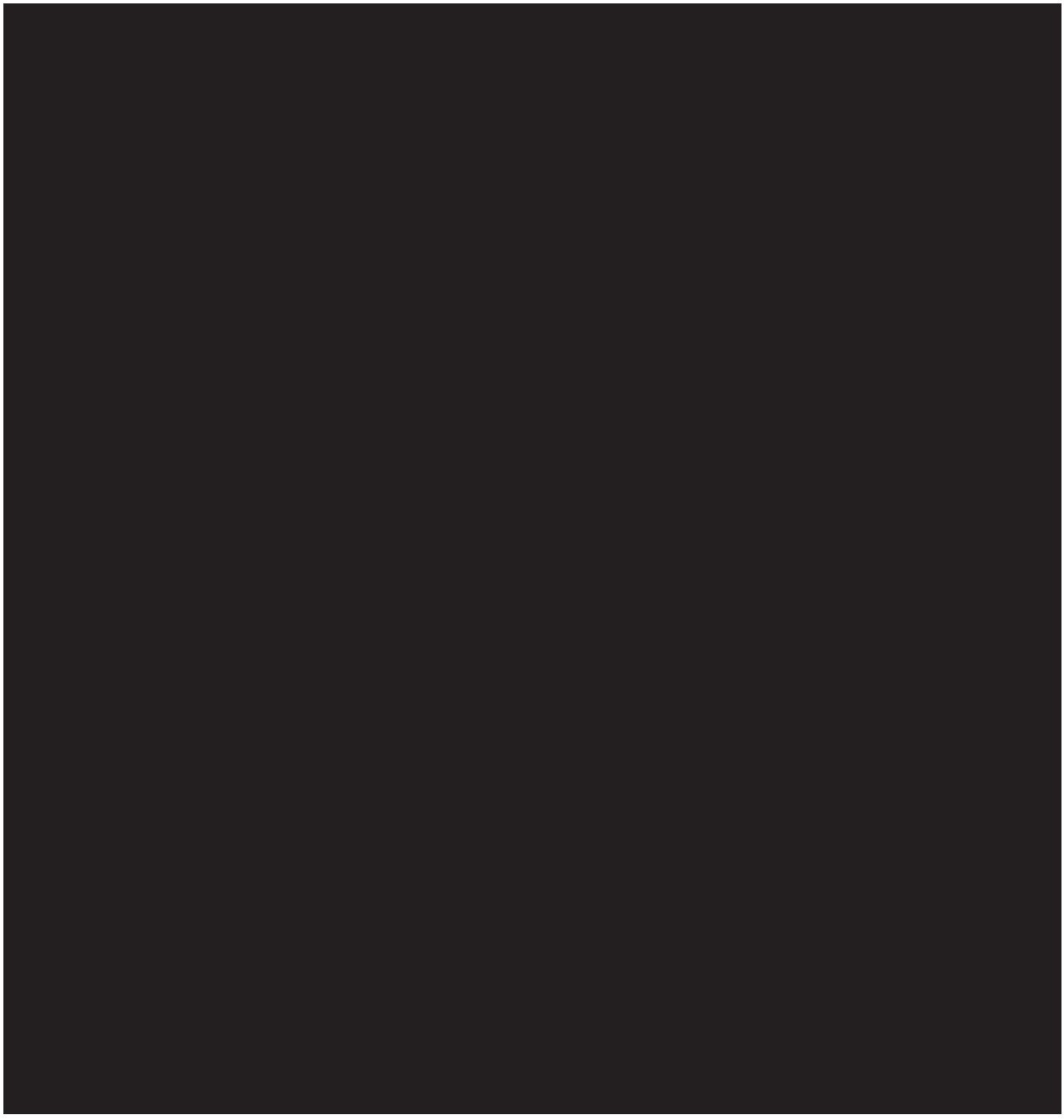
1. To evaluate the long-term safety of BI 655130 (SPESOLIMAB)in patients with moderate to severely active ulcerative colitis, who have completed treatment in previous trials
2. To evaluate the long-term efficacy of BI 655130 (SPESOLIMAB) in patients with moderate to severely active ulcerative colitis, who have completed treatment in previous trials

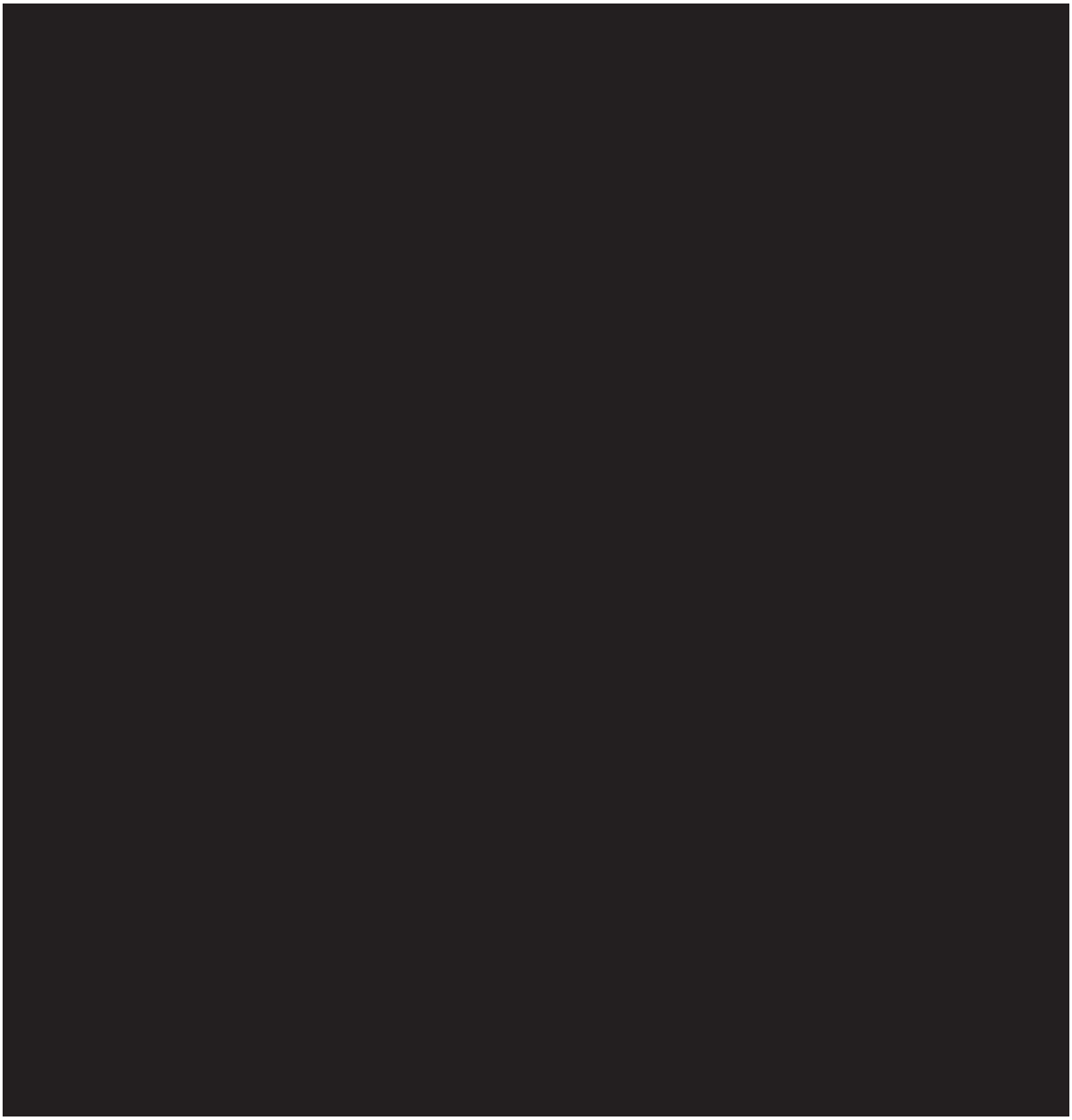
2.1.2 Primary endpoint(s)

Primary endpoint is the exposure adjusted rate of patients reporting a treatment emergent adverse event (TEAE) up to week 336 of maintenance treatment

2.1.3 Secondary endpoint

Proportion of patients with clinical remission at week 336 of maintenance treatment (as defined in table 2.1: 1)





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This open label (OL), 7 year, single group, long-term extension study investigates the long term safety and efficacy of BI 655130 (SPESOLIMAB) in patients with moderate-to-severe ulcerative colitis who have completed treatment in previous BI 655130 (SPESOLIMAB) induction trials 1368-0005 Part I and 1368-0004.

Approximately 160 patients who meet the entry criteria are planned to be included in the trial from previous induction trials 1368-0005 Part I and 1368-0004. The treatment will be open-label. Trial will consist of a screening period lasting up to 7 days, followed by a 336 weeks maintenance treatment period and a 16 weeks safety follow-up period. Patients rolling-over into 1368-0017 trial must complete the 12 weeks treatment period (until EOT visit) in the previous induction trial. Patients will be treated according to their previous trial outcome in a following way:

- Patients who have completed treatment in the previous trials showing a clinical response at week 12 will receive BI 655130 (SPESOLIMAB) s.c. maintenance treatment (300mg q4w s.c.) through week 336 of this extension study (Flowchart 1).
- Patients who have completed treatment in the previous trials, but did not achieve a clinical response at week 12, will receive BI 655130 (SPESOLIMAB) i.v. re-induction treatment (1200mg q4w i.v. for 12 weeks). Those patients who subsequently reach the clinical response (versus baseline of original induction trial) at week 12 of re-induction period, will be entered into the 336 weeks s.c. maintenance treatment phase (Flowchart 2); while non-responders will be discontinued from treatment and complete early EOT visit and safety follow-up period.
- Patients ongoing on maintenance treatment when CTP version 05 is approved will be asked to re-consent to the change in treatment frequency. After consent, patients will switch from q12w regimen to q4w regimen. Patients who do not wish to consent to this change will be discontinued from the study.

A schematic overview of trial design is shown in Figures 3.1:1 and 3.1:2.

Figure 3.1:1 Trial design for responders and non-responders

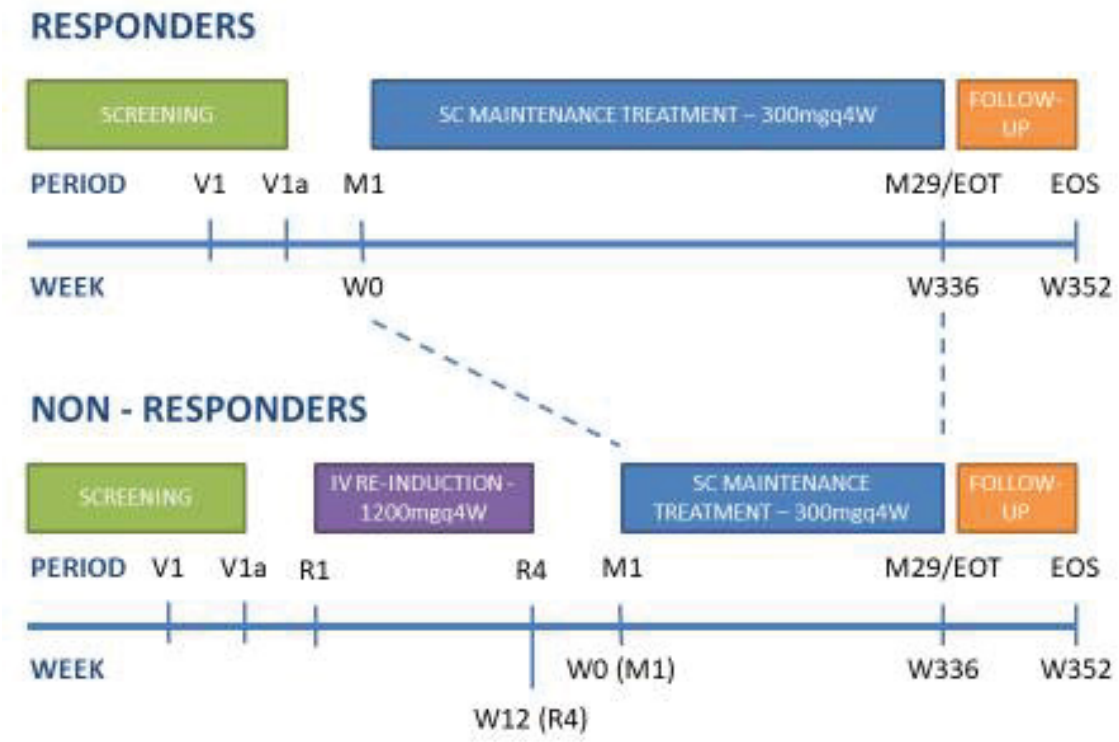
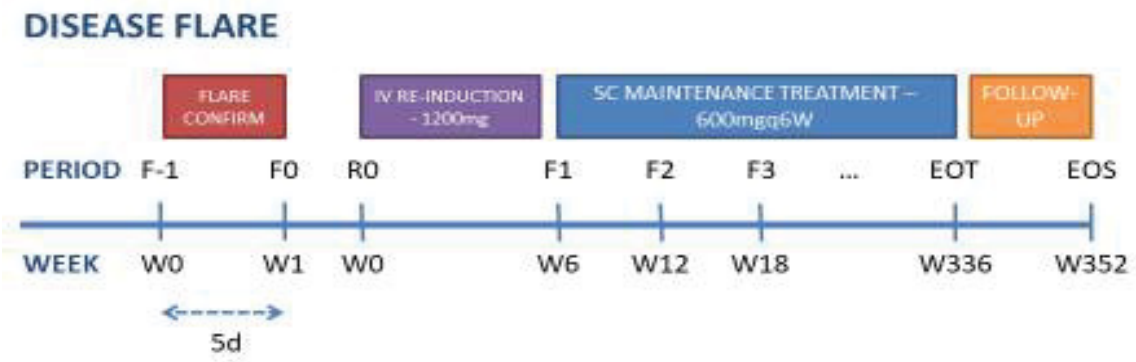


Figure 3.1:2 Trial design in case of a disease flare



d, day; EOS, end-of-stud; EOT, end-of-trial; F, flare; M, maintenance; Q12w, every 12 weeks; R, rescue; SC, subcutaneous; SCR, screening; V, visit; W, week

Patients who terminate study drug in 1368-0017 prematurely will be invited to early EOT visit instead of next planned visit followed by safety follow up (EOS) 16 weeks after last study drug intake.
Several interim analyses of PK, biomarker and clinical data will be performed throughout the conduct phase of this 7-year study to support future trial applications, investigator brochures, regulatory documents and scientific publications. The final analysis of the entire trial data

will be performed once all patients have completed the last scheduled trial visit. The end of trial is defined as "last patient out"; i.e. last scheduled visit completed by last patient.

Steroid tapering:
All patients on oral corticosteroids entering s.c. maintenance treatment who achieve clinical response or clinical remission will be requested to taper their prednisone dose or equivalent (see Appendix 10.3) of other systemic corticosteroids following a pre-defined scheme (see Appendix 10.7).
Patients on oral corticosteroids entering i.v. re-induction treatment due to lack of a clinical response in the parent study shall start tapering if response is subsequently confirmed at Week 12.
Patients receiving budesonide MMX at study entry will taper their initial daily dose for 2 weeks every other day before stopping the drug.
Patients on stable dose of beclomethasone dipropionate will be requested to stop using it after they achieve clinical response or clinical remission.
If a patient undergoing steroid dose reduction in line with the tapering scheme experiences disease worsening, further dose reduction may be suspended or the daily corticosteroid dose could be reverted to the preceding daily dose, but must not exceed the original daily dose (or equivalent) at baseline.

Disease flare treatment:
A disease flare may occur at any time after achievement of a clinical response during *maintenance s.c. treatment* period and is defined as a re-increase in partial MCS score, and a re-increase in rectal bleeding score, observed during a regular or unscheduled study visit, confirmed in an independent subsequent visit and by sigmoidoscopy, in absence of enteric pathogens in stool (for complete definition see table 2.1: 1). In case of a suspected disease flare, the site will ask the patient to immediately start entering his Mayo score data into the eDiary until the next scheduled or unscheduled visit, and then continue entering the data as planned (i.e. for 14 days preceding each visit). A patient with a (endoscopically confirmed) flare will receive a single i.v. infusion of 1200mg BI 655130 (SPESOLIMAB) as a flare treatment followed by intensified maintenance dosing with 600mg sc. BI 655130 (SPESOLIMAB) q6w. No further maintenance dose escalation is foreseen in case of repeated flares. An additional unscheduled sigmoidoscopy has to be planned at week 12 after the i.v. infusion to check the patient`s response status to disease flare treatment.

Patients who experience a disease flare during steroid tapering should follow the same flare treatment instructions specified above, but may suspend further steroid dose reduction or re-escalate dose once in line with the instructions above.
For details of trial procedures please follow the Flowchart 3 (Patients with Disease Flare).

Patients will be discontinued from treatment if they do not achieve clinical response (compared to baseline of original induction trial) or clinical remission within 12 weeks after the initiation of disease flare treatment, or if they experience more than 1 confirmed flares during the trial.

Allowed concomitantly given immune modulators (AZA, 5MP, MTX; see table 4.2.2:1) can be discontinued after ≥52 weeks of s.c. maintenance treatment in patients with durable clinical remission per the Investigator`s judgement.

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

All patients who complete induction treatment with BI 655130 (SPESOLIMAB) or placebo in previous trials 1368-0004 or 1368-0005/Part 1 will roll-over into this trial to receive long-term treatment with active drug, provided patients derived an individual health benefit from either induction or re-induction treatment by achieving a clinical response. Patients not responding to induction/re-induction treatment or experiencing more than 1 disease flare in the maintenance part of 1368-0017 will be discontinued from the trial treatment per the pre-defined stopping criteria (cf. section 3.3.4.1) and receive individualized treatment at the discretion of the investigator.

Patients rolling over from 1368-0005 Part 1 or 1368-0004 will be monitored for induction outcome at the EOT visit of these trials and initiate treatment in 1368-0017 upon availability of the centrally read endoscopy score (within ≤1 week). The treatment regimen will depend on the individual patient outcome in 1368-0005 Part 1 and 1368-0004 (cf. section 3.1 and below).

The open label re-induction treatment in non-responders to BI 655130 (SPESOLIMAB) induction therapy in the original study will offer extended and high dose treatment and help to further characterize the response kinetics to BI 655130(SPESOLIMAB). Although currently approved or investigational biologics (e.g. tofacitinib, TNFi, vedolizumab) have established 4-8 weeks duration of induction treatment in UC [R17-3426, R15-5737, R15-4915, R17-2217], the new MoA of BI 655130 (SPESOLIMAB) may have a delayed onset of action. Re-induction treatment for additional 12 weeks or with escalated dose has been shown with other drugs (e.g. JAK inhibitor tofacitinib, IL23 inhibitor risankizumab) to increase response and remission rates in IBD [P17-11924]. A similar effect may apply to BI 655130 (SPESOLIMAB) in UC. For original placebo patients, this trial will provide active induction treatment. The re-induction dosing interval of every 4 weeks is supported by the long half-life of BI 655130 (SPESOLIMAB) of approximately four weeks and safety data generated in Phase I studies. It aims to achieve a high plasma exposure on the plateau of the dose-response curve in order to maximize the treatment effect (ref: [c03320877]). Clinical responders to BI 655130 (SPESOLIMAB) induction are likely to require maintenance treatment in order to achieve deeper remission or mucosal healing, and to prevent the occurrence of relapses. The initial open label maintenance s.c. dosing interval every 12 weeks was supported by the long half-life, sustained target engagement and the high relative bioavailability of the sc. formulation found in phase I studies (ref. IB). However, the dosing interval for the maintenance dosing interval has been adapted to q4w based on the current observed study relapse rate (see Section 11). For dose selection refer to section 4.1.2.

This long-term study mainly aims to offer active maintenance treatment to patients having benefited from such induction or re-induction treatment, and to characterize the safety and tolerability of BI 655130 (SPESOLIMAB) long-term treatment. It will also characterize the persistence of clinical outcome over a long period of BI 655130 (SPESOLIMAB) treatment. Although a placebo control would improve this safety and efficacy assessment, it would withhold patients in need from active treatment and is not justifiable for longer than the 12 weeks in the initial induction study. An active comparator is not suitable for this highly treatment-experienced and heterogeneous study population, where any approved treatment would have to be tailored towards the patient`s individual treatment history. Moreover, patients responding to BI 655130 (SPESOLIMAB) induction treatment are likely to fail maintenance treatment if switched to a drug with a different MoA, which they may have failed in the past. Therefore, neither an active comparator nor placebo can be justified for the time frame and the population studied in this trial.

It is acknowledged that the reporting of data for this open-label, single-arm trial will likely be biased due to, among others, selection and reporting bias. This is, however, deemed acceptable given that all patients who respond to previous induction/re-induction treatment and who continue into this extension trial will be able to receive an active maintenance treatment with BI 655130 (SPESOLIMAB) for their ongoing disease.

3.3 SELECTION OF TRIAL POPULATION

Patients in this long-term open label extension trial will be rolled-over from previous induction trials 1368-0004 and 1368-0005 Part I. All patients enrolled into the preceding trial 1368-0005 Part I have failed conventional and/or biologic drugs in the past. Due to the wide availability of biologics approved in this indication, it is expected that the vast majority of patients enrolled into this first-in-class program will have failed several other biologics in the past and thus represent a very advanced population which has the highest unmet medical need and will be a typical population for a newly approved biologic.

Patients enrolled in the preceding phase II exploratory 1368-0004 trial are required to be on conventional, non-biologic treatment for UC, with stable treatment doses throughout the trial. Patients screened in the 1368-0017 trial have tolerated treatment with study drug in 1368-0005 Part I and 1368-0004 trials and have completed the 12 weeks treatment period. They must be willing to continue long term treatment with BI 655130 (SPESOLIMAB) for up to 7 years.

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 moderate-to-severely active ulcerative colitis who have completed treatment in induction trials 1368-0004 or 1368-0005 Part I.

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

3.3.2 Inclusion criteria

Each patient must meet all of the following inclusion criteria to be included into the trial:

1. Male or female patients, aged ≥18 years
2. Signed and dated written informed consent for 1368-0017, in accordance with GCP and local legislation prior to admission into the trial
3. Women of childbearing potential (WOCBP) must be ready to use highly effective methods of birth control per 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 (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tuba ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

4. Have completed treatment and the EOT visit in the previous trial and are willing and able to continue treatment in 1368-0017.

3.3.3 Exclusion criteria

Patients meeting any of these exclusion criteria must not be enrolled into the trial:

1. Have experienced study treatment-limiting adverse events during induction treatment with study drug
2. Have developed any of the exclusion criteria from the original induction study with the following exceptions:

   - Cases of disease limited to the rectum extending <15 cm past the anal verge are allowed to be included in study 1368.17.
   - Cases of latent TB. Patients with newly emerging **latent** TB during preceding study are allowed to be included in study 1368.17, provided they receive appropriate treatment according to local guidelines.

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 sections 3.3.4.1 and 3.3.4.2 below.

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 CRF.

3.3.4.1 Withdrawal from trial treatment

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

- A patient assigned to re-induction treatment does not achieve clinical response at week 12 compared to baseline of the original induction trial.
- A patient treated for a disease flare does not achieve clinical response (compared to baseline of the original induction trial) or clinical remission within 12 weeks after the initiation of disease flare treatment.
- A patient experience more than 1 confirmed flares during the trial.
- 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. Please refer to section 4.2.1 and 4.2.2 .
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, 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 comply with the trial requirements in the future.
- A patient can be discontinued from trial medication at any time if in the opinion of the Investigator, continuation with trial medication is not in the patient's best interest.
- For individual stopping rules related to specific adverse events, please see section 4.2.1 "Other treatments and emergency procedures".
- If peripheral neuropathy is suspected, treatment with spesolimab should be temporarily discontinued until a full neurological investigation has been conducted. After completion of the neurological investigation, treatment can be restarted based on medical judgement of the investigator.

If a patient has not achieved clinical remission within the first 48 weeks of maintenance treatment, investigator should consider trial drug termination based on individual patient history and available alternative treatment options.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Charts and section 6.2.3.
For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. This 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 and explain the options for continued follow up after withdrawal from trial treatment.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

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

4.1.1 Identity of the Investigational Medicinal Product

Table 4.1.1: 1 Description of test product BI 655130 (SPESOLIMAB) i.v. infusion

Substance:	BI 655130 (SPESOLIMAB)
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-36 Receptor mAb
Molecular weight:	146 kDa
Unit strength:	BI 655130 (SPESOLIMAB) 300mg/vial (60 mg/mL), 5 mL fill volume
Route of administration:	Intravenous infusions
Posology:	1200 mg at Week 0, 4 and 8 for re-induction
	1200 mg single dose in case of disease flare
Duration of use:	12 weeks

Table 4.1.1: 2 Description of test product BI 655130 (SPESOLIMAB) s.c. solution for injection

Substance:	BI 655130 (SPESOLIMAB)
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-36 Receptor mAb
Molecular weight:	146 kDa
Unit strength:	BI 655130 (SPESOLIMAB) 150mg/pre-filled syringe (150mg/mL)
Route of administration:	Subcutaneous injections
Posology:	300 mg at Week 0 and then every 4 weeks 600 mg every 6 weeks as intensified treatment for patients with disease flare
Duration of use:	336 weeks

4.1.2 Selection of doses in the trial

A 12 week re-induction dose regimen of 1200mg i.v. q4w will be administered to patients not responding to the original induction treatment with study medication in the parent trial. Based on data indicating high and sustained target engagement at doses ≥3mg/kg biweekly and a half-life as long as 4-5 weeks in healthy volunteers (cf. sections 6.1 and 6.2 of IB c03320877), this dose is expected to be at the plateau of the dose/response curve and to provide maximal efficacy. This dosing regimen also approximates the highest dose regimen

that has been tested and was found safe in preceding phase I studies. It therefore is being tested in ongoing studies in ulcerative colitis of 1368-0004 and 1368.10.
This dose will provide (i) active induction treatment to patients originally randomized to placebo, (ii) dose escalation to patients originally randomized to lower doses of BI 655130 (SPESOLIMAB) (i.e. 300mg SD or 450mg q4w), and (iii) extended duration of high dose induction to patients originally randomized to the same dose level. Under the assumption of a monotonic dose response curve, as found for other biologics in IBD treatment, this intensified dosing regimen may increase the induction efficacy of BI 655130 (SPESOLIMAB) as compared to lower doses or shorter duration of treatment.

The maintenance dose strength of 300mg s.c. was selected based on the assumed need for lower BI 655130 (SPESOLIMAB) exposures once a response or remission has been induced, as shown for other biologics in the IBD area. It is supported by the favourable bioavailability of the s.c. relative to the i.v. formulation (approx. 70%; cf. section 6.2 of [c03320877]). The dosing interval of q12w was initially selected based on the phase I findings of a long half-life (4-5 weeks) and sustained target engagement (≥90% as compared to baseline for at least 22 weeks after the last dose administered;[c03320877]). However, regular medical review meetings by the sponsor during the study conduct have demonstrated loss-of-response rates in initial responders after dose reduction to maintenance dosing, which were higher than those found with approved regimens. Under the assumption of a positive dose response relationship and given the favourable safety profile of BI 655130 (SPESOLIMAB) even at several fold higher IV doses (up to 1200mg q4w for up to 24 weeks), the sponsor has amended the trial to increase the *regular* maintenance dose to 300mg SC every 4 weeks, and the *intensified* maintenance dose after flare treatment to 600mg q6w.

4.1.3 Method of assigning patients to treatment groups

During visit M1 eligible patients will be allocated to receive open-label treatment based on the clinical outcome achieved in previous trials.

Patients rolling over from previous induction trials who have achieved a clinical response at week 12 in the preceding trial will receive OL BI 655130 (SPESOLIMAB) s.c. maintenance treatment (300mg q4w s.c.) until week 336 (for definition of clinical response see Table 2.1:1).

Patients rolling over from previous induction trials who did not achieve a clinical response in the preceding trial will receive 12 weeks of OL BI 655130 (SPESOLIMAB) re-induction treatment (1200mg q4w i.v.), and if they respond to this treatment they will continue BI 655130 (SPESOLIMAB) s.c. maintenance (300mg q4w s.c.) treatment until week 336 (for definition of clinical response see Table 2.1:1).

The assignment to treatment will be done via Interactive Response Technology (IRT).

4.1.4 Drug assignment and administration of doses for each patient

In this trial a dose of 300 mg of BI 655130 (SPESOLIMAB) will be administered during study visit as subcutaneous injection in the abdomen , in accordance with local standard

procedure and as described in "BI 655130 Solution for Injection 150 mg/mL s.c. Instructions for Handling and Use"

every 4 weeks for patients starting from visit M1 until EOT visit for patients who responded to treatment with study drug in previous trials or gained response after i.v. re-induction period. The concentration of the application solution will be 150 mg/ml.
Injection site should not be close to a vein and it should avoid sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses.
Detailed instructions for Handling and Use of s.c. injection are provided in the ISF.
Patients have to be closely monitored for local or systemic hypersensitivity reactions for 1 hour following s.c. study drug administration. Subcutaneous administration of biologic agents involves the risk of local (injection site) or systemic hypersensitivity reactions. Therefore, patients should be closely monitored for signs and symptoms of injection site or systemic hypersensitivity reactions following study drug administration. Study personnel should observe the injection site for signs of redness, swelling or hardness. They should also ask subjects about itching, dizziness or shortness of breath. Patients should be advised that if they experience redness, swelling or other changes at the injection site, they should notify site personnel. They should further be advised that if they experience itching all over or a feeling of being swollen, dizzy or short of breath, they should seek emergency medical attention immediately and notify site personnel.

1200mg BI 655130 (SPESOLIMAB) i.v. q4w administration for 12 weeks will be used for patients assigned to i.v. re-induction.
Single 1200 mg BI 655130 (SPESOLIMAB) i.v. administration will be used as disease flare treatment. Intravenous infusion including observational time for possible infusion reactions will last approximately 2.5 hours. The i.v. treatment will be followed by intensified maintenance treatment with 600mg BI 655130 (SPESOLIMAB) q6w.
Detailed instructions for the preparation of the i.v. infusion solution, the volume to be administered and the infusion rate are provided in the ISF.

In case of safety concerns, e.g., due to infusion reactions, it is in the discretion of the investigator or his/her designee to adapt the infusion scheme (cf. Section 4.2.1 for handling of infusion reactions). Detailed instructions for handling of infusion reactions are also provided in the ISF.

The administration of the trial medication intravenously on all applicable study days will be done under supervision of the investigating physician or a designee at the site. If available, a pharmacist should prepare the study medication. The four eye principle (two-person rule) should be applied for preparation (e.g. choosing the correct vials with the correct medication number) and administration of trial medication.

Dose modifications or adjustments are not permitted. In exceptional cases of missed or delayed visits, if any of these visits has to be rescheduled, the date of subsequent visit should be calculated from Day 1 of maintenance treatment or if the patient is on flare treatment from the first s.c. drug administration after the last disease flare. There should be at least 14 days between two consecutive study drug administrations.

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. In this open-label trial, treatment allocation will not be concealed throughout the trial.
With regard to the blind of the parent study (1368-0005 part I), patients and investigators will remain blinded with regard to the original randomised treatment assignments until after the final database lock for the initial induction trial has been performed.

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). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

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 local clinical monitor (as provided in the list of contacts) must be contacted immediately. Refer to ISF. Trial medication must be securely stored, e.g. in a locked refrigerator at the site or at a pharmacy. The medication may only be dispensed to trial patients according to the Clinical Trial Protocol (CTP) by authorized personnel as documented in the trial staff list.
Trial medication will be prepared for infusion just prior to infusion, for further details please see preparation instructions in the ISF.

4.1.8 Drug accountability

The investigator/pharmacist /investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB/ethics committee ,
- Availability of a signed and dated clinical trial contract between the sponsor and 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,

- Availability of the proof of a medical license for the Principal Investigator (if applicable),
- Availability of FDA Form 1572 (applicable for US).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other physicians or clinics.
The investigator/pharmacist/ 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 the investigational product and 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 or appointed CRO, the investigator/pharmacist / investigational drug storage manager must verify that all unused drug supplies have been returned by the clinical trial patient 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

If the patient requires additional medical therapy or dose increase of baseline ulcerative colitis medication (other than BI 655130 (SPESOLIMAB) to treat a disease flare or a reversion to the preceeding higher daily steroid dose during tapering of steroids) to treat the underlying ulcerative colitis due to disease worsening (cf. Table 2.1:1 Definition of Study Outcomes), the study drug must be discontinued and patients may receive conventional treatment for active disease. In case of disease flare during maintenance treatment period, patient must be provided with disease flare treatment (single i.v. dose of 1200 mg BI 655130 (SPESOLIMAB) infusion) followed by intensified maintenance treatment with 600mg BI 655130 (SPESOLIMAB) q6w.
In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator. If the subject receives a live virus vaccination during the study, the subject must discontinue study treatment.
Systemic steroids dosed intravenously or orally for less than 24 hours as treatment of infusion or anaphylactic reactions are permitted and do not lead to treatment discontinuation (see Table 4.2.2: 1).

If mild-to-moderate infusion or anaphylactic reaction had already occurred in the very same patient in the past, pre-treatment with steroids before next IMP administration is permitted as secondary prophylaxis.

Locally administered steroids as e.g. intraarticular, nasal inhalation or intraocular administration are allowed, but their application has to be carefully monitored and reported in CRF (see Table 4.2.2: 1).

Management of Adverse Events:

Infusion reactions / Systemic hypersensitivity including anaphylactic reaction

In case of infusion reactions / systemic hypersensitivity including anaphylactic reaction emerging during or after infusion / injection(s) of study drug, the investigator should consider in accordance with severity of the reaction and local standard of care to:

- Immediately interrupt the infusion / Stop further injections
- Treat with systemic anti-histamines, intravenous steroids, and in case of a severe allergic reaction (e.g., anaphylactic reaction) epinephrine

Also draw a plasma sample for IgE and ADA as detailed in the Lab Manual (available in ISF). Additionally consider the evaluation of histamine, serum tryptase, and complement components.

In case of infusion reaction / systemic hypersensitivity reaction, based on patient`s clinical course and medical judgment, the infusion / injections may be re-initiated in case of mild or moderate infusion reactions / systemic hypersensitivity reactions (according to RCTC grading of "allergic reaction/hypersensitivity" in ISF) at lower speed with gradual increase to complete the infusion (in case of an infusion reaction) as detailed in the Instructions for Preparation and Handling of BI 655130 (SPESOLIMAB) in the Investigator Site File.

In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.5 R11-4890) suspected to be caused by the trial medication, the investigator should discontinue treatment with study drug (see Appendix 10.5 for criteria of anaphylaxis).

When a non-acute hypersensitivity reaction related to immune complexes (i.e., serum sickness) is suspected, please draw a sample for the laboratory assessment for circulating immune complexes (referring to Lab manual).

Severe infections (according to RCTC grading in Appendix 10.6), serious infections, opportunistic or mycobacterium tuberculosis infection

Treatment of the infection should be initiated promptly according to local standard of care. No further trial medication should be administered until the active infection is resolved. Treatment with trial medication may be restarted when the patient has recovered according to investigator's assessment.

- Latent TB must be treated according to local guidelines. Patient can continue the treatment.

Malignancies

- In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with study drug. Diagnostics and treatment have 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**
Any biologic *approved* for UC (i.e. adalimumab, infliximab, golimumab, vedolizumab)	Not allowed until end of the end of IMP treatment For use as rescue medication, refer to Section 4.2.1.
Any *investigational or non-approved* biologic for UC (incl. ustekinumab, other IL-23 inhibitors, etrolizumab, certolizumab)	Not allowed until end of the trial For use as rescue medication, refer to Section 4.2.1.
Any *non-biologic* immunomodulator, (incl. cyclosporine, tofacinib and other JAK inhibitors, tacrolimus, sirolimus, mycophenolate mofetile)	Not allowed until end of the trial For use as rescue medication, refer to Section 4.2.1.
Any immunomodulator allowed per inclusion criteria in previous trial (Azathioprine, 6-mercaptopurine or methotrexate)	Only allowed during the trial, if dose is stable prior to treatment initiation until end of the trial For use as rescue medication, refer to Section 4.2.1 After ≥52 weeks of maintenance, such treatment can be discontinued in patients with durable clinical remission per the Investigator`s judgement
natalizumab or rituximab	Any prior exposure is prohibited
5-ASA	*Oral administration:* Only allowed during the trial, if dose is stable prior to treatment initiation until end of the trial *Rectal route of administration:* Not allowed from screening up to end of the trial For use as rescue medication, refer to Section 4.2.1.

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

Corticosteroids (incl. budesonide)	*Oral administration:* Oral systemic corticosteroids only allowed at a dose of ≤ 20mg per day of prednisone or equivalent and with stable dose prior to treatment initiation. Short decrease of dose for treatment of AEs with subsequent increase back to initial baseline dose level is allowed Oral budesonide MMX (≤9 mg per day), provided that dose has been stable prior to treatment initiation. Beclomethasone dipropionate allowed with stable dose prior to treatment initiation. *Parenteral administration:* Not allowed from prior to screening up to end of the trial. *Rectal administration:* Not allowed from screening up to end of the trial **Note**: steroids will be tapered upon achievement of a clinical response or remission *Allowed steroid treatments:* Short-term use (<7 days) of systemic (oral or parenteral) corticosteroids is allowed for treatment of AE not related to the underlying UC. Parenteral corticosteroids dosed for less than 24 hours as treatment of infusion or anaphylactic reactions are permitted. Locally administered steroids as e.g. intra-articular, nasal inhalation or intra-ocular administration are allowed. For use of steroids as rescue medication, refer to Section 4.2.1.

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

NSAID	Chronic use not allowed from screening up to end of the trial (Note: Occasional use of NSAIDs and acetaminophen for transient symptoms - headache, arthritis, myalgias, menstrual cramps, etc., and daily use of baby or low dose (81-162.5mg) aspirin for cardiovascular prophylaxis are permitted.)
Antidiarrheals	Allowed during the trial as needed
Live-attenuated vaccines	Not allowed from screening up to end of the trial
Antibiotics for IBD	Not allowed from screening up to end of the trial (antibiotics given for other indications are allowed if taken for no longer than 3 weeks)

4.2.2.1 Restrictions on diet and life style

No restrictions.

4.2.2.2 Restrictions regarding Women of Childbearing Potential

Women of childbearing potential must use the contraception methods described below.

Highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly for female participants who are able to become pregnant include:

1. Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation.
2. Progestogen-only hormonal birth control associated with inhibition of ovulation.
3. Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS).
4. Tubal occlusion (blocking of the fallopian tubes).
5. Vasectomy of sexual partner (proven effective by absence of sperm on the ejaculation).
6. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to the investigational medicinal product, and withdrawal are not acceptable methods of contraception

4.3 TREATMENT COMPLIANCE

Study medication will be administered in accordance with the protocol under supervision of the investigating physician or a designee at the site.

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The changes in UC activity during the trial will be assessed at visits including endoscopies using the modified Mayo score (disease activity score, not including the PGA (physician global assessment) item, but including the modified ESS (any degree of friability defines a score of at least 2), and the Robarts histopathology index (RHI). In addition, the total Mayo score (including PGA) will be explored as further endpoint to facilitate indirect comparisons against currently approved or investigational drugs.

Please refer to Appendix 10.1 (Mayo Score/modified Mayo score) and to Appendix 10.2 (Robarts histopathology index) for further details.

Endoscopic and histological endpoints will be assessed and scored using independent central readers.

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Clinical laboratory values (haematology, clinical chemistry, coagulation and urinalysis)
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to Appendix 10.6 and ISF for details)
- Physical examination
- Vital signs
- 12-lead ECG

5.2.1 Physical examination

Complete physical examination will include vital sign assessment and general appearance as well as evaluation of all organ systems, Targeted physical examination will include vital sign assessment and evaluation of organ systems associated with AE(s) symptoms or extra intestinal manifestations as well as laboratory abnormalities.

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

5.2.2 Vital signs

Vital signs evaluations will be performed at visits as shown in the Flow Chart. This includes temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least five minutes. Measurement of vital signs should precede blood

sampling to avoid the impact of blood sampling on the vital measurements. At dosing visits vital signs evaluations will be performed pre-dose for both visits with i.v. and s.c. administration of study drug. Vital signs will be measured additionally 10 min post-dose after s.c. administration and 5 and 60 min. post-dose in case of i.v. study drug administration.

Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for 1 hour following i.v. study drug administration. Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further injections might be considered and will be agreed on between investigator and BI clinical monitor.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1. For the sampling time points please see the Flowcharts.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.
Patients are not required to be fasting for at least 8 hours prior to the blood sample being taken.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.
The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events or baseline conditions. (please refer to Section 5.2.6).
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.

A clinically relevant value may be either within- or outside the reference range. Clinically relevant abnormal laboratory test results must 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 5.2.6.1 and the DILI Checklist provided in the ISF EDC system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Table 5.2.3: 1 Additional testing

Category	Test name
Serum Pregnancy test (only for female patients of childbearing potential)[1]	Human Serum Chorionic Gonadotropin
Stool studies to evaluate for enteric pathogens (Faecal assessment for enteric pathogens has to be done at suspicion of an disease flare to exclude enteric infection)	Salmonella Shigella Yersinia Campylobacter Vibrio E. coli O157/H7 Clostridia difficile toxin Enteric parasites and their ova (including Cryptosporidia)

[1] At screening only (visit 1)

Table 5.2.3: 2 Laboratory tests

Category	Test name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hbc (HbA1c) (required to be tested every 48 weeks) Red Blood Cell Count/ Erythrocytes Reticulocyte Count White Blood Cells / Leukocytes Platelet Count/ Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Basophils (relative and absolute count) Monocytes (relative and absolute count) Lymphocytes (relative and absolute count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine eGFR (estimated by CKD-EPI formula) (only at screening) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (Reflex, in case of elevated CK) Protein, Total Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol

Table 5.2.3: 2 Laboratory tests (continued)

Category	Test name
Specific gamma-globulin quantification	IgE[1], IgG
Urine Pregnancy test (only for female patients of childbearing potential)	Human Chorionic Gonadotropin in urine
Serum Pregnancy test (only for female patients of childbearing potential if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Hormones (required to be tested every 48 wks)	TSH (free T3 and free T4 in case of abnormal TSH result)
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urine (only at screening)	Albumin (quantitative)
TB	QuantiFERON®-TB[2]
Faecal sample	Calprotectin Lactoferrin

[1]Only in case of allergic reaction

2 If the 1st QuantiFERON®-TB test result is undetermined, a re-test should be performed. If the restest QuantiFERON-TB test result is undetermined, a PPD skin test should be performed.

5.2.4 Electrocardiogram

The 12-lead ECGs will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.
Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.
Clinically relevant abnormal findings will be reported as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Local tolerability at the administration site of the subcutaneous injection will be assessed by the investigator at the specified visits as noted in the Flow Chart see section 4.1.1 for further details. Any observed local tolerability reactions like "swelling", "induration", "heat", "redness", "pain", or any other findings should be reported as an adverse event in the eCRF. In case of an infusion reaction monitor the patient per standard of care, grade the intensity of the reaction according to RCTC grading (cf. ISF) and proceed as described in section 4.2.2.1. Also draw plasma sample for IgE and ADA (anti-drug antibodies), as detailed in the CTP section 5.2.3 and the lab manual. Assessment according to RCTC implies also reporting as AE.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

Adverse Event
An adverse event (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
A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

1. results in death,
2. 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.
3. requires inpatient hospitalisation or
4. requires prolongation of existing hospitalisation,
5. results in persistent or significant disability or incapacity, or
6. is a congenital anomaly / birth defect,
   or
7. 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.

For Japan only: the following events will be handled as "deemed serious for any other reason". AEs which possibly lead to disability will be reported as SAEs.

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 section 5.2.6.2, subsections " AE Collection" and **AE reporting to sponsor and timelines"**

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

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. 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 interest or prospective safety monitoring and safety assessment within this trial. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see above.

The following are considered as AESIs:

- Systemic hypersensitivity including infusion reaction and 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 (Appendix 10.5, R11-4890).

Severe infections (according to (according to RCTC grading in Appendix 10.6)

Opportunistic and mycobacterium tuberculosis infections

These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species

(chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617]

Hepatic injury

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

a. ALT or AST >5x ULN

b. ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

c. AST and/or ALT >3 fold ULN combined with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample

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 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.

If an alternative cause for the hepatic injury cannot be identified in the follow-up assessments specified in the "DILI checklist", discontinuation of treatment with study drug should be considered.

Peripheral Neuropathy

Any event suspected or diagnosed as Peripheral Neuropathy would be considered as an AESI. For the treatment interruption rules, please see section 3.3.4.1

Intensity (severity) of AEs

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by [redacted] (Appendix 10.6, R13-3515). Refer to the ISF for intensity/severity classification. Intensity options are:

Grade 1	mild
Grade 2	moderate
Grade 3	severe
Grade 4	life-threatening

Causal relationship of AEs

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.

5.2.6.2 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 the time of first dose of trial drug administration in the extension trial 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 new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Figure 5.2.6.2:1), but not on the CRF.

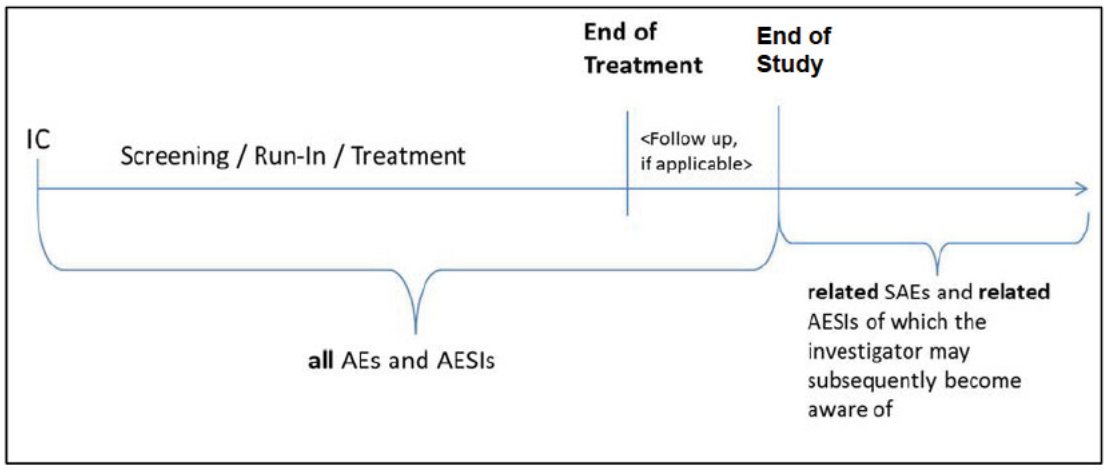


Figure 5.2.6.2: 1 Adverse event collection and reporting

However, patients who discontinue trial medication prematurely and agree to be contacted further should be followed up as described in section 3.3.4.1, withdrawal from trial treatment. From then on until the initially planned completion date of each individual patient the investigator must report all deaths/fatal AEs regardless of relationship, related SAEs and related AESIs the investigator becomes aware of.

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 immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete andsend the BI SAE form.

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

Information required
For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable.

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.

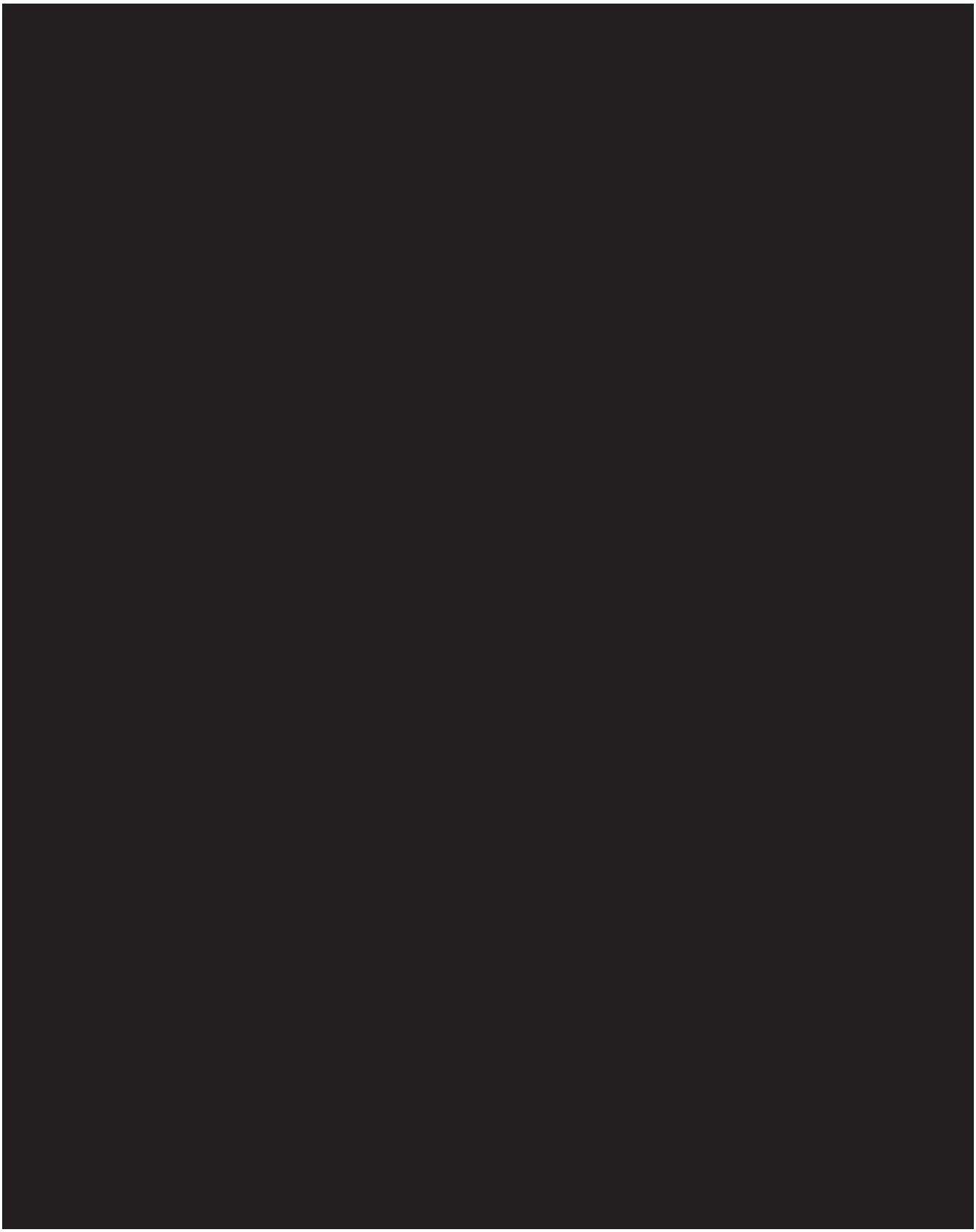
If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

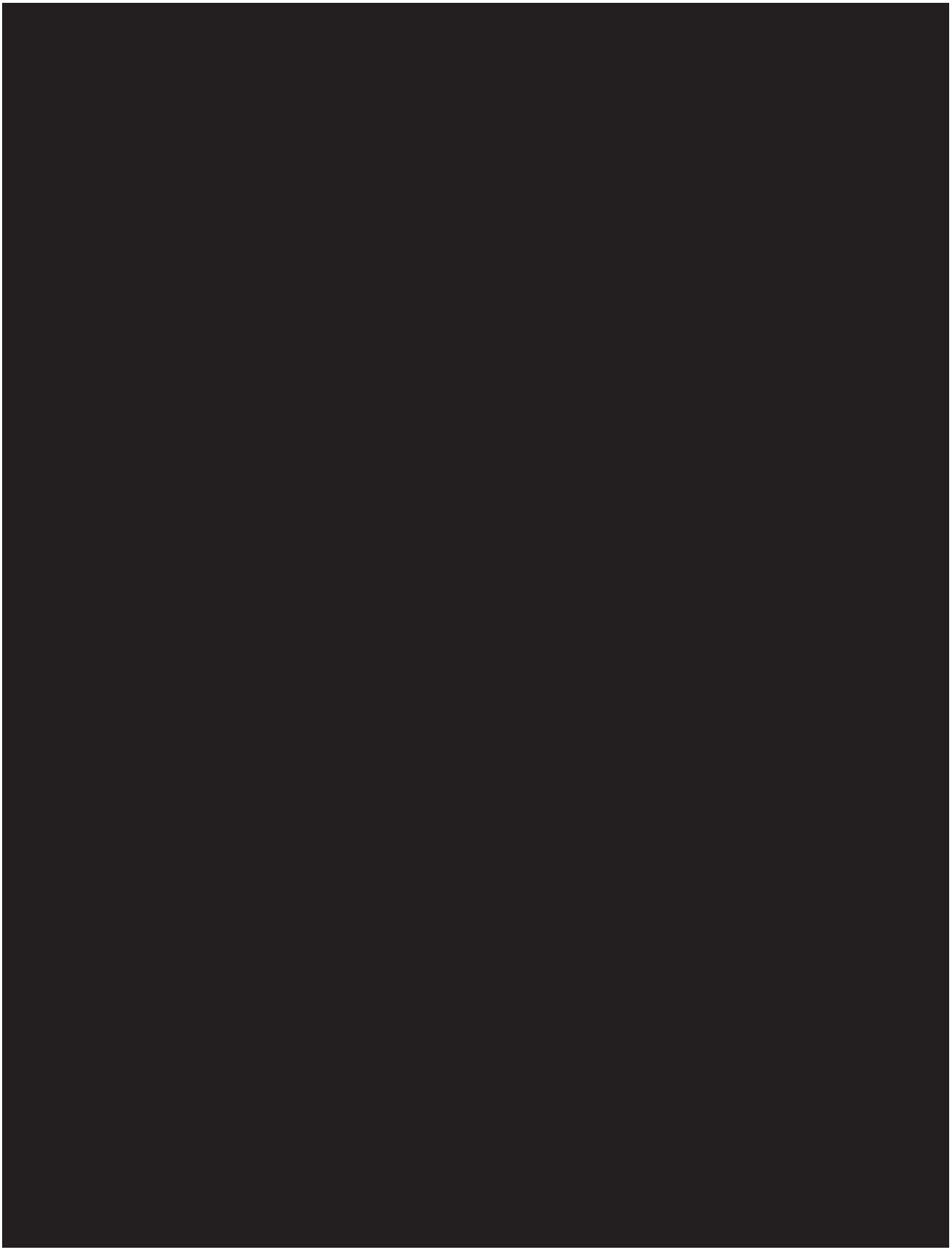
Pregnancy
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy 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 Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Studies 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.

[redacted]





[redacted]

5.6 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements in UC treatment trials and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way.

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Charts. Each visit date (with its window) up to EOT is to be counted from Day 1. If any of these visits has to be rescheduled, the date of subsequent visit should be calculated from Day 1. EOT refers to the last dose administration of BI 655130 (SPESOLIMAB) at week 336. 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 relevant Flow Chart and the respective protocol sections. Refer to Section 5 and Section 10 (Appendices) for explanations of procedures. Additional details on procedures at selected visits are provided below.

Patient Reported outcomes (PROs) should be completed by the patient on his/her own in the pre-specified order in a quiet area/room before any other visit assessments or treatments and, as much as possible, before any interaction with the investigator or other members of the study team.

The order of completion for PROs is as follows, as applicable for each PRO at relevant visits according to the Flow Chart:
1. IBDQ
2. EQ-5D-5L

6.2.1 Screening and run-in period(s)

Screening Period

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 1):
The Screening visit (Visit 1) should occur 7 days before Visit M1 and be complete no less than 3 days prior to Visit M1.

At this visit, information will be collected for evaluation of trial eligibility as indicated in the Flow chart 1 or Flow chart 2.

Visit 1 should be performed in one visit, in combination with EOT visit of the previous induction trials 1368-0005 Part 1; 1368-0004. Procedures performed at EOT visit of previous trial should not be repeated at V1 of 1368-0017.

For more details regarding procedures at V1 please refer to Flow chart 1 or Flow chart 2.

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 M1 (Day 1).

Demography
Informed consent date, gender, age, race and ethnic origin will be collected in the eCRF page. Also, the patient's smoking history will be assessed. Information concerning race/ethnicity will be collected, as it has been suggested that there may 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 diseases, other than UC, should be registered in Baseline conditions as follow up from the previous induction studies.

Blood sampling
Blood samples will be drawn for safety lab, PK, ADA and biomarkers. TSH and Glycosylated Hbc (HbA1c) does not need to be assessed at screening visit. These need to be assessed first at W36 of maintenance treatment period and then every 48 weeks.
For women of childbearing potential, a serum pregnancy test will be performed.

Stool sampling
A stool sample will be collected for faecal biomarkers (calprotectin, lactoferrin).

Patient diary
Patients will use an eDiary provided at screening visit for reporting of stool frequency and rectal bleeding (blood in stool). Patients have to be asked to enter these data into the eDiary 14 consecutive days prior to each visit which includes assessment of Mayo score, and as well when a patient perceives worsening of UC symptoms at any time between visits as a precursor to disease flare assessment (see section 3.1).
The diary will be returned at EOS visit.

Visit 1.a
Visit 1a should take place approx. 3-7 days after Visit 1 when sigmoidoscopy assessment will be provided by central reader to finalize eligibility assessment. This visit can be done per telephone. Patients should be asked for any changes in concomitant therapy or potential AEs from V1.

6.2.2 Treatment period

The treatment period is lasting from Visit M1/R1 until End of Treatment (EOT) Visit.

Study related procedures during treatment period will be performed as specified in the Flow chart 1, Flow chart 2 or Flow chart 3, in case patients develop a disease flare.

Patients can be discontinued from trial medication at any time if in the opinion of the Investigator, continuation with trial medication is not in the patient's best interest.

Pregnancy testing
Urine pregnancy testing for all women of child-bearing potential will be conducted on-site at visits with study drug administration (4 weeks during i.v. re-induction phase) and must be negative to continue treatment. More frequent testing should be done if required by the local regulation and / or authority or per investigator judgment.
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. It is not requested that patient is fasted prior to collection of the safety laboratory testing as indicated in Flowcharts, but patient has to be asked and information will be collected on lab requisition form if patient was fasting or not 8h prior to blood sampling

Sigmoidoscopies
Sigmoidoscopies will be done after blood sampling and **prior to** study drug administration. Sigmoidoscopies will be performed every 48 weeks during maintenance treatment period and at end of re-induction period as indicated in the Flowcharts. Additionally sigmoidoscopies have to be done in case of disease flare as indicated in Flowchart 3. 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.
Colonoscopy instead of sigmoidoscopy can be performed if required as colon cancer screening per local guidelines.

PK and ADA sampling
Blood sampling for PK assessments should be done within one hour **prior to** study drug administration**.**

Clinical monitoring after study drug administration:
The patient will be monitored for infusion reactions at the site for approximately 1 hour following study drug administration. Local tolerability at the administration site of the subcutaneous injection will be assessed by the investigator at the specified visits as noted in the Flow Chart.
At all dosing visits vital signs will be assessed pre- and post-dose, please see section 5.2.2 for further details.

Unscheduled visits
The patient may be asked 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 Charts. These data will be obtained at scheduled or unscheduled trial visits based on information 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 safety FU period, the EOS visit is scheduled at 16 weeks after the last dose of study drug. For more details please follow Flow Charts.

6.2.3.1 Early treatment discontinuation

Patient who discontinue treatment prior to the planned EOT visit have to be invited for an early EOT visit as soon as possible. .These patients should be registered as withdrawn from treatment in IRT and return to the site for the End of Study (EOS) visit 16 weeks after last study drug intake.

6.2.3.2 Trial completion

Patients who finish the treatment period will return to the site for the End of Study (EOS) visit 16 weeks after the EOT visit. Completion is defined as a patient having reached the EOS visit.

6.2.3.3 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).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial is designed as a single arm, open-label trial in patients with ulcerative colitis who have completed the planned treatment period in previous trials 1368-0004 or 1368-0005/Part 1. The following treatments are planned:

- For patients who do not have a clinical response at week 12 of parent trial:
  - Multiple active doses of intravenous BI 655130 (SPESOLIMAB) 1200 mg q4w to be administered for 12 weeks (re-induction); responders at week 12 will subsequently receive subcutaneous BI 655130 (SPESOLIMAB) 300 mg q4w as maintenance treatment for up to 7 years;

- For patients who do have a clinical response at week 12 of parent trial:
  - Subcutaneous BI 655130 (SPESOLIMAB) 300 mg q4w as maintenance treatment for up to 7 years.

Patients who experience a disease flare (as defined in section 2.1) will be administered disease flare rescue medication as a single dose of BI 655130 (SPESOLIMAB) 1200 mg followed by an intensified maintenance dosing schedule with 600 mg q6w.

For both efficacy and safety data, the following reporting periods will be defined:

- Maintenance Period
  Includes data from the maintenance part of this extension trial.

- Re-Induction Period
  Includes data from the re-induction part of this extension trial, where applicable.

[redacted]

There is no confirmatory statistical testing planned during the analysis of this extension trial; only descriptive analyses are intended.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Given the single arm and open-label nature of this trial, all statistical assessments will be performed in a descriptive manner only. No hypothesis testing is intended to be performed.

7.3 PLANNED ANALYSES

There will be 2 main patient populations in this trial for analyses: the treated set for maintenance treatment (TS-MT) and the treated set for re-induction treatment (TS-RT).

Treated Set for Maintenance Treatment (TS-MT)
This patient set includes all patients who received at least one dose of maintenance treatment in the extension trial. It will be the main analysis set for presentation of safety and efficacy during the maintenance part of the extension trial.

Treated Set for Re-induction Treatment (TS-RT)
This patient set includes all patients who received at least one dose of re-induction treatment in the extension trial. It will be the main analysis set for presentation of safety and efficacy during the re-induction part of the extension trial.

Further analysis sets will be defined in the TSAP if necessary.

Important violations of the protocol will include violations of the key inclusion and exclusion criteria, concomitant use of restricted medications, and any other violations of the protocol deemed important by the study team. All decisions concerning important protocol violations will be made prior to final database lock for this extension trial.

Standard statistical parameters (number of non-missing values, mean, standard deviation (SD), median, quartiles, minimum and maximum) or frequency tables (including patient frequencies and percentages) will be calculated where appropriate.

A Clinical Trial Report will be prepared once the final database lock for this extension trial has been performed.

7.3.1 Primary endpoint analyses

Refer to section 7.3.4 for the description of safety analyses including that for the primary endpoint. The primary endpoint will be summarized for the maintenance period (described in section 7.1).

7.3.2 Secondary endpoint analyses

The evaluation of clinical outcomes based on the Mayo Clinical Score, i.e. clinical remission, is based upon the endoscopy results obtained from central reading. Only if the centrally read endoscopy result is missing at a time-point will the locally read result be used instead.

For the stool frequency and rectal bleeding items reported in the patient diary, an average of the last 3 non-missing daily assessments collected within the last 7 days prior to the applicable visit will be used for the determination of clinical outcome. If the patient

undergoes bowel preparation for endoscopy on any of the days before a visit, the stool frequency and rectal bleeding subscores on that day(s) should be considered to be missing. In addition, the stool frequency and rectal bleeding subscore will be considered to be missing both on the day of and the day after the endoscopy.

Secondary endpoint will be assessed descriptively. Further details will be provided in the TSAP.

[redacted]

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 16 after the last dose of trial medication, will be assigned to the on-treatment period for evaluation. Adverse events occurring in the maintenance and re-induction periods will be separately described.
All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the residual effect period. For patients who switch directly to maintenance treatment at week 12 of the re-induction period, adverse events occurring on and after the first day of maintenance treatment will be included in summaries of the maintenance period only. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’. For all subjects who received disease flare treatment with BI 655130 (SPESOLIMAB), safety assessments including adverse events, laboratories, vital signs etc. which occurred subsequent to such intake will be excluded from presentations according to the planned treatment; these data will, however, be included in summaries where all data after any use of BI 655130 (SPESOLIMAB) are displayed.

[redacted]

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at the database lock.

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 summarised. Laboratory data will be analysed descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values

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

7.4 INTERIM ANALYSES

In order to ensure the patient's safety during the trial, an external DMC, independent of the trial and project teams, will be set-up to review all available un-blinded safety data as well as selected efficacy data at regular intervals following first-patient-in. A separate DMC SAP

will be produced which describes the analyses required for assessment by the DMC. Further details will be provided in a DMC charter.

As the primary aim of this study is to collect long-term safety and efficacy data on the use of BI 655130 (SPESOLIMAB) in this population, multiple interim analyses will be done over the 7-year conduct phase of this trial to support, for example, regulatory interactions, CTA and MAA/BLA submissions, but also to provide important safety and efficacy information to the sponsor to guide further development of the compound, and to the investigators via IB updates and publications.

[redacted]

A CTR describing all data collected within this trial will be produced once the last patient in the trial has completed the final follow-up visit.

7.5 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at all visits. However, missing data will still occur and approaches to handle this are proposed below.

For the safety data, including the primary endpoint, no missing data imputations are planned.

For efficacy data, if one or more subscores on the clinical remission (or clinical response), calculated using the Mayo Clinic score, are missing at a visit then the overall outcome at that visit is also considered to be missing.

With regards to the handling of missing data on those efficacy outcomes derived from the MCS, no missing data imputations are planned to be performed.

If a patient experiences disease worsening during the re-induction period, or a disease flare during the maintenance period prior to observing the efficacy outcome at a specific visit, then all data subsequent to the intake of such rescue medication will be set to missing. Additional summaries including all data observed even following rescue medication intake will also be done. Further details with regard to what constitutes a rescue intake with potential impact on the efficacy data will be described in the TSAP.

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

7.6 RANDOMISATION

Given the single arm nature of this trial, no randomization will be performed.

7.7 DETERMINATION OF SAMPLE SIZE

Given the descriptive nature of this trial, no sample size calculation has been performed.

Approximately 160 patients who meet the entry criteria are planned for inclusion into this trial, rolling over from the preceding trials of 1368-0005 part 1and 1368-0004.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

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 the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains 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 patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a 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 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

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

place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

CRFs 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 patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

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

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see section 8.3.2). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.
If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history (if applicable)
- Adverse events and outcome events (onset date (mandatory), and end date (if available)
- Serious adverse events (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 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 site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and 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 contract or the local requirements valid at the time of the end of the trial (whatever is longer).
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 and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with 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, by the IRB / IEC and the regulatory authorities.

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

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

- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
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 per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days 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).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.
A project-independent, fully-external data-monitoring committee (DMC), will be established to assess the progress of the clinical trial, including an unblinded safety and efficacy assessment at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop either a single BI 655130 (SPESOLIMAB) dose or the trial due to safety or ethical concerns. 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 (e.g. their curricula vitae) will be filed in the (Investigator Site File) ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Trial Clinical Monitor, 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 (CML), 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, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract 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, a central images service, e-Diary and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R09-1299 Greenland S, Robins JM
Estimation of a common effect parameter from sparse follow-up data.
Biometrics 41, 55-68 (1985)

R10-0936 Walters SJ, Brazier JE
Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D.
Qual Life Res 14, 1523 - 1532 (2005)

R11-4890 Sampson HA, et al
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.
2nd Symp of the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis (FAA) Network on the Definition and Management of Anaphylaxis, Jul 2005
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 91 (4), 635 - 646 (2012)

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 34 (6), 1401 - 1414 (2007)

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 142 (1), 46 – 54 (2012)

R15-1340 Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Assche G van, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A, GEMINI 1 Study Group
Vedolizumabasinduction and maintenance therapy for ulcerative colitis.
N Engl J Med 369 (8), 699 - 710 (2013)

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). http://ec.europa.eu/health/documents/communityregister/ 2015/20150728132555/anx_ 132555_en.pdf (access date: 31 August 2015) (2015)

R15-5737 Entyvio (vedolizumab) for injection, for intravenous use (Takeda Pharmaceuticals America) (U.S. prescribing information, revised: 05/2014).

R15-5868 Koenig HH, Ulshoefer A, Gregor M, Tirpitz C von, Reinshagen M, Adler G, Leidl R
Validation of the EuroQol questionnaire in patients with inflammatory bowel disease.
Eur J Gastroenterol Hepatol 14 (11), 1205 - 1215 (2002)

R15-5871 Stark RG, Reitmeir P, Leidl R, Koenig HH
Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany.
Inflamm Bowel Dis 16 (1), 42 - 51 (2010)

R16-0030 Pickard AS, Neary MP, Cella D
Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer.
Health Qual Life Outcomes 5, 70 (2007)

R16-0031 Alrubaiy L, Rikaby I, Dodds P, Hutchings HA, Williams JG
Systematic review of health-related quality of life measures for inflammatory bowel disease.
J Crohns Colitis 9 (3), 284 - 292 (2015)

R16-0240 Irvine EJ Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients with inflammatory bowel disease.
J Pediatr Gastroenterol Nutr 28 (4), S23 - S27 (1999)

R16-0572 Dave M, Loftus EV
Mucosal healing in inflammatory bowel disease – a true paradigm of success?
Gastroenterol Hepatol (New York) 8 (1), 29 – 38 (2012)

R16-2287 Frewer P, Mitchell P, Walkins C, Matcham J
Decision-making in early clinical drud development
Pharm Stat 15, 255-263 (2016)

R16-4413 Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, et al, 20000223 Study Group
Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate.
Arthritis Rheum 50 (5), 1412 – 1419 (2004)

R16-4414 Reeve R. Confidence interval of difference of proportions in logistic regression in presence of covariates. Statistical Methods in Medical Research. (2016) DOI : 10.1177/0962280216631583

R16-4481 Kineret (anakinra) (Amgen) (U.S.prescribing information).
http://www.accessdata.fda.gov/drugsatfda_docs/label
/2003/anakamg062703LB.pdf (access date: 8 September 2016) (2003)

R16-4482 Jharap B, Sandborn WJ, Reinisch W, D'Haens G, Robinson AM, Wang W, et al
Randomised clinical study: discrepancies between patient-reported outcomes and endoscopic appearance in moderate to severe ulcerative colitis. Aliment Pharmacol Ther 42, 1082 – 1092 (2015)

R16-4637 Han SW, McColl E, Barton JR, James P, Steen IN, Welfare MR
Predictors of quality of life in ulcerative colitis: the importance of symptoms and illness representations. Inflamm Bowel Dis 11 (1), 24 – 34 (2005)

R16-5360 Ge M, Durham LK, Meyer RD, Xie W, Thomas N
Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences.
Drug Inf J 45, 481 - 493 (2011)

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

R17-0038 Guidance for industry: ulcerative colitis: clinical trial endpoints (draft guidance) (this guidance document is being distributed for comment purposes only) (August 2016, clinical/medical).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guida nces/UCM515143.pdf (access date: 5 January 2016); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (2016)

R17-0243 Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, et al
Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management.
J Crohns Colitis 6, 991 - 1030 (2012)

R17-2216 Yarlas A, Yen L, Hodgkins P
The relationship among multiple patient-reported outcomes measures for patients with ulcerative colitis receiving treatment with MMX formulated delayed-release mesalamine.
Qual Life Res 24, 671 - 683 (2015)

R17-2217 Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, Danese S, Feagan BG, Reinisch W, Niezychowski W, Friedman G, Lawendy N, Yu D, Woodworth D, Mukherjee A, Zhang H, Healey P, Panés J; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators.
Tofacitinib as Induction and Maintenance
Therapy for Ulcerative Colitis. N Engl J Med. 2017

R17-2218 Gibson PR, Vaizey C, Black CM, Nicholls R, Weston AR, Bampton P, et al
Relationship between disease severity and quality of life and assessment of health care utilization and cost for ulcerative colitis in Australia: a cross-sectional, observational study.
J Crohns Colitis 8, 598 - 606 (2014)

R17-2219 Assche G van, Peyrin-Biroulet L, Sturm A, Gisbert JP, Gaya DR, Bokemeyer B, et al
Burden of disease and patient-reported outcomes in patients with moderate to severe ulcerative colitis in the last 12 months - multicenter European cohort study.
Dig Liver Dis 48, 592 - 600 (2016)

R17-2221 Feagan BG, Patel H, Colombel JF, Rubin DT, James A, Mody R, et al
Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial.
Aliment Pharmacol Ther 45, 264 - 275 (2017)

R17-2222 Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, et al
The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients.

R17-2223 Colombel JF, Sandborn WJ, Ghosh S, Wolf DC, Panaccione R, Feagan B, et al
Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: data from ULTRA 1, 2, and 3.
Am J Gastroenterol 109, 1771 - 1780 (2014)

R17-2467 Jairath V, Zou G, Parker CE, Macdonald JK, Mosli MH, Khanna R, et al
Systematic review and meta-analysis: placebo rates in induction and maintenance trials of ulcerative colitis.
J Crohns Colitis 10 (5), 607 - 618 (2016)

R17-2617 Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al
Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance.
Ann Rheum Dis 74, 2107 - 2116 (2015)

R17-3426 Remicade (infliximab) lyophilized concentrate for injection, for intraveno use (Janssen Biotech) (U.S. prescribing information, revised: November 2013).

R17-3632 Mahil SK, Catapano M, Meglio P di, Dand N, Ahlfors H, Carr IM, et al
An analysis of IL-36 signature genes and individuals with IL1RL2 knockout mutations validates IL-36 as a psoriasis therapeutic target.
Sci Transl Med 9, eaan2514 (2017)

R96-2382 EuroQol - a new facility for the measurement of health-related quality of life.
Health Policy 16, 199 - 208 (1990)

R97-3472 Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JWD,
Quality of life: A valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease.
Gastroenterology 106, 287 - 296 (1994)

R97-3596 Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C
A new measure of health status for clinical trials in inflammatory bowel disease.
Gastroenterology 96, 804 - 810 (1989)

P14-15417 Assche G van, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, Beaugerie L, Gomollon F, Haeuser W, Herrlinger
K, Oldenburg B, Panes J, Portela F, Rogler G, Stein J, Tilg H, Travis S, Lindsay JO
Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations.
J Crohns Colitis 7 (1), 1 - 33 (2013)

P17-11924 Feagan BG, Sandborn WJ, Panes J, Ferrante M, Louis E, D'Haens G, et al
Efficacy and safety of re-induction treatment with the selective IL-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease.
24th United Eur Gastroenterology Week (UEGW), Vienna, 15 - 19 Oct 2016
United Eur Gastroenterol J 4 (6), 806 - 807, Abstr LB17 (2016)

9.2 UNPUBLISHED REFERENCES

c03320877 Investigator’s Brochure, BI 655130 for IL36R antibody in Ulcerative Colitis, Palmoplantar Pustulosis and Pustular Psoriasis; version 06, dated 04 April 2019

c03361085 [redacted] Clinical Trial Protocol: Single-blind, partially randomised, placebo-controlled Phase I study to investigate safety, tolerability,
pharmacokinetics and pharmacodynamics of single rising intravenous doses of BI 655130 in healthy male volunteers. 1368.1. Version 6. 27 Jan 2016.

10. APPENDICES

10.1 MAYO SCORING SYSTEM FOR THE ASSESSMENT OF ULCERATIVE COLITIS ACTIVITY

The Mayo score (Schroeder et al., N Engl J Med, 1987) 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 based on the last 3 non-missing scores from the 7 days prior to each applicable visit, as collected from the patient diary. If the patient undergoes bowel preparation for colonoscopy on any of the days before a visit, the stool frequency and rectal bleeding subscore for that day(s) should be considered missing. In addition, the stool frequency and rectal bleeding subscore will be considered to be missing both on the day of and the day after the endoscopy.

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

Table 10.1: 1 Mayo score (adopted from Schroeder et al, 1987)

Components	Subscore	Severity	Score
CLINICAL RESPONSE (Patient's Symptoms)	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[d]	Normal	0
		Mild disease	1
		Moderate disease	2
		Severe disease	3
MODIFIED ENDOSCOPIC RESPONSE (Objective Evidence of Inflammation)	Endoscopic Appearance[c]	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 Modified endoscopic appearance: 0 (normal), Mild (erythema, decreased vascular pattern, granularity), Moderate (marked erythema, loss of vascular pattern, any friability, erosions), Severe (spontaneous bleeding, ulceration).
d 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.

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 1987; 317 (26):1625-1629

10.2 HISTOLOGIC ACTIVITY SCORE

The Robarts histopathology index is a histologic activity score (Mosli et al, Gut2015). The total score ranges from 0 (no disease activity) to 33 (severe disease activity).

Table 10.2: 1 Robarts Histopathology Index (RHI) by components

Component	
Intercept	
Chronic inflammatory infiltrate	0=No Increase
	1=Mild but unequivocal increase
	2=Moderate increase
	3=Marked increase
Lamina propria neutrophils	0=None
	1=Mild but unequivocal increase
	2=Moderate increase
	3=Marked increase
Neutrophils in epithelium	0=None
	1=<5% crypts involved
	2=<50% crypts involved
	3=>50% crypts involved
Erosion or ulceration	0=No erosion, ulceration, or granulation tissue
	1=Recovering epithelium + adjacent inflammation
	1=Probably erosion-focally stripped
	2=Unequivocal erosion
	3=Ulcer or granulation tissue

Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. Gut 2015.

Based on this, the RHI will be calculated as follows:
RHI = 1 x chronic inflammatory infiltrate level (4 levels) + 2 x lamina propria neutrophils (4 levels) + 3 x neutrophils in epithelium (4 levels) + 5 x erosion or ulceration (4 levels after combining Geboes 5.1 and 5.2)

10.3 EQUIVALENT DOSES OF CORTICOSTEROIDS

Drug	Equivalent dose (mg)	Conversion factor
Prednisone	5	X 1
Prednisolone	5	X 1
Triamcinolone	4	X 1.25
6-Methylprednisolone	4	X 1.25
Dexamethasone	1	X 5
Betamethasone	0,75	X 6.7
16-Methylprednisolone	6	X 0.8
Fluocortalon	5	X 1
Cloprednol	3,75-5	X 1.0-1.5
Deflazacort	6	X 0.8
Cortisol (hydrocortisone)	20	X 0.25
Cortisone	25	X 0.20

10.4 PATIENT REPORTED OUTCOMES

10.4.1 Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ [R97-3472] is a 32-item self-report questionnaire for patients with IBD to evaluate the patient reported outcomes across 4 dimensions: bowel symptoms (loose stools, abdominal pain), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). Scores range from 32 to 224 with higher scores indicating better outcomes.

10.4.2 EQ-5D-5L

The EQ-5D(-5L) is a standardized instrument developed by the EuroQoL Group for use as a generic, preference-based measure of health outcome. The EQ-5D(-5L) questionnaire captures two basic types of information, an overall health rating using a visual analog scale and a descriptive “profile,” or “health state”. The health state is converted to a single weighted index score by applying coefficients from a validated value set. The index score is used in both clinical and economic evaluations of health care. These two basic types of information cannot be combined and will be reported separately.

The health state index measures five health dimensions. The health states for each respondent are converted into a single index number using a specified set of country-specific weights. A

higher score indicates a more preferred health status with 1.0 representing perfect health and 0 representing death. A missing answer on any one question leads to a missing overall score.

For purposes of the analyses for this study, all patients' EQ-5D(-5L) index scores will be calculated using the UK weights.

The VAS asks respondents to rate their present health status on a 0 - 100 visual analog scale, with 0 labelled as "Worst imaginable health state" and 100 labelled as "Best imaginable health state." The VAS score is determined by observing the point at which the subject's hand drawn line intersects the scale.

10.5 DIAGNOSIS OF ANAPHYLAXIS

Clinical Criteria for diagnosing anaphylaxis [R11-4890]

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg +[2 x age] from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.6 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA ([redacted])

Table 10.6:1 Severity of AE as described in the Rheumatology common Toxicity Criteria ([redacted])

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
	Asymptomatic, or transient Short duration (< 1 week) No change in life style No medication or OTC	Symptomatic Duration (1–2 weeks) Alter lifestyle occasionally Meds relieve. (may be prescription), Study drug continued	Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized<24h Temporary study drug discontinuation, or/and dose reduced	At risk of death Substantial disability, especially if permanent. Multiple meds Hospitalised >24h Study drug discontinued
A.ALLERGIC/IMMUNOLOGIC				
A1. Allergic reaction/ hypersensitivity (including drug fever)	Transient rash; drug fever < 38° C, transient asymptomatic bronchospasm	Generalized urticaria responsive to meds; or drug fever > 38° C, or reversible bronchospasm	Symptomatic bronchospasm, requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/ angioedema	Anaphylaxis, laryngeal/ pharyngeal edema, requiring resuscitation
A2. Autoimmune reaction	Serologic or other evidence of autoimmune reaction but patient asymptomatic: all organ function normal and no treatment is required (e.g., vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g., transient colitis or anemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy

Table 10.6: 1 Severity of AE as described in the Rheumatology common Toxicity Criteria ([redacted]) (Cont.)

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
A3. Rhinitis (includes sneezing, nasal stuffiness, post nasal discharge)	Transient, non-prescription meds relieve	Prescription med required, slow	Corticosteroids or other prescription med. with persistent disabling symptoms such as impaired exercise tolerance	NA

10.7 STEROID TAPERING SCHEME

Recommended tapering schedule for systemic corticosteroids:

- Dose > 15 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until receiving 10 mg/day, then continue tapering at 2.5 mg/week until 0 mg/day.
- Dose 11 to 15 mg/day prednisone or equivalent: taper daily dose to 10 mg/day for 1 week, then continue at 2.5 mg/week until 0 mg/day.
- Dose ⩽ 10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.

Recommended tapering schedule for oral corticosteroids (other than budesonide):

.

- Dose > 15 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until receiving 10 mg/day, then continue tapering at 2.5 mg/week until 0 mg/day.
- Dose 11 to 15 mg/day prednisone or equivalent: taper daily dose to 10 mg/day for 1 week, then continue at 2.5 mg/week until 0 mg/day.
- Dose ⩽ 10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.
- For oral budesonideAdminister initial daily dose every other day for 2 weeks before stopping the drug

  For oral beclomethasone dipropionate
- Stop using after achieving clinical response or clinical remission

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		11 Jun 2018
EudraCT number **EU number**		2018-000334-35
BI Trial number		1368-0017
BI Investigational Product(s)		BI 655130
Title of protocol		An open label, long term safety trial of BI 655130 treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 trials
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**		x
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		All sections in the Protocol
Description of change		Trial numbers 1368.4; 1368.5 and 1368.17 changed to 1368-0004; 1368-0005 and 1368-0017
Rationale for change		Change in sponsor`s systems
Section to be changed		Flowchart 1
Description of change		Day for V1 changed from -7 to -1 to -7 to -2; Vital status collection removed from EOT visit, e-diary review added at EOS
Rationale for change		Typo
Section to be changed		Flowchart 2
Description of change		Day for V1 changed from -7 to -1 to -7 to -2; EOS: 48 day after EOT correct to 113 days
Rationale for change		Typo
Section to be changed		Flowchart 3
Description of change		Day for flare confirmation changed from 0 to -5 to -3 and i.v. re-induction day changed to 0
Rationale for change		Typo
Section to be changed		Footnotes to Flowcharts; No. 11
Description of change		An e-diary will be used by the patient for the reporting of bowel movement frequency and

		rectal bleeding (blood in stool) for a period of 14 days prior to visits. *Added:* and when a patient perceives a worsening of UC symptoms at any time between visits as a precursor to disease flare assessment
Rationale for change		Added for completness
Section to be changed		Footnotes to Flowcharst; No. 13
Description of change		For patients who discontinue treatment prematurely, vital status will be collected once a year starting from EOT visit until initially planned completion date of each individual patient. *Removed:* ..collected by calls by investigators *and* until EOS *added:* until initially planned completion date of each individual patient
Rationale for change		Clarification of vital status collection timelines
Section to be changed		Footnotes to Flowcharts; No.15
Description of change		EOS visit has to be performed 16 weeks after last dose of study medication (12 weeks *changed to*16 weeks after R4 *changed to* R3 visit). Sigmoidoscopy does not need to be done at EOT visit for these patients
Rationale for change		Mistakenly entered
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		Section 3.1
Description of change		Patients who terminate study drug in 1368-0017 prematurely will be invited to early EOT visit instead of next planned visit followed by safety follow up 16 weeks after last study drug intake.For these patients vital status will be collected once a year starting from EOT visit until EOS visit. *Added:*…until the initially planned completion date of each individual patient. …safety follow-up (EOS)… *Removed:* until EOS visit
Rationale for change		More precise description of vital status collection timelines
Section to be changed		Section 3.1. Steroid tapering
Description of change		*Added:* Patients receiving budesonide MMX at study entry will taper their initial daily dose for 2 weeks every other day before stopping the drug. Patients on stable dose of beclomethasone dipropionate will be requested to stop using it after they achieve clinical response or clinical remission.
Rationale for change		Information on steroid tapering / stopping rules for budesonide MMX and beclomethasone dipropionate missing

Section to be changed		Section 3.3.4.1 Withdrawal from trial treatment
Description of change		*Withdrawal criteria*: A patient does never achieve clinical remission within the first 48 weeks of maintenance treatment *was moved out and re-worded:* If a patient has not achieved clinical remission within the first 48 weeks of maintenance treatment, investigator should consider trial drug termination based on individual patient history and available alternative treatment options.
Rationale for change		Decision on withdrawal of patient was moved to investigator`s decision based on individual patient history and available alternative treatment options
Section to be changed		Section 4.1.4 Study Drug Assignment and Administration of Doses per patient
Description of change		Wording for s.c. study drug administration updated: In this trial a dose of 300 mg of BI 655130 will be administered during study visit as subcutaneous injection in the abdomen every 12 weeks for patients starting from V2 until EOT visit for patients who responded to treatment with study drug in previous trials or gained response after i.v. re-induction period. *Added:* subcutaneous injection in the abdomen *Removed:* in two separate injections 1 mL each in abdomen, thighs, gluteal region or upper arms. Injections being given in he same area should be at least 2 cm apart and should not be close to a vein...
Rationale for change		Dosing regimen updated based on results of phase I trial 1368-0003
Section to be changed		Section 4.1.4 Study Drug Assignment and Administration of Doses per patient
Description of change		*Added:* Patients have to be closely monitored for local or systemic hypersensitivity reactions for 1 hour following s.c. study drug administration. …They should further be advised that if they experience itching all over or a feeling of being swollen, dizzy or short of breath, they should seek emergency medical attention immediately

		Intravenous infusion including observational time for possible infusion reactions will last approximately 2.5 hours.
Rationale for change		Detailed instructions on handling of systemic hypersensitivity reactions and observational time were missing in previous version
Section to be changed		Section 4.1.4 Study Drug Assignment and Administration of Doses per patient
Description of change		Dose modifications or adjustments are not permitted. In exceptional cases of missed or delayed visits, if any of these visits has to be rescheduled, the date of subsequent visit should be calculated from Day 1. *Added:* of maintenance treatment or if the patient is on flare treatment from the first s.c. drug administration after the last disease flare
Rationale for change		Additional clarification needed
Section to be changed		4.1.8 Drug Accountability
Description of change		Availability of the proof of a medical license for the Principal Investigator *Added:* if applicable
Rationale for change		Additional explanation needed as it is not applicable in all countries
Section to be changed		Tab. 4.2.2:1
Description of change		Any immunomodulator allowed per inclusion criteria *Added:* .... in previous trial
Rationale for change		Added for clarification
Section to be changed		Tab.4.2.2:1

Description of change		*Added:* Oral systemic corticosteroids only allowed at a dose of ≤ 20mg per day of prednisone or equivalent and with stable dose prior to treatment initiation. *Allowed steroid treatments:* Short-term use (<7 days) of systemic (oral or parenteral) corticosteroids is allowed for treatment of AE not related to the underlying UC. Parenteral corticosteroids dosed for less than 24 hours as treatment of infusion or anaphylactic reactions are permitted. Beclomethasone dipropionate allowed with stable dose prior to treatment initiation. Locally administered steroids as e.g. intra-articular, nasal inhalation or intra-ocular administration are allowed. steroids will be tapered upon achievement of a clinical response or remission in the subsequent maintenance trial. *Removed:* ...in the subsequent maintenance trial
Rationale for change		Information for use of corticosteroids was clarified for clinical practice
Section to be changed		Section 5.2.1 Physical examination
Description of change		Targeted physical examination will include vital sign assessment and evaluation of organ systems associated with AE(s) symptoms… *added:* or extra intestinal manifestations ….
Rationale for change		Missing information for completeness
Section to be changed		Section 4.2.2 Vital signs, 1st paragraph
Description of change		*Added text in bold*: . At dosing visits vital signs evaluations will be performed **pre-dose for both visits with i.v. and s.c. administration of study drug**. **Vital signs will be measured additionally** 10 min post-dose **after s.c. administration and 5 and 60 min. post-dose in case of i.v. study drug administration.**
Rationale for change		Omitted in previous version
Section to be changed		5.2.5 Other safety parameters
Description of change		*Sentence re-phrased and added text:* Original:

		Local tolerability at the administration site of the subcutaneous injection will be assessed by the investigator according to "swelling", "induration", "heat", "redness", "pain", or "other findings" at the specified visits as noted in the Flow Chart. This assessment should be done post-dose. Changed to: Local tolerability at the administration site of the subcutaneous injection will be assessed by the investigator at the specified visits as noted in the Flow Chart see section 4.1.1 for further details. Any observed local tolerability reactions like "swelling", "induration", "heat", "redness", "pain", or any other findings should be reported as an adverse event in the eCRF.
Rationale for change		More detailed information provided
Section to be changed		5.2.5 Other safety parameters
Description of change		Removed text: All cases of malignancies that are detected during the trial will be reported as SAEs. Patients with a history of malignancy (except for specific cancers) will be excluded from this trial per the exclusion criteria (Section 3.3.3).
Rationale for change		Redundant information
Section to be changed		5.2.6.2 AE Collection and Reporting
Description of change		*Sentence re-phrased from:* From then on until the individual patient's end of trial the investigator must report all deaths/fatal AEs regardless of relationship, related SAEs and related AESIs the investigator becomes aware of. *New wording:* From then on until the initially planned completion date of each individual patient the investigator must report all deaths/fatal AEs regardless of relationship, related SAEs and related AESIs the investigator becomes aware of.
Rationale for change		Align with wording for prematurely discontinued patients in Footnotes for Flowcharts
Section to be changed		Section 5.3.1 Assessment of Pharmacokinetics

Description of change		[redacted]
[redacted]		
Section to be changed		[redacted]
[redacted]		
Rationale for change		
[redacted]		
[redacted]		
[redacted]		Section 5.5 Biopsy Collection Instructions
Description of change		With proper consent, two sets of three biopsies (a total of 6 biopsies) will be obtained during each endoscopy procedure *Changed to:* During each endoscopy procedure two sets of three biopsies (a <u>total of 6 biopsies</u>) will be obtained in the following order: Three (3) for

		RNA analysis, and three (3) for Histology and Immunohistochemistry (IHC) analysis
Rationale for change		Consent for biopsies not needed separately, this is part of main ICF.
Section to be changed		Section 6.2 Details of trial procedures for selected visits
Description of change		Following paragraph removed:Measurement of vital signs should precede blood sampling and be assessed pre-dose at all i.v. dosing visits and at approx.5 and 60 minutes after end of infusion At visits with s.c. study drug administration, vital signs will be assessed at approximately 10 minutes after study drug administration.
Rationale for change		Redundant information, already in Section 4.2.2.
Section to be changed		Section 6.2.1 Screening visit
Description of change		Visit 1 should **preferably** be performed in one visit combined with EOT visit of previous induction trials *Removed:* preferably
Rationale for change		Removed to avoid misunderstandings
Section to be changed		Section 6.2.1 Medical and Surgical History
Description of change		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 extent and severity, hospitalizations, and extraintestinal manifestations will be collected. Also, previous and concomitant treatment for UC will be recorded. *Changed to:* Information on clinically significant previous and concomitant diseases, other than UC, should be registered in Baseline conditions as follow up from the previous induction studies.

Rationale for change		Not all information is required as it is roll-over trial
Section to be changed		Section 6.2.2 Treatment period
Description of change		The treatment period is lasting from M1 until End of Treatment (EOT) Visit *Changed to:* The treatment period is lasting from Visit M1/R1…
Rationale for change		typo
Section to be changed		Section 6.2.2 Treatment period
Description of change		Removed paragraphs: If upon completion of screening patient eligibility was confirmed by achievement of clinical response, patients can directly be assigned to open label s.c. maintenance treatment (see Flow chart 1). However, if clinical response has either not yet been achieved or has been lost prior to screening, patients will receive open label i.v. re-induction treatment with three infusions of 1200 mg BI 655130 (SPESOLIMAB) every 4 weeks. At week 12 of re-induction period, patient`s response status will be assessed again. If clinical response or remission compared to BL in induction trial is achieved, patients will switch to s.c. maintenance treatment, (see Flow chart 2). Other patients will be discontinued from treatment, complete the trial, and receive standard of care treatment. During the s.c. maintenance treatment patients will be administered BI 655130 300 mg every 12 weeks until EOT visit. Medication will be assigned by IRT. All study medication will be stored and administered on site by authorized study staff only.
Rationale for change		Redundant information
Section to be changed		Section 6.2.2 Treatment period
Description of change		Study related procedures during treatment period will be performed as specified in the Flow chart 1 and Flow chart 2.

		Patients who develop a disease flare during *maintenance SC treatment* period will receive a single i.v. infusion of 1200mg BI 655130 as a flare treatment followed by intensified maintenance dosing with 300mg sc. BI 655130 q6w More details regarding disease flare confirmation please see in **Section 3.1 Disease Flare Treatment.** *Changed to:* Study related procedures during treatment period will be performed as specified in the Flow chart 1, Flow chart 2 or Flow chart 3, in case patients develop a disease flare
Rationale for change		Redundant information removed
Section to be changed		Section 6.2.2 Treatment period
Description of change		*Removed sentence:* For details of trial procedures please follow the Flowchart 3 (Patients with Disease Flare).
Rationale for change		Already included in previous sentence
Section to be changed		Section 6.2.2 Treatment period / Clinical Monitoring after Study drug Administration
Description of change		*Removed:* according to “swelling”, “induration”, “heat”, “redness”, “pain”, or “other findings”. This assessment should be done post-dose. *Added:* At all dosing visits vital signs will be assessed pre- and post-dose, please see section 5.2.2 for further details.
Rationale for change		Redundant information already provided in previous sections
Section to be changed		Section 6.2.2 Treatment period / Concomitant Medication Review
Description of change		These data will be obtained at scheduled or unscheduled trial visits based on information provided in the patient diaries. Removed: provided in patient diaries
Rationale for change		Amended for patient convenience
Section to be changed		Section 6.2.3.1 Early Treatment Discontinuation
Description of change		*Paragraph:* Patient who discontinue treatment prior to the planned EOT visit will complete the EOT procedures instead of the planned treatment period visit. These patients should be registered

		as withdrawn from treatment in IRT and return to the site for the End of Study (EOS) visit 16 weeks after the early EOT visit. Vital status for prematurely discontinued patients will be collected by trial staff on a yearly basis per telephone until study completion. **Changed to:** Patient who discontinue treatment prior to the planned EOT visit have to be invited for an early EOT visit as soon as possible. These patients should be registered as withdrawn from treatment in IRT and return to the site for the End of Study (EOS) visit 16 weeks after last study drug intake. Vital status for prematurely discontinued patients will be collected by trial staff on a yearly basis until the patient`s initially planned study completion date.
Rationale for change		Clarification regarding EOT and EOS timing for prematurely discontinued patients needed
Section to be changed		Section 7.1 Statistical Design-Model
Description of change		*Paragraph*: For efficacy endpoints in both the maintenance and re-induction periods, such as for clinical remission/response, baseline as the last non-missing value prior to first treatment in the preceding induction (parent) trial will be used. For safety endpoints, baseline for the maintenance period is considered to be the last non-missing value prior to first treatment in the maintenance part of the extension trial, while baseline for the re-induction period is considered to be the last non-missing value prior to first treatment in the re-induction part of the extension trial. Additional analyses on the safety data may also be performed via comparisons against the last non-missing value in the original induction (parent) trial. *Changed to:* For efficacy endpoints, baseline as the last non-missing value prior to first treatment in the preceding induction (parent) trial will be used. For safety endpoints, baseline for the maintenance and re-induction periods is considered to be the last non-missing value in the original induction (parent) trial. Additional

		analyses on the safety data for the maintenance period may also be performed via comparisons against the last non-missing value prior to first treatment in the maintenance part of the extension trial, while baseline for the re-induction period may also be done versus the last non-missing value prior to first treatment in the re-induction part of the extension trial.
Rationale for change		Align the efficacy and safety baseline definitions
Section to be changed		Section 7.3.4 Safety analyses
Description of change		*Added:* For all subjects who received disease flare treatment with BI 655130, safety assessments including adverse events, laboratories, vital signs etc. which occurred subsequent to such intake will be excluded from presentations according to the planned treatment; these data will, however, be included in summaries where all data after any use of BI 655130 are displayed.
Rationale for change		Align exposure for safety across projects where BI 655130 is given as rescue
Section to be changed		Section 7.3.4 Safety analyses
Description of change		Time at risk [subject years] = (date of onset of AE – study drug start date **in parent trial** + 1) / 365.25 *Removed:* in parent trial
Rationale for change		Align exposure for safety across projects where BI 655130 is given as rescue
Section to be changed		Section 7.3.4 Safety analyses
Description of change		If, for a subject, no treatment emergent adverse event occurred, then the time at risk will be censored at the minimum of (drug stop date + 112 days; last contact date; or, date of database snapshot if interim analysis performed). *Changed to:* ….(date of death; drug stop date + 112 days; start date of disease flare treatment with BI 655130;
Rationale for change		Align exposure for safety across projects where BI 655130 is given as rescue
Section to be changed		Section 7.5 Handling of Missing data

Description of change		If a patient experiences disease worsening during the re-induction period, or a disease flare during the maintenance period prior to observing the efficacy outcome at a specific visit, then all data subsequent to the intake of such rescue *Added:* ….to the intake of such rescue **medication**
Rationale for change		Mistakenly forgotten word
Section to be changed		Section 7.7 Determination of sample size
Description of change		Approximately 170 patients who meet the entry criteria…. *Updated:* Approximately 160 patients who meet the entry criteria…
Rationale for change		typo
Section to be changed		Section 8 Informed Consent, Trial Records, Data Protection, Publication Policy and Administrative Structure
Description of change		*Removed:* The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).
Rationale for change		Not applicable
Section to be changed		Section 8.5.1 Collection, storage and future use of biological samples and corresponding data
Description of change		Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular *Removed:*… for the collection , biobanking *and* *Removed:* Sample and data usage has to be in accordance with the separate biobanking informed consent Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF
Rationale for change		Not applicable as there will be no biobanking in the trial
Section to be changed		10.7 steriod tapering scheme
Description of change		Recommended tapering schedule for oral corticosteroids (other than budesonide):

		Changed to: Recommended tapering schedule for systemic corticosteroids:
Rationale for change		Typo
Section to be changed		Section 10.7 Steroid tapering scheme
Description of change		Recommended tapering schedule for oral budesonide MMX *Changed to:* Recommended tapering schedule for oral corticosteroids with limited systemic bioavailability *Added sentence:* Patients on stable dose of beclomethasone dipropionate will be requested to stop using it after they achieve clinical response or clinical remission.
Rationale for change		Added for clarification

11.2 GLOBAL AMENDMENT 2

Date of amendment		6 Nov 2018
EudraCT number **EU number**		2018-000334-35
BI Trial number		1368-0017
BI Investigational Product(s)		BI 655130
Title of protocol		An open label, long term safety trial of BI 655130 treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 trials
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		x
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Protocol Synopsis, Main Inclusion and Exclusion Criteria
Description of change		Men able to father a child removed
Rationale for change		Reflecting updated IB ver.5.0
Section to be changed		Flowchart 2
Description of change		Coding to visits R1, R2, R3 and R4 added I01, I02, I03 and I04 respectively
Rationale for change		To be in line with internal and external databases
Section to be changed		Flowchart 3
Description of change		Sigmoidoscopy note – updated from : first sigmoidoscopy 12 weeks from Flare confirmation (F0y) to - first sigmoidoscopy 12 weeks from i.v. re-induction (R0y), then every 48 weeks from R0y
Rationale for change		Mistakenly entered in previous version
Section to be changed		Flowchart 3
Description of change		Diary review requirement added at visit F0y
Rationale for change		Forgotten to be ticked in previous version
Section to be changed		Footnotes to Flowcharts; Footnote 3
Description of change		In case of disease flare, an unscheduled confirmatory sigmoidoscopy has to be performed, followed in12 weeks after disease flare

		confirmation replaced by …..after i.v. re-induction
Rationale for change		Mistakenly entered in previous version
Section to be changed		Section 2.1, tab. 2.1.1
Description of change		Added text: all criteria have to be met to qualify for the respective outcome
Rationale for change		Added clarity to definition of outcomes
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 3.3.2, p.34
Description of change		Inclusion criteria#3 removed – men able to father a child
Rationale for change		Reflecting changes in IB version 5.0
Section to be changed		Section 4.2.1, p. 42 Management of AE
Description of change		Section cytokine Release Syndrome removed
Rationale for change		Reflecting changes in IB version 5.0
Section to be changed		Section 4.2.1, p. 41 Other Treatments and Emergency Procedures
Description of change		Added: If mild-to-moderate infusion or anaphylactic reaction had already occurred in the very same patient in the past, pre-treatment with steroids before next IMP administration is permitted as secondary prophylaxis.
Rationale for change		More clarity for use of steroids as secondary prophylaxis
Section to be changed		Section 4.2.2.3 Restrictions regarding women of childbearing potential
Description of change		Removed restrictions regarding men and female partner(s) of male participants removed
Rationale for change		Reflecting updated IB ver.5.0
Section to be changed		Section 4.2.2.4 Restrictions regarding male participants
Description of change		Restriction regarding sperm donation for male participants for the whole duration of the trials was removed
Rationale for change		Reflecting updated IB ver.5.0

Section to be changed		Section 5.2.6.1 Definition of Adverse events
Description of change		Cytokine release syndrome removed from AESI
Rationale for change		Reflecting updated IB ver.5.0

11.3 GLOBAL AMENDMENT 3

Date of amendment		14 Nov 2018
EudraCT number **EU number**		2018-000334-35
BI Trial number		1368-0017
BI Investigational Product(s)		BI 655130
Title of protocol		An open label, long term safety trial of BI 655130 treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 trials
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		x
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Flowchart 3
Description of change		Physical examination added at visit R0y
Rationale for change		Forgotten to be ticked

11.4 GLOBAL AMENDMENT 4

Date of amendment		04 December 2019
EudraCT number **EU number**		2018-000334-35
BI Trial number		1368-0017
BI Investigational Product(s)		BI655130 (SPESOLIMAB)
Title of protocol		An open label, long term safety trial of BI 655130 (SPESOLIMAB) treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 (SPESOLIMAB) trials
Global Amendment due to urgent safety reasons		☐
Global Amendment		**X**

Section to be changed		All sections
Description of change 1		BI 655130 *changed to:* BI 655130 (SPESOLIMAB)
Rationale for change		Brand name added

Section to be changed		Flowchart 1A, 1B, 2 and 3
Description of change 2		Requirement to add QuantiFERON-TB test
Rationale for change		Requirement for TB test every 48 weeks added

Section to be changed		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]

Section to be changed		Flowchart 1A, 1B, 2 and 3
Description of change 4		Requirement to contact IRT at EOS visit removed
Rationale for change		Typo in previous version

Section to be changed		Flowchart 1A, 1B, 2 and 3
Description of change 5		PGA assessment added in separate line; Footnote 11 – PGA collection requirement clarified
Rationale for change		To ensure protocol compliance
Section to be changed		Flowchart 3

Description of change 6		Day update for F0y and R0y
Rationale for change		To reflect the operational aspects

Section to be changed		1.4 BENEFIT-RISK ASSESSMENT
Description of change 7		Benefit-Risk assessment section was re-phrased
Rationale for change		To reflect latest IB wording and BI project standard wording
Section to be changed		Flowcharts, Footnote 1 amended
Description of change 8		Visit V1 of this long-term extension study should be performed during the last visit (V6/EOT) of the preceding trial 1368-0005 Part 1 or 1368-0004. Assessments performed at last visit (V6/EOT) in the previous trial do not have to be repeated at visit 1 in this trial. *Changed to:* 1. Visit V1 of this long-term extension study should be performed during the last visit (V6/EOT) of the preceding trial 1368-0005 Part 1 or 1368-0004. Assessments performed at last visit (V6/EOT) in the previous trial do not have to be repeated at visit 1 in this trial. Patients not eligible to take part in trial 1368-0017 shall complete follow-up visit 16 weeks after last dose given in trial 1368-0004 or 1368-0005 Part I.
Rationale for change		Clarification of footnote
Section to be changed		Exclusion criteria 3.3.3 amended
Description of change 9		Have developed any of the exclusion criteria from the original induction study *Changed to:* Have developed any of the exclusion criteria from the original induction study with the following exceptions: • Cases of disease limited to the rectum extending <15 cm past the anal verge are allowed to be included in study 1368.17. • Cases of latent TB. Patients with newly emerging **latent** TB during preceding study are allowed to be included in study 1368.17, provided they receive

		appropriate treatment according to local guidelines.
Rationale for change		This criterion might be met by clinical patients with reduced colonic extension of their initial mucosal inflammation who respond to the inductions treatment and who could benefit from the maintenance treatment in study 1368.17. In line with the recommendations for patients already recruited in study 1368.17 who develop latent TB during participation in the study 1368.17, patients with latent TB could benefit from the maintenance treatment in study 1368.17.

Section to be changed		Section 2.1, table 2.1:1 Definitions of Study Outcomes + all sections referring to disease flare definition
Description of change 10		Disease flare definition Increase in partial MCS score by ≥2 points from nadir observed during a regular or unscheduled study visit, confirmed subsequently by sigmoidoscopy with the modified Endoscopic Subscore (mESS) ≥2 AND a second partial Mayo score measurement confirming the increase from nadir by ≥2, in absence of enteric pathogens in stool - after achievement of a clinical response *Changed to:* Increase in partial MCS score by ≥ 2 points from baseline (in 2 subsequent visits) and increase in rectal bleeding score by ≥ 1 point from baseline (in 2 subsequent visits), confirmed by increase of modified endoscopic subscore by ≥ 1 point from baseline with absolute modified endoscopic subscore ≥ 2 points in absence of enteric pathogens in stool
Rationale for change		alignment with expert experiences with other UC programs
Section to be changed		Flowcharts 1A, 1B, 1C and corresponding footnotes, 3; trial design 3:1:1, 3:1:2; sections 4.1; 7.1
Description of change 11		Change in the dose interval (increased from q12w to q4w) for the maintenance treatment and

		in the dose for intensified maintenance treatment after disease flare treatment.
Rationale for change		Amongst the first 24 patients who responded to the induction treatment in the previous trials and rolled over to trial 1368.17, more than 50% have experienced a relapse/flare during the first 6 months after switch from the induction to the maintenance dose. This rate is higher compared to the one observed with approved drugs for the same condition. The switch from the higher spesolimab induction doses (450 mg q4w i.v. for 12 weeks and 1200 mg q4w i.v. for 12 weeks) in the previous trials to the current maintenance dose in trial 1368,17 (300 mg q12w s.c.) represent a reduction in exposure by a factor of 6.4 and 17.1 respectively (given a 70% bioavailability of the s.c. vs the i.v. dose) during a 12 week period. The observed drop in efficacy may thus be explained by a decrease of drug exposure below the threshold required to maintain maximum target engagement. The individual 300mg SC dose corresponds to ~210mg IV dose, which for an average 70kg person represents the lowest dose of ≥3mg/kg achieving maximal target engagement, though target engagement in HV was quite sustainable for more than 10 weeks (see IB section 6). However, in UC patients a higher clearance rates of biologics and the need for target engagement in the gut tissue may require higher dosing than HV. Therefore, after one half-life of about 4 weeks (or shorter), patients may have developed insufficient drug exposure to maintain full target engagement in the gut, while q4w dosing may maintain drug exposure in the therapeutic range. Since for study logistics reasons the SC injection interval in the intensified maintenance treatment cannot be reduced to q4w, a higher dose of 600mg will be applied to double the exposure compared to the original regimen. Even assuming a negative spesolimab efficacy on ulcerative colitis, the proposed dose change, is considered not harmful for the patients, since it is lower than the doses previously tested in healthy

		volunteers (up to 4 doses of spesolimab 20mg/kg every 7 days) and the doses administered to ulcerative colitis patients (up to 1200 mg i.v. q4w for 24 weeks for patients who do not respond to the initial induction treatment and receive a re-induction treatment). Therefore, this dose may increase the individual benefit without increasing risks to study participants.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change 12		In this trial a dose of 300 mg of BI 655130 (SPESOLIMAB) will be administered during study visit as subcutaneous injection in the abdomen *Changed to:* In this trial a dose of 300 mg of BI 655130 (SPESOLIMAB) will be administered during study visit as subcutaneous injection in the abdomen , in accordance with local standard procedure and as described in "BI 655130 Solution for Injection 150 mg/mL s.c. Instructions for Handling and Use"
Rationale for change		Inclusion of reference document in the protocol

11.5 GLOBAL AMENDMENT 5

Date of amendment		24 June 2020
EudraCT number **EU number**		2018-000334-35
BI Trial number		1368-0017
BI Investigational Product(s)		BI655130 (SPESOLIMAB)
Title of protocol		An open label, long term safety trial of BI 655130 (SPESOLIMAB) treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 (SPESOLIMAB) trials
Global Amendment due to urgent safety reasons		☐
Global Amendment		**X**

Section to be changed		1.4 BENEFIT - RISK ASSESSMENT
Description of change 1		Section 1.4 has been updated based on the results of an unblinded interim analysis of the preceding induction trial 1368-0005.
Rationale for change		Based on the results of the interim analyses of trials 1368-0005 and 1368-0017, the general benefit-risk assessment for patients currently treated in trial 1368-0017 cannot be evaluated. Therefore for these patients, the benefit-risk should be assessed by the investigator on an individual basis to evaluate patient continuation in the trial.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN 3.3.4.1 Withdrawal from trial treatment
Description of change 2		Recommendations for discontinuation for patients experienced flares changed from >2 confirmed flares within a 12 month time period to more than 1 confirmed flares during the trial.
Rationale for change		In line with change1, to allow discontinuation of patients who experience > 1 flares during the trial.

Section to be changed		3.3.4.1 Withdrawal from trial treatment 6.2.2 Treatment period
Description of change 3		Text added in relation to discontinuation of patients from trial medication at any time if in the opinion of the Investigator, continuation with trial medication is not in the patient's best interest.

Rationale for change		To provide clarification that patients can be discontinued from trial medication at any time if in the opinion of the Investigator, continuation with trial medication is not in the patient's best interest.

Section to be changed		CTP Flowchart 1B 12lead ECG procedure
Description of change 4		12 lead ECG deleted at visits M6a and M7b and added at visit M7
Rationale for change		Typos correction

Section to be changed		Table 4.2.2: 1 Restrictions regarding previous and concomitant treatment
Description of change 5		Any biologic *approved* for UC (i.e. adalimumab, infliximab, golimumab, vedolizumab) "not allowed until end of the trial" Changed to "not allowed until end of the IMP treatment"
Rationale for change		To provide clear instruction about end of restriction period

Section to be changed		Flowchart footnote #6, Table 5.2.3: 2 Laboratory tests
Description of change 6		TSH and Glycosylated Hbc (HbA1c) tests have to be done only once per year Changed to TSH and Glycosylated Hbc (HbA1c) tests have to be done every 48 wks
Rationale for change		Specification of the timepoint when the specific test are required

11.6 GLOBAL AMENDMENT 6

Date of amendment		05 November 2020
EudraCT number **EU number**		2018-000334-35
BI Trial number		1368-0017
BI Investigational Product(s)		BI655130 (SPESOLIMAB)
Title of protocol		An open label, long term safety trial of BI 655130 (SPESOLIMAB) treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 (SPESOLIMAB) trials
Global Amendment due to urgent safety reasons		☐
Global Amendment		**X**

Section to be changed		Flow chart 1, footnote 9)
Description of change 1		Stool sampling for faecal biomarkers (calprotectin, lactoferrin) to be reduced to 1/24 weeks for patients in maintenance treatment.
Rationale for change		To simplify the procedures of the trial and reduce the long-term burden for patients participating in the trial. The proposed schedule of stool sampling for faecal biomarkers (calprotectin, lactoferrin) is considered adequate for patients in maintenance treatment.

Section to be changed		Flowcharts, sections 3.1 and 6.2.3.1
Description of change 2		Requirement of Vital Status collection for patients who discontinue study medication before EOT is deleted.
Rationale for change		Collection of vital status for patients who have discontinued treatment is not considered necessary for this long term trial and will reduce the burden of visit for these patients.

Section to be changed		5.2.6.2
Description of change 3		Requirement to collect SAE via fax form removed
Rationale for change		Alignment with sponsor internal procedures

Section to be changed		Section 5.2.6.2. AE reporting to sponsor and timelines
Description of change 4		Pregnancy testing Urine pregnancy testing for all women of child-bearing potential will be conducted on-site every 12 weeks at visits with study drug administration Changed to: Urine pregnancy testing for all women of child-bearing potential will be conducted on-site at visits with study drug administration
Rationale for change		Typo correction in CTP AM 6

Section to be changed		1.4. Benefit – risk assessment
Description of change 5		Table 1.4:1 amended with information related to SARS CoV-2 infection
Rationale for change		Implementation of possible impact of SARS CoV-2 infection on clinical study

11.7 GLOBAL AMENDMENT 7

Date of amendment		23 May 2022
EudraCT number **EU number**		2018-000334-35
BI Trial number		1368-0017
BI Investigational Product(s)		BI655130 (SPESOLIMAB)
Title of protocol		An open label, long term safety trial of BI 655130 (SPESOLIMAB) treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 (SPESOLIMAB) trials
Global Amendment due to urgent safety reasons		☐
Global Amendment		**X**

Section to be changed		1.4 Benefit risk assessment, table 1.4.1
Description of change 1		Peripheral Neuropathy added
Rationale for change		Project level update

Section to be changed		3.3.4.1 Withdrawal
Description of change 2		Stopping ruled by Peripheral Neuropathy added
Rationale for change		Project level update
Section to be changed		5.2.6.1 AESI
Description of change 3		Peripheral Neuropathy added as AESI
Rationale for change		Project level update
Section to be changed		4.1 Description of test product
Description of change 4		Tables for two old formulations were deleted
Rationale for change		2 old formulations were deleted to align with actual IMPD

APPROVAL / SIGNATURE PAGE

Document Number: c18806983 **Technical Version Number:8.0**

Document Name: clinical-trial-protocol-version-08

Title: An open label, long term safety trial of BI 655130(SPESOLIMAB) treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 trials

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	25 May 2022 10:21 CEST
Approval-Team Member Medicine		25 May 2022 12:14 CEST
Approval-Biostatistics		31 May 2022 09:26 CEST
Verification-Paper Signature Completion		03 Jun 2022 10:52 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed