Boehringer Ingelheim

Clinical Trial Protocol

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EudraCT No.: **EU Trial No:**	2017-003090-34	
BI Trial No.:	1368-0008	
BI Investigational Product(s):	BI 655130	
Title:	Mechanism of Action and Clinical Effect of BI 655130 in Patients with fistulizing Crohn's Disease	
Lay Title:	A study testing how BI 655130 works in patients with fistulizing Crohn's Disease	
Clinical Phase:	IIa	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final Protocol (Revised Protocol (based on global amendment 3))	
Version and Date:	**Version:**	**Date:**
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name:	BI 655130
Protocol date	12 Sep 2018
Revision date	23 Oct2020
Trial number	1368-0008
Title of trial:	Mechanism of Action and Clinical Effect of BI 655130 in Patients with fistulizing Crohn's Disease
Principal Investigator < for single-centre trial or > Coordinating Investigator< for multi-centre trial if applicable >:	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s):	Multi-center trial
Clinical phase:	IIa
Objective(s):	• To explore the pathomechanisms involved in the generation and healing of Crohn's Disease (CD) associated perianal fistulas • To understand the mode-of-action (MoA) of BI 655130 in patients with CD and draining perianal fistulas
Methodology:	Screening Cohort: is designed as a non-randomized screening cohort in patients with perianal fistulizing CD Study Cohort: is designed as a randomized, double-blind and placebo-controlled, parallel-group phase IIa study of BI 655130

Number of patients entered:	Screening Cohort : Approximately 5 to 8 patients Study Cohort : Approximately 20 patients
Number of patients on each treatment:	Screening Cohort: not applicable Study Cohort: • Period 1: Approx. 10 patients per treatment arm (BI 655130 1200mg i.v. or placebo) • Period 2: Treatment assignment in period 2 will be determined by the achievement of combined perianal fistula remission at week 12.
Diagnosis :	Patients with previously treatment-resistant perianal fistulizing CD with clinical indication for seton drainage
Main inclusion criteria:	1. 18-75 years at date of signing informed consent 2. Diagnosis of clinical Crohn´s Disease ≥ 3 months prior to screening by clinical and endoscopic evidence and corroborated by a histopathology report 3. Has ≥ 1 **perianal active* fistula(s)** with clinical indication for seton drainage (≥ 4 weeks duration before enrolment, as a complication of CD). **. * Criteria for Active Fistula: As per clinical evaluation: *Presence of spontaneous drainage or drainage after gentle finger compression at the external openings* **&** as confirmed by radiological (MRI) exploration . ** Patients who are screened with a seton drainage in place are eligible provided the drainage has not been in place for > 3 months and the patient meets the rest of the eligibility criteria 4. Additional enterocutaneous or abdominal fistulas are permitted (except rectovaginal fistulas) 5. Absent, mild or moderate clinical activity with CDAI ≤ 250. CDAI is not applicable for Screening Cohort. 6. Demonstrated in the past inadequate fistula response or loss of response or have had unacceptable side effects with approved doses of at least one of the following compounds: Immunesuppressive agents (e.g. thiopurines, methotrexate), TNFα antagonists (e.g. infliximab, adalimumab, certolizumab pegol; or respective biosimilars), vedolizumab, ustekinumab, azathioprine and / or antibiotics (cf. section 10.7)
Main exclusion criteria (Not applicable for Screening Cohort)	1. Complications of Crohn's Disease such as symptomatic strictures, functional stenosis distal from fistula(s), short gut syndrome, or any other manifestation that might require surgery, could preclude the use of the PDAI and CDAI to assess response to therapy, or

	would possibly confound the evaluation of benefit from treatment with BI 655130 2. Rectovaginal fistulas 3. Anticipated to require surgical intervention for CD, including any surgical fistula procedures (except seton drainage). See Table 4.2.2.2:1 for a detailed list of restricted interventions 4. Has an abscess that the investigator feels requires drainage beyond fistula drainage with a seton (based on either clinical assessment or MRI) 5. Any kind of bowel resection or diversion within 6 months or any other intraabdominal surgery within 3 months prior to screening. 6. Ileostomy, colostomy or known fixed symptomatic stenosis of the intestine at screening. 7. Evidence of colonic mucosal dysplasia or colonic adenomas, unless properly removed (properly according to the investigator's assessment) 8. Faecal Microbiota transplant (FMT) within 6 months prior to randomization 9. Treatment with: (See table 4.2.2.1:1 for a detailed list of restricted treatments) • any non-biologic medication (incl. cyclosporine, JAK inhibitors such as tofacitinib, tacrolimus, sirolimus, mycophenolate mofetile, S1P modulators, SMAD7 antisense inhibitors such as mongersen), other than those allowed per chapter 4.2.1 within 30 days prior to randomisation unless these patients show an undetectable plasma concentration • any biologic treatment approved for CD other than TNFα inhibitors, within 8 weeks prior to randomization unless these patients show an undetectable plasma concentration • any investigational or non-approved biologic for CD (including but not limited to IL-23 inhibitors) within 12 weeks prior to randomisation or etrolizumab within 8 weeks prior to randomization unless these patients show an undetectable plasma concentration • rectal 5-ASA, rectal Tacrolimus, parenteral or rectal corticosteroids (incl. budesonide) within 2 weeks prior to randomisation • any antibiotics within 1 week prior to randomisation • any prior autologous or allogeneic, haematopoietic (HSC) or mesenchymal stem cell (MSC) therapy • any prior exposure to BI 655130 • any chronic use of NSAID within 2 weeks prior to randomisation

	(occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc., and daily use of baby or low dose (81-162.5mg) aspirin for cardiovascular prophylaxis are permitted) • any life-attenuated vaccines within 6 weeks prior to randomization
Test product(s):	BI 655130 (Screening Cohort: not applicable)
dose:	1200 mg every 4 weeks (q4w): • Period 1: at week 0, 4, 8 • Period 2: at week 12, 16, 20
mode of administration:	Intravenous (i.v.)
Comparator products:	Placebo (Screening cohort: not applicable)
dose:	0 mg (placebo) every 4 weeks (q4w): • Period 1: at week 0, 4, 8 • Period 2: at week 12, 16, 20
mode of administration:	Intravenous (i.v.)
Duration of treatment:	Screening Cohort: not applicable Study Cohort: 24 weeks
Endpoints	Primary endpoint: The primary endpoint is the total number of deregulated genes at week 4 comparing changes in gene expression from baseline between the two treatment groups. Thereby, deregulation of a gene is defined based on the baseline adjusted mean difference to placebo of gene expression fulfilling the following criteria: • False discovery rate (FDR) adjusted p-value ≤ 0.05 • |fold change| ≥ 1.5 • genes can be annotated with Ensembl identifiers (version 84 or later) Gene expression is analysed based on biopsies (curettage and inner fistula orifice) via RNA sequencing; more details on the gene expression analysis can be found in Section 7.3.1 Secondary endpoints: • Proportion of patients with perianal fistula response at week 12 (defined as closure of at least 50% of external openings, no drainage / discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas)

	• Proportion of patients with perianal fistula remission at week 12 (defined as closure of all external openings, no drainage / discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas) • Proportion of patients with combined perianal fistula remission at week 12 (defined as closure of all external openings, no drainage / discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas, AND absence collections of >2 cm, confirmed by MRI in at least two of three dimensions – blinded and centrally read)
Safety criteria:	Physical examination, vital signs, 12-lead ECG, laboratory tests, adverse events, serious adverse events and drug-related adverse events. The intensity grading of AEs and abnormal laboratory values will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0
Statistical methods:	Gene expression analysis via repeated measures linear regression model (calculation of total number of deregulated genes at Week 4). Descriptive statistics for safety, [redacted] and efficacy endpoints. If feasible, 95% confidence intervals for rate difference in perianal fistula response, perianal fistula remission, and further clinical efficacy endpoints regarding proportions of patients.

FLOW CHART A: SCREENING COHORT

Trial Periods	Screening Visit	Fistula Preparation Visit	Follow-up Visit
Visit	V1	V2	V3
Week	-4 to 0	0	3
Day	-28 to -1	1	21
Time window for visits (days)	n.a.		±7
Informed consent	X		
In-/exclusion criteria	X		
Demographics, Medical history incl. smoking, Crohn's Disease history, Prior therapies	X		
Physical examination (incl. vital signs) 1)	X C	X T	X T
Weight, Height 2)	X	X	X
Rectoscopy and Proctoscopy		X	
[redacted]	X		X
Biopsy at the inner fistula orifice 3)		X	
Curettage at the fistula canal 3)		X	
Seton placement 3)		X	
Biopsy at the outer fistula orifice 3)		X	
Rectal luminal biopsy 3)		X	
Concomitant therapy	X	X	X
Adverse events	X	X	X

1) Physical examination: C=complete, T=targeted. Refer to Section 5.2.1.
Vital signs: Measurement should precede blood sampling to avoid the impact of blood sampling on the vital measurements.

2) Height: To be done at screening visit 1, only.

3) Refer to section 3.1 for requested tissue samples.

FLOW CHART B: STUDY COHORT, PERIOD 1 (SCREENING – WEEK 8)

Trial Periods	**Screening Period***			**Randomized Treatment Period**			
Visit	V1a (Screen-ing)	V1b (Pre-baseline)	V1c	V2 (Base-line)	V3	V4	V5
Week	-5 to -3	-5 to -3	-3	0	2	4	8
Day	-35 to -22	-35 to -21	-21	1	15	29	57
Time window for visits (days)	n.a.	n.a.	+ 4	n.a.	± 4	± 4	± 4
Informed consent	X						
In-/exclusion criteria	X		X				
Demographics	X						
Medical history incl. smoking, Crohn's Disease history	X						
Prior therapies	X						
Physical examination (incl. vital signs) 1)	X C			X T	X T	X T	X T
Weight, Height 15)	X			X		X	X
Pregnancy Test 2)	X			X		X	X
[redacted]			[redacted]			[redacted]	
[redacted]			X			X	
Fistula preparation visit: 4) **Biopsy at the inner fistula orifice** **Curettage at the fistula canal** [redacted]			X			X	
Seton placement			X				
Seton removal						X	
[redacted]			X			X	
[redacted]			X Before Surgical Procedure			X	
[redacted]	D		X R Before Surgical Procedure	D	XR D	XR D	XR D
Imaging **Pelvic MRI** [redacted]		X[5] Before Surgical Procedure at V1c					
Concomitant therapy	X			X	X	X	X
Adverse events	X	X	X	X	X	X	X
12 lead-ECG	X			X			
Safety laboratory tests 6)	X			X	X	X	X
Infection testing 7)	X						

Flow Chart B: STUDY Cohort, Period 1 (Screening – Week 8) (cont.)

Trial Periods	**Screening Period***			**Randomized Treatment Period**			
Visit	V1a (Screen-ing)	V1b (Pre-baseline)	V1c	V2 (Base-line)	V3	V4	V5
Week	-5 to -3	-5 to -3	-3	0	2	4	8
Day	-35 to -22	-35 to -21	-21	1	15	29	57
Time window for visits (days)	n.a.	n.a.	+ 4	n.a.	± 4	± 4	± 4
QuantiFERON-TB test	X						
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				X	X	X	X
[redacted]				X		X	X
[redacted]				[redacted]			
[redacted]				[redacted]		[redacted]	[redacted]
[redacted]				[redacted]		[redacted]	
[redacted]	X						
[redacted]				X			X
Contact IRT	X			X		X	X
Randomization				X			
Study drug administration				X 12,13		X 13, 14	X 13

*) Once the gene expression analyses from the obtained fistula canal samples in the SCREENING COHORT have confirmed the eligibility criteria, enrolment of the STUDY COHORT will be initiated. Otherwise, the sponsor may decide to amend the study in order to obtain the relevant tissue from all study participants.

1) Physical examination: C=complete, T=targeted. Refer to Section 5.2.1.
Vital signs: Measurement should precede blood sampling to avoid the impact of blood sampling on the vital measurements. In addition, at dosing visits vital signs will be assessed pre-dose, approximately 10 minutes and 1 hour after study drug administration.
Monitor for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered at Visit 2 and 1 hour following all other doses of study drug.

2) Only applicable for women of childbearing potential. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all other visits indicated in the Flow Chart. In case of a positive urine pregnancy test, a serum pregnancy test will be done. Urine pregnancy testing should be done prior to administration of study drug in case there is dosing at study visits. Study drug should only be administered in case of a negative test result.

[redacted]

4) Based on the outcome of the Screening Cohort it has been decided to keep the tissue sampling approach as initially planned. (cf. section 3.1)

5) *MRI*
Decision on eligibility (exclude abscesses ≥ 2 cm, confirm fistula activity according to inclusion criterion 4) and progress of patients is based on assessment by investigator(s) on site.
Visit 1b: MRI results to be reviewed PRIOR to surgical procedures at visit 1c.

[redacted]

6) Includes parameters as listed in Table 5.2.3:1 and 5.2.3:2.
It is preferred but patients do not have to be fasted for the blood sampling for the safety laboratory. At visits with study drug administration this should be done prior to the study drug infusion.

7) Infection Testing: See section 5.2.3 safety laboratory parameters for complete list of testing required.

8) At study visits with study drug administration, pre-dose PK/ADA/nAb and biomarkers samples should be obtained within 1 hour prior to start of i.v. infusion.

9) If collection is not possible at Visit 1a, stool sample has to be collected at (or prior to) Visit 1c.

[redacted]

11) A diary will be used by the patient for the daily reporting of bowel movement frequency, abdominal pain and general

[redacted]

Refer to Section 6.2.

12) First study drug will be administered at V2.

13) Patients who terminate study drug early should be encouraged to follow all study procedures per the Flow Chart until week 24, but not receive any more study drug at the respective visits. These patients do have the option to do EOS visit earlier than week 36 (their EOS visit should not be earlier than 16 weeks after their last study drug administration). Until then they should follow the Flow Chart.

14) Visit 4: I.v. administration and related procedures may be done within max. of 3 days after other investigations / procedures, if otherwise too difficult due to logistical reason.

15) Height: To be done at screening visit 1a, only.

[redacted]

[redacted]

FLOW CHART C: STUDY COHORT, PERIOD 2 (WEEK 12 – WEEK 36)

Trial Periods	**Randomized Treatment Period**				**Follow-up Period**
Visit	V6 (treatment decision)	V7	V8	V9 / EOT	V10 / EOS 11)
Week	12	16	20	24	36
Day	85	113	141	169	253
Time window for visits (days)	± 4	± 4	± 4	+7	+7
Physical examination (incl. vital signs) 1)	X C	X T	X T	X C	X C
Weight	X	X	X	X	X
Pregnancy Test 2)	X	X	X	X	X
[redacted]	[redacted]			[redacted]	
[redacted]	X			X	
[redacted]	X			X	
[redacted]	X 4)			X	
[redacted]	XR D	XR D	XR D	XR D	XR
Imaging: **Pelvic MRI** [redacted]	X 5)			X	
Concomitant therapy	X	X	X	X	X
Adverse events	X	X	X	X	X
12 lead-ECG	X			X	X
Safety laboratory tests 6)	X	X	X	X	X
QuantiFERON-TB test				X	
[redacted]	X	X	X	X	X
[redacted]	X		X	X	X
[redacted]	X	X	X	X	
[redacted]	X	X	X	X	

Flow Chart C: Study Cohort, Period 2 (Week 12 – Week 36) (cont.)

Trial Periods	**Randomized Treatment Period**				**Follow-up Period**
Visit	V6 (treatment decision)	V7	V8	V9 / EOT	V10 / EOS 12)
Week	12	16	20	24	36
Day	85	113	141	169	253
Time window for visits (days)	± 4	± 4	± 4	+7	+7
Stool sampling for microbiome and miRNA analysis	X			X	
[redacted]	X			X	
Contact IRT	X 12)	X 12)	X 12)	X	
Study drug administration	X 4) 10), 11)	X 4) 10)	X 4) 10)		
Study completion 12)				X	X
Roll-over into 1368-0007 12)				X 12)	

1) Physical examination: C=complete, T=targeted. Refer to Section 5.2.1.
Vital signs: Measurement should precede blood sampling to avoid the impact of blood sampling on the vital measurements. In addition, at dosing visits vital signs will be assessed pre-dose, at approximately 10 minutes and 1 hour after study drug administration.
Monitor for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered at Visit 2 and 1 hour following all other doses of study drug.

2) Only applicable for women of childbearing potential. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all other visits indicated in the Flow Chart. In case of a positive urine pregnancy test, a serum pregnancy test will be done. Urine pregnancy testing should be done prior to administration of study drug in case there is dosing at study visits. Study drug should only be administered in case of a negative test result.

[redacted]

4) Perianal fistula activity at week 12: Refer to chapter 3.1 and 5.1.2
Treatment assignment in period 2 will be determined by the achievement of combined perianal fistula remission at week 12 based on assessment by investigator(s) on site.

- Combined perianal fistula remission = yes: stay on current drug
- Combined perianal fistula remission = no: switch to active drug if treated with placebo in period 1
  proceed with active drug if treated with active drug already in period 1

5) *MRI*
Visit 6:
MRI to be performed in a time window of 2 weeks PRIOR to visit 6. MRI result to be available at visit 6 for the evaluation of combined perianal fistula remission performed by investigator(s) on site.
[redacted]

6) Includes parameters as listed in Table 5.2.3:1 and 5.2.3:2.
It is preferred but patients do not have to be fasted for the blood sampling for the safety laboratory. At visits with study drug administration this should be done prior to the study drug infusion.

[redacted]

10) Patients who terminate study drug early should be encouraged to follow all study procedures per the Flow Chart until week 24, but not receive any more study drug at the respective visits. These patients do have the option to do EOS visit earlier than week 36 (their EOS visit should not be earlier than 16 weeks after their last study drug administration). Until then they should follow the Flow Chart.

11) Visit 6: I.v. administration and related procedures may be done within max. of 3 days after other investigations / procedures, if otherwise too difficult due to logistical reason

12) All patients completing week 24 of the study and having an individual clinical benefit may be offered to enter open label long-term extension study 1368-0007. These patients are not requested to complete follow up period and the visit 09 is the last visit for trial 1368-0008, probably co-inciding with the first visit in 1368-0007. For AE and Concomitant therapy reporting the end of study participation is defined as the day of first administration of study drug in 1368-0007.

[redacted]

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS

ADCC	antibody-dependent cellular cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	[redacted]
BI	Boehringer Ingelheim
b.i.d.	bis in die (twice daily dosing)
BM	Biomarker
CCDS	Company Core Data Sheet
CD	Crohn's Disease
CDC	complement-dependent cytotoxicity
[redacted]	[redacted]
CI	Confidence Interval
[redacted]	[redacted]
CTM	Clinical Trial Manager
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EC	enterocutaneous
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMT	Epithelial-mesenchymal transition
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDR	false discovery rate
FIH	First in Human
FMT	Faecal Microbiota Transplant
FPV	fistula preparation visit
FUP	Follow-up period
GCP	Good Clinical Practice
GPPGA	Generalized Pustular Psoriasis Physician Global Assessment
GPPASI	Generalized Pustular Psoriasis Area and Severity Index
GPP	Generalized Pustular Psoriasis
[redacted]	
HSC	Haematopoietic stem cell

IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
[redacted]	[redacted]
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITE	indirect target engagement
i.v.	Intravenous
LoEE	List of Essential Element
MedDRA	Medical Dictionary for Drug Regulatory Activities
MIP	Macrophage Inflammatory Protein
MABEL	Minimum Anticipated Biological Effect Level
MoA	mode-of-action
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal stem cell
[redacted]	[redacted]
MST	Medical Sub Team
nAb	Neutralizing Antibodies
nM	nanomolar
NOAEL	no-observed-adverse-effect level
OPU	Operative Unit
PDAI	perianal disease activity
PBMC	Peripheral Blood Mononuclear Cell
PBO	placebo
PD	Pharmacodynamics
[redacted]	[redacted]
p.o.	per os (oral)
PoC	Proof of Concept
PPP	[redacted]
[redacted]	[redacted]
q.d.	quaque die (once a day)
pM	picomolar
eDC	electronic Data Capturing
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
RS	Randomized Set
RSS	RNA Sequencing Set
SAE	Serious Adverse Event
SAF	Safety Set
s.c.	Subcutaneous
SES-CD	Simple Endoscopic Score in Crohn's Disease
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics

SOC	standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
CTL	Clinical Trial Leader
TDMAP	Trial Data Management and Analysis Plan
TGF	Tissue growth factor
t.i.d.	ter in die (3 times a day)
TMDD	target-mediated drug disposition
TMF	Trial Master File
TNF	Tumor necrosis factor
TSAP	Trial Statistical Analysis Plan
UC	Ulcerative colitis
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Crohn's Disease (CD) is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract characterized by abdominal pain, fever, and bloody or mucus-containing diarrhoea [R13-2231]. The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the ileum and colon (40%), followed by the small bowel only (30%), and the colon only (25%) [R13-2232, R13-2233]. The mean age at CD diagnosis is approximately 30 years with a slight predominance of women [R16-1923].
The incidence of CD seems to be increasing with more recent estimates varying from 7.9 to 20.2 cases/100,000, and a prevalence of 161 to 319 cases/100,000 in North America and Europe [R13-2231]. Mucosal lesions may be complicated not only by stricture formation, but also by perforation and fistula formation, which may require hospitalization for medical or surgical management.

Fistulas represent one of the most important complications in patients with CD. One third of CD patients will develop fistulas at least once during the course of the disease. Perianal fistulas are the most common clinical manifestation. At time of CD diagnosis, two third of patients present with inflammatory disease and only up to one-third of the patients reveal stricturing or penetrating complications in the gastrointestinal tract. Thus, the number of patients with severe and recurrent problems arising from CD fistulas is considerably high. Surgery, though often required, does not always provide a definitive cure [R17-3555].

The mainstay of treatment of moderate to severe CD without fistulae has been with glucocorticoid therapy, azathioprine, or 6-mercaptopurine [R13-2269]. More recently, biologics consisting of monoclonal antibodies directed at cytokines, thought to mediate the pathology, have been used extensively for this indication.

Routine medical treatment of perianal CD fistulas includes antibiotics, immunosuppressives, and anti-TNF antibodies. Most of the evidence on routinely used medical treatment is derived from subgroup analyses or secondary outcome measures, while dedicated clinical trials with healing of perianal fistula or reduction in the amount of secreting fistula tracts are still limited. Amongst anti-TNF antibodies, infliximab is approved in the indication of treatment of perianal fistulising, active Crohn`s disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). However, only approximately half of infliximab treated patients achieved closure of all fistulas [R00-0812] and relapses were common. After 1 year in only approximately a third of patients all fistulas are closed [R04-0551]. A recently approved approach of injecting allogenic mesenchymal stem cells into the surgically prepared fistula canal has represented the latest major progress in fistula treatment achieving remission rates of around 50% after one year [R18-2555]. Surgical therapies aim to achieve fistula closure while preserving the anal sphincter function, but show limited efficacy based on the limited available evidence. Thus, there remains a significant unmet medical need for better treatments of this CD complication [R17-3555].

1.2 DRUG PROFILE

1.2.1 Mode of action

BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signalling. Binding of BI 655130 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 to 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).

1.2.2 Data from non-clinical and toxicology studies

Preclinical studies
BI 655130 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 also inhibits IL8 release in primary human intestinal myofibroblasts and Interferon gamma (IFNγ) secretion in human Peripheral Blood Mononuclear Cell (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 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 does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with BI 655130. However, hazard identification studies of the mode-of-action (MoA) of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (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 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 dosing in humans.

1.2.3 Data from clinical studies

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

PK analysis showed that exposure (AUC0-tz and Cmax) to BI 655130 increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. The effective half-life of BI 655130 is approximately 4 weeks in the linear dose range. Overall, PK data so far suggests target-mediated drug disposition (TMDD) kinetics for BI 655130. Anti-drug antibodies (ADA) were detected in 8 patients, 3 of those had pre-existing levels. Pharmacodynamic effects in this FIH Single Rising Dose trial [c03361085-07] were assessed by indirect target engagement (ITE) of IL36R by BI 655130 using an ex-vivo whole blood stimulation assay. All doses higher than 0.001 mg/kg were biologically active, corresponding to the minimum anticipated biological effect level, MABEL.

In a multiple rising dose trial, BI 655130 or placebo have been administered to healthy volunteers at multiple ascending i.v. doses of 3, 6,10 and 20 mg/kg given qw for 4 weeks (i.e. 4 administrations) or a single dose of 20 mg/kg (8 subjects each, 3:1 on active or PBO). Overall, BI 655130 was well tolerated. All AEs were of mild or moderate intensity; drug-related AEs of moderate intensity were observed in one subject in the highest dose cohort (20 mg/kg multiple dosing) BI 655130 treatment group (suspected infusion reaction leading to study drug withdrawal). Furthermore, there were no clinically relevant abnormalities on treatment with BI 655130 with respect to safety laboratory, vital signs, or ECGs as assessed by a central reader. Importantly, based on the preliminary analysis of the ITE studies, more than 90 % of peripheral IL36R was engaged for at least 22 weeks after the last application of four weekly doses. For further details and most recent results refer to the current Investigator`s Brochure [c03320877].

Studies in Patients
Efficacy data are available from a proof of concept study in patients with generalized pustular psoriasis (GPP). In trial 1368.11, seven patients received a single intravenous dose of 10 mg/kg BI 655130, and were monitored for 20 weeks. At week 1 after dosing, Generalized

Pustular Psoriasis Physician Global Assessment (GPPGA) score of clear or almost clear (0 or 1) was achieved in five patients, and by Week 4 in all seven patients. Within 48 hours post-dose, pustules were completely cleared in three patients, by week 1 in five patients and by week 2 in six of seven patients. A major improvement in (GPPASI) was observed in all patients with a mean (SD) percent change from baseline of 73.2% (16.2) at week 2; by week 4, this was further reduced to 82.0% and was maintained to week 20 (83.6%).

Residual Effect Period
The Residual Effect Period (REP) of BI 655130 is 16 weeks after the last administration. This is the period after the last dose with measurable drug levels and pharmacodynamic effects still likely to be present.

Summary
BI 655130 is an anti-IL-36R antibody targeting a molecule likely to be involved in intestinal fibrosis and fistula generation, and has shown a strong clinical activity to block IL-36R signaling in an inflammatory skin disease. IL36R inhibition shows a favorable nonclinical safety profile. BI 655130 has been tested in healthy volunteers with single or multiple dosing up to four weeks of 20 mg/kg i.v. q.w. Therefore, BI 655130 might be a promising drug to treat patients suffering from CD.

BI 655130 drug [c03320877].

1.3 RATIONALE FOR PERFORMING THE TRIAL

This study is planned as a mechanistic pilot study in patients with CD complicated by perianal fistulas, who have a clinical indication for surgical treatment with a seton drainage to alleviate symptoms and condition the tissue for potential subsequent surgical interventions. The objective is to explore the pathomechanisms involved in the generation and healing of CD associated perianal fistulas, and to investigate the effect of BI 655130 on these mechanisms by using gene expression analyses. Moreover, clinical effect, safety and tolerability of BI 655130 treatment in patients with fistulizing CD will also be explored.

The current understanding of the pathomechanisms involved in the evolution of perianal or other fistulas arising as complication of CD is limited and based on studies in surgically resected tissue specimens or in-vitro studies (Panes, Rimola; Nat Rev Gastroenterol & Hepatol 2017, doi:10.1038/nrgastro.2017.104). This study will be the first to investigate mechanisms involved in fistula generation and healing *sequentially* in the same fistula tracts and/or openings. Since the collection of tissue using curettage and small biopsies has not yet been systematically explored, the study will start with a Screening Cohort to establish the technical feasibility of the tissue sampling approach. The Study Cohort will initiate as soon as feasibility has been confirmed. Irrespective of a potential treatment effect of BI 655130 will the mechanistic studies of sequentially assessed fistula tissue increase the understanding of the mechanisms underlying fistula generation, which may lead to the identification of new treatment targets for this disabling complication of CD.
BI 655130 is currently under development for the treatment of inflammatory skin and bowel diseases such as generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), Atopic

dermatitis (AtD) and Hadrenitis suppuratuva (HS) and inflammatory bowel disease (IBD) such as ulcerative colitis (UC) and CD. Its unique dual modes of action includes anti-inflammatory effects as well as tissue remodeling effects and thus may provide a clear advantage over current drugs and investigational compounds, which target inflammatory pathways only. Single dose administration of BI 655130 has been shown to be highly effective and safe in a pilot study in 7 patients with moderate or severe acute GPP, irrespective of their IL36RA mutation status (refer to current IB section 6/efficacy).
The link between IL-36R driven inflammation and epithelial inflammation has led to the hypothesis that IL-36R signalling may play an important role in inflammatory bowel diseases:

- IL-36R and its ligands are expressed in intestinal biopsies from patients with chronic IBD;
- IL-36-induced genes are upregulated in human intestinal myofibroblasts and correlate with gene signatures observed in UC and CD patients;
- Human IL-36 ligands in cell culture enhance epithelial intestinal barrier permeability, a hallmark of IBD pathogenesis;
- IL-36R signalling induces in human intestinal myofibroblasts and macrophages not only pro-inflammatory but also tissue remodelling related mediators (e.g., tissue growth factor TGF-β, matrix metalloproteinase), which differentiates this mechanism from TNF alpha and IL-23 pathways;
- An antagonist anti-mouse IL-36R antibody or knock-out of the IL36R ameliorates intestinal inflammation and fibrosis in various acute and chronic murine colitis models [R16-2299].

Gene expression data in skin from GPP patients has identified marker genes such as TGFB1, TIMP1, LOXL1, IL6 involved in tissue remodelling processes that were subsequently down-regulated by BI655130. In addition, BI655130 also down-regulated genes in these patients with a pivotal role in the pathogenesis of IBD such as TNFα and IL23A.
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 suggest a prominent role of IL36R in driving intestinal inflammation and fibrosis in patients with fistulizing CD [R18-0017]. The potential simultaneous BI 655130 effects on inflammation and tissue remodeling may turn into increased mucosal healing and reduced stricturing and fistulizing complications of CD. Therefore, the effect of IL36R inhibition on the involved mechanisms will be assessed on tissue level, as well as the clinical effect on fistula healing and luminal activity.

[redacted]

[redacted] The outcome of this study will set the stage for large scale studies in patients with fistulizing CD.

The therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup. Later on there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking. If the patient agrees, banked samples may be used for future drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event, and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

BI 655130 represents an investigational drug which has largely completed phase I and is currently undergoing phase II evaluation in various indications (GPP, PPP, AtD and UC). In line with this stage of development, clinical evidence for efficacy of spesolimab in patients is limited However, preclinical profiles of BI 655130 and clinical data from healthy volunteer trials suggest that BI 655130 is safe, tolerable and may address an unmet medical need in CD patients by a dual anti-inflammatory and anti-fibrotic mechanism of action, cf. Section 1.2 and the IB [c03320877].

BI has decided to discontinue the development of spesolimab in UC. The decision is based on available results of the phase II clinical trials (1368-0004, 1368-0005, 1368-0010, and 1368-0017) conducted in patients with UC which show a lower than expected efficacy on clinical endpoints. The decision is not related to or triggered by any safety findings. Data from ongoing and completed clinical trials in UC and other conditions show a good safety and tolerability profile of spesolimab with no evidence of any new safety risks.

The anticipated benefit and the safety data obtained thus far support the continuation of the spesolimab clinical development programme in all other indications under study.

Although no relevant animal species is available for toxicology testing of the highly human specific antibody BI 655130, preclinical toxicology studies with a rat anti-mouse surrogate antibody have demonstrated the safety of IL-36R inhibition in mice (c03320877), IB Section 5.1.2). Moreover, a total of 148 healthy volunteers have been exposed in four completed phase I studies to single or multiple doses of BI 655130 up to very high dose levels of 20mg/kg given once weekly (qw) for 4 weeks. In all these studies BI 655130 has been safe and well tolerated at all tested dose groups (for details cf. IB section 6/safety). In addition, a first proof-of-concept trial (1368.11) in moderate/severe acute GPP has been completed confirming that a single IV dose of 10mg/kg of BI 655130 was safe and tolerable in seven patients with moderate or severe acute GPP. As of July 2017, three clinical studies are ongoing: a 16 week proof-of-concept trial exploring efficacy and safety of BI 655130 in patients with moderate/severe Palmoplantar Pustulosis (PPP; 1368.15; n=60); and two (1368.4, 1368.10) small pilot studies exploring mechanism and effect of BI 655130 in patients with UC (n=10 and 30, respectively). These studies are carefully monitored by the sponsor and an independent Data Safety Monitoring Board (DSMB) and have not identified

any severe or serious safety signal. Thus, no clearly compound related adverse effect or other safety signals have been identified in preclinical or clinical phase I studies.

As with any immune modulating agent, BI 655130 has the theoretical potential to impair immune function increasing the risk of infection or cancer. A recent publication has identified 12 healthy individuals carrying an inherited loss-of-function mutation of the IL-36 receptor gene [R17-3632]. The authors found that normal immune function was broadly preserved in these individuals, who showed no phenotype of increased risk in infection or cancer. In accordance with this observation, no evidence of an increased infection risk has emerged from the early trials, though larger studies with a longer follow-up are needed to draw such a conclusion. The role of IL-36 in tumour immunity is also not well established at this time and an increased risk of cancer from an IL-36R antagonist cannot be excluded. These risks will be addressed in the study program by careful safety monitoring and risk mitigation measures: (a) exclusion of patients with history or increased risk of malignancies or infections; (b) close clinical monitoring for AEs, including use of Rheumatology Common Toxicity Criteria (RCTC) for severity grading, definition of emerging malignancies as always-serious adverse events, definition of opportunistic infections and infusion and anaphylactic reactions as adverse events of special interest (AESI); (c) selection of sites experienced in treatment of IBD patients with biologics; and (d) surveillance by a fully independent Data Safety Monitoring Committee (DMC).

With regard to potential benefits, BI 655130 (i) has a unique bimodal MoA providing a strong scientific rationale to be tested in fistulising CD; (ii) has shown high (>94% inhibition of TNFα or MIP1β secretion) and sustained (>22 weeks after last dose) biological activity in healthy volunteers based on an indirect target engagement assay (reference IB, section 6.1 pharmacology); and (iii) has rapidly cleared pustules and other skin lesions in GPP, a disease closely linked to excessive IL36 activity, which indicates that BI 655130 inhibits IL36 in human disease and has the potential to treat inflammatory epithelial diseases. Based on the PoC achieved in GPP and the strong preclinical rationale, there is a reasonable chance that BI 655130 may not only alleviate signs and symptoms of active CD but even directly promote mucosal and histological healing in luminal and fistulising CD. Mucosal healing is associated with improved clinical outcomes (reductions in immunosuppressive treatments, hospitalizations, colectomy and colorectal cancer [R16-0572].

Moreover, as the pathogenesis of this condition is not well understood, an improved characterisation of the underlying changes in various genetic and epigenetic markers may result in the discovery of novel therapeutic targets. The nature of the regulated genes and biomarkers will shape the subsequent development of BI 655130 and other compounds in IBD to define potential new endpoints, target indications and biomarkers to identify responder patient populations.
Therefore, participation in this study may help to generate a future group benefit for patients with CD and fistulas, if BI 655130 or other compounds acting on yet to be identified new targets prove to be successful in treating this disease.

This trial is a 2-part trial. The *Screening Cohort* will determine in a small number of patients undergoing standard of care surgical procedure, whether identical cytokines and

pathomechanisms are active in tissue samples collected from the fistula canal (curettage) and/ or from the inner and outer orifice (biopsy), where fistula generation starts with the emergence of epithelial-mesenchymal transition (EMT) and tissue invasion. Based on the outcome of this cohort, feasibility criteria for *Study Cohort* may have to be adapted (via substantial amendment) to exclude patients where for technical reasons a sufficient biopsy of the inner orifice cannot be obtained. Patients in the *Screening Cohort* will only receive standard of care (SOC) for their disease, without subsequent randomization to IMP or PBO. The only additional study related procedures are sampling of the curettage tissue and biopsies for gene analyses and histology, which should not increase the risks over that of the standard procedure. Should these patients not respond to surgical or standard treatment, they can be re-screened at a later point in time for participation in the *Study Cohort*, which may come with a benefit.

The *Study cohort* is designed as a randomized, double-blind and placebo-controlled phase IIa study of BI 655130 in patients with perianal fistulizing CD . Patients may continue pre-existing conventional or anti-TNF treatment as defined in Section 4.2.2.1. The placebo controlled period 1 of 12 weeks will be followed by additional 12 weeks of blinded treatment. Treatment in period 2 will depend on the original treatment group and the achievement of a strict combined perianal fistula remission outcome at week 12: all patients in the original BI 655130 group and non-remitters from the original placebo group will be treated with BI 655130 from week 12 to 24. Remitters to placebo at week 12, will continue placebo till week 24. The double blinding will be kept by IRT assigning active or placebo based on these decision criteria. The total treatment duration is up to 24 weeks; after that time all patients having derived an individual benefit will be offered to roll-over into a long-term open label extension study (1368-0007).

- The surgical fistula preparation visit (FPV) under anaesthesia and/or sedation is indicated as standard of care in the eligible patient population per inclusion criteria. Curettage of the fistula canal and insertion of a seton drain represents standard surgical treatment, which requires identification of an inner fistula orifice and allows to collect a small (1mm) biopsy, while a biopsy at the outer orifice is not compulsory and may be taken only in those patients where a clinical indication for unroofing of a perianal abscess or fistula exists. The same applies for the second FPV with removal of the seton drain. Thus, the FPV procedures are unlikely to increase risks over those inherent to the standard of care treatment in these patients.
- While a placebo control is needed to explore the efficacy endpoint and safety profile, the design will assure that all placebo patients not achieving a very strict remission criterion will switch over to active drug at week 12, and that patients deriving an individual benefit can stay on maintenance treatment for extended periods of time. An active comparator would confound safety evaluation and largely reduce the eligible patient population due to the expected extensive and diverse pre-treatment history.
- The selected dose regimen of BI 655130 is the highest dose evaluated in ongoing programs and will at the same time maximize the change of being effective and even at steady state will not exceed the exposure tested and found safe in phase I study 1368.2.
- Only patients with treatment-resistant perianal fistulizing CD may be enrolled into the study demonstrated by primary or secondary failure or unacceptable side effects with approved doses of biologics and / or antibiotics. Patients also must have a clinical

indication for surgical fistula cleaning and seton drainage. This also indicates the high medical need in this patient group.

- Reactions to IV administered biologic agents represent the manifestations of systemic hypersensitivity reactions including allergic reactions and can occur as anaphylaxis, pruritus, hypotension and respiratory distress. Systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. Specific safety measures will be taken during the trial. Although this has not represented an issue in phase I, all patients will be monitored for infusion reactions at the site according to Instructions for preparation and Handling of BI 655130.

Other risks of participating in this study include risks related to the trial specific procedures including blood sampling, intravenous infusion of study medication, and rectoscopy or proctoscopy with biopsy: Blood sampling and intravenous infusions can cause local bruising, inflammation, nerve damage and pain. Rectoscopy or proctoscopy with biopsy, although generally well tolerated, can be associated with diarrhoea, abdominal pain, perforation, bleeding, effects from anaesthetic medications, and infection.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also section 5.2.6, adverse events of special interest.

Benefit-Risk Assessment in context of COVID-19 pandemic.

BI 655130 is an immune-modulating humanized monoclonal antibody that blocks the human IL-36 receptor and thereby the pro-inflammatory IL-36 pathway. Available non-clinical and clinical data in 378 subjects (see Investigators Brochure Version 7) have not shown an increased risk of infections with BI 655130. However, similar to other immune modulating biological treatments, BI 655130 may hypothetically increase the risk of infections. Risk mitigation measures, such as exclusion of patients with increased risk of infections, close monitoring of adverse events, as well as guidance on treatment and handling of acute infections occurring during the trial are described in the clinical trial protocol.
As any other acute infection, a suspected or diagnosed COVID-19 infection should be treated according to the standard of care and interruption of study medication should be considered. Currently, information about the immune response in patients with COVID-19 is sparse and inconclusive. There are some reports suggesting high-levels of pro-inflammatory cytokines in the severe cases, with much of the morbidity associated with coronavirus infection, potentially related to immune activation and inflammation. To date, there is no reliable evidence suggesting a link between SARS-CoV-2 infections and the IL-36 pathway targeted by BI 655130. Considering the current knowledge of COVID-19 and the implemented risk mitigation measures addressing the potential risk of infections, patients studied in trials with BI 655130 are not believed to be at higher risk of COVID-19 due to their background or concomitant diseases. Protocol-defined procedures do not impose undue risk to study participants.
The benefit-risk assessment of BI 655130 remains favourable in the context of the COVID-19 pandemic.

To address potential risks associated with operational aspects related to the participation in clinical trials in context of COVID-19 pandemic, different risk mitigation measures are considered in ongoing and planned BI 655130 clinical trials based on local requirements and development of 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.

Summary of benefit-risk assessment
Due to the current lack of significant mechanism- or compound-related safety signals of BI 655130 it is considered likely that patients with perianal fistulizing CD will not be exposed to undue risks and adverse events in relation to the information that is expected to be gained from this trial. Considering the medical need of the development of an effective and well tolerated drug specifically and directly treating the structural aspects of CD complicated by fistulas, the benefit of this trial is considered to outweigh the potential risks for individual patients with perianal fistulizing CD participating in this trial.
The benefit-risk profile is thus considered appropriate for an experimental therapy at this early stage of clinical development.

2. TRIAL OBJECTIVES AND ENDPOINTS

The Screening Cohort does not directly contribute to the assessment of the trial objectives; its purpose is to assess whether eligibility criteria for the Study Cohort have to be amended in order to enable an assessment of the trial objectives in the Study Cohort. The patients of the Screening Cohort will not be treated with trial medication.

All objectives and endpoints defined in this section are only applicable for the Study Cohort. Endpoints for the Screening Cohort and their analysis will be defined in the Trial Statistic Analysis Plan (TSAP).

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objectives of this trial are:
- To explore the pathomechanisms involved in the generation and healing of CD associated perianal fistulas
- To understand the MoA of BI 655130 in patients with CD and draining perianal fistulas

2.1.2 Primary endpoint

The primary endpoint is the total number of deregulated genes at week 4 comparing changes in gene expression from baseline between the two treatment groups. Thereby, deregulation of a gene is defined based on the baseline adjusted mean difference to placebo of gene expression fulfilling the following criteria:
- FDR adjusted p-value ≤ 0.05
- $|\text{fold change}| \geq 1.5$
- genes can be annotated with Ensembl identifiers (version 84 or later)

Gene expression is analysed based on biopsies (curettage and inner fistula orifice) via RNA sequencing; more details on the gene expression analysis can be found in Section 7.3.1.

2.1.3 Secondary endpoints

- Proportion of patients with perianal fistula response at week 12 (defined as closure of at least 50% of external openings, no drainage / discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas)
- Proportion of patients with perianal fistula remission at week 12 (defined as closure of all external openings, no drainage / discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas)
- Proportion of patients with combined perianal fistula remission at week 12 (defined as closure of all external openings, no drainage / discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas, AND absence collections of >2 cm, confirmed by MRI in at least two of three dimensions – blinded and centrally read)

Further details on the planned analyses are given in Section 7.3.

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial is divided into two cohorts.

Screening Cohort
The Screening Cohort is designed as a non-randomized screening cohort in patients with perianal fistulizing CD and will determine, whether identical cytokines and pathomechanisms are active in tissue samples collected from the fistula canal or from the inner orifice of the fistula, where fistula generation starts with the emergence of epithelial-mesenchymal transition (EMT) and tissue invasion.
Based on the outcome of this cohort, feasibility criteria for the Study cohort may have to be amended (via substantial amendment) to exclude patients where for technical reasons a sufficient biopsy of the inner orifice cannot be obtained.

A schematic overview of the trial design is shown in figure 3.1:1

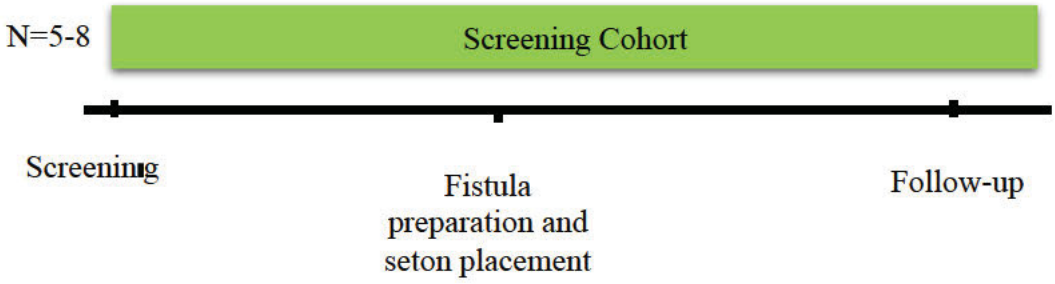


Figure 3.1:1 schematic overview trial design screening cohort

The Screening Cohort will consist of:

- Screening period
- Fistula preparation and seton placement visit
- Follow-up period

Screening period
The screening period will take up to a maximum of 4 weeks.

Fistula preparation visit (FPV)
Approximately 5-8 patients with perianal fistulizing CD and a clinical indication for seton drainage will be included in the Screening Cohort. The final sample size will be driven by the availability of tissue samples not only from curettage but also inner fistula orifice biopsy. Enrolment will be stopped once both tissues have been obtained from at least 5 patients.
The aim of the Screening Cohort is to determine which tissue samples are suitable for analysis of the primary endpoint in Study Cohort, and will thus confirm whether the eligibility criteria for the Study Cohort have to be amended.

The following tissue samples will be collected from all perianal fistulas drained by a seton:

- Biopsy at the inner fistula orifice
- Curettage of the fistula canal
- Biopsy at the outer fistula orifice, if clinically indicated
- Rectal luminal biopsy (endoscopic):
  2 pairs of biopsies: inflamed region and non-inflamed region

Follow-up period:
The follow-up period will take approx. 3 weeks. The patients can be enrolled in other trials of the BI 655130 program and the study cohort of the trial 1368-0008, if they meet the in- and exclusion criteria.

Study Cohort
The Study Cohort is designed as a randomized, double-blind and placebo-controlled, parallel-group phase IIa study of BI 655130, an anti IL-36R antibody, in patients with perianal fistulizing CD.

Once the gene expression analyses from the obtained fistula canal samples in the SCREENING COHORT have confirmed the eligibility criteria, enrolment of the STUDY COHORT will be initiated. Otherwise, the sponsor may decide to amend the study (via substantial amendment) in order to obtain the relevant tissue from all study participants.

A schematic overview of trial design is shown in figure 3.1:2

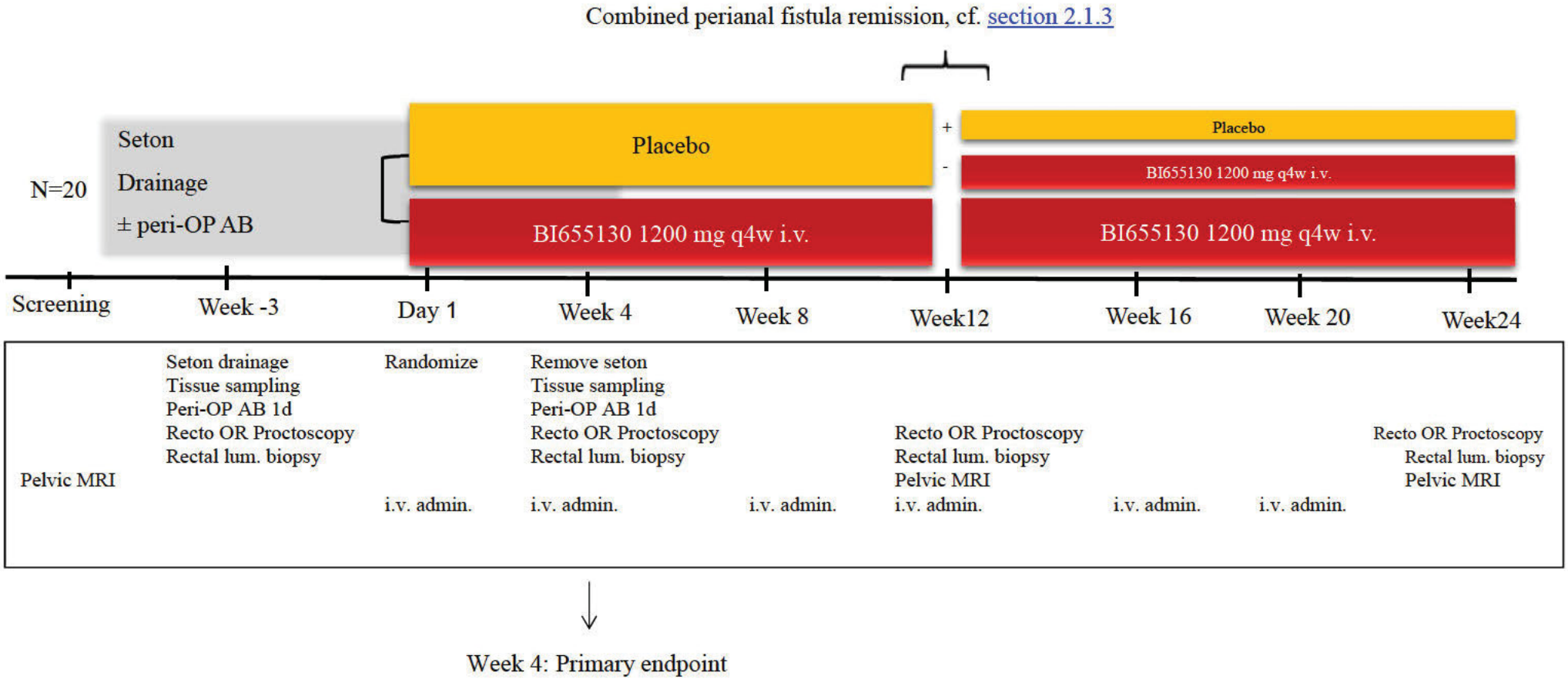


Figure 3.1:2 schematic overview trial design study cohort

Abbreviations figure 3.1:2
Peri-OP AB: perioperative antibiotic
i.v. admin.: i.v. administration

The Study Cohort will consist of:

- screening period, including fistula preparation visits
- period 1: 12-week blinded intravenous therapy period
- period 2: 12-week blinded intravenous therapy period (treatment assignment depends on randomized treatment and achievement of combined perianal fistula remission after treatment period 1)
- Roll over into open label long-term extension study 1368-0007 after EOT (Patients completing week 24 of the study and *having* an individual clinical benefit)
  OR
  12-week safety follow up period for patients not rolling-over into open label long-term extension study 1368-0007 (corresponding to 16 weeks after the last dose of BI 655130)

Screening period, including fistula preparation visit 1c (week -3) and visit 4 (week 4)
The screening period will take up to a maximum of 5 weeks.
During the fistula preparation visit 1c (- 3 weeks), fistula(s) will be drained and a seton will be placed and removed at visit 4.

Based on the outcome of the Screening Cohort (gene expression analysis by RNAseq), it will be decided whether eligibility criteria have to be amended for Study Cohort.

- If only the tissue from the inner orifice but not the fistula canal allows assessing gene expression changes the eligibility criteria for Study Cohort will be amended to require the availability of an inner orifice biopsy during the baseline FPV.
  The following samples will be collected at visit 1c and 4 from all perianal fistulas drained by a seton placed at visit 1c:
  - Biopsy at the inner fistula orifice, *mandatory*
  - Curettage of the fistula canal
  - Biopsy at the outer fistula orifice, if clinically indicated
  - Rectal luminal biopsy (endoscopic):
    2 biopsies: inflamed region and non-inflamed region

- If both tissue sources (inner orifice and fistula canal) allow assessing gene expression changes, the eligibility in study cohort will not need to limit the study population to patients where both tissues are available from the baseline FPV.
  The following samples will be collected at visit 1c and 4 from all perianal fistulas drained by a seton placed at visit 1c:
  - Biopsy at the inner fistula orifice, *optional*
  - Curettage of the fistula canal
  - Biopsy at the outer fistula orifice, if clinically indicated
  - Rectal luminal biopsy (endoscopic):
    2 biopsies: inflamed region and non-inflamed region

Screening Cohort tissue analyses have shown that all tissue sources allow assessing gene expression. However, they have also shown differences in gene expression depending on the tissue location. (inner / outer fistula orifice and curettage). Thus, it has been decided:

1. Not to change the eligibility criteria: No need to limit the study population to patients where both, tissue from the inner orifice and fistula canal, are available
2. To keep the tissue sampling approach as stated in the screening cohort and described below:
   The following samples will be collected at visit 1c and 4 from all perianal fistulas drained by a seton placed at visit 1c:
   - Biopsy at the inner fistula orifice
   - Curettage of the fistula canal
   - [redacted]

Please refer to section 3.3 for inclusion and exclusion criteria.

Period 1 (week 1-8):
Approximately 20 patients with perianal fistulizing CD will be randomized in a ratio 1:1 to one of the following treatment groups:

- Group 1: BI 655130 1200 mg i.v. every 4 weeks (week 0, week 4 and week 8)
- Group 2: Placebo; overall dosing schedule will be the same in all treatment arms in order to keep the blind (see also Section 4.1.5)

At week 12 the patients will be evaluated for combined perianal fistula remission, cf. Section 5.1.

Period 2 (weeks 12 – 24):
Treatment assignment in period 2 will be determined by the achievement of combined perianal fistula remission at week 12 (cf. chapter 5.1).

- Patients *with combined perianal fistula remission* will stay on current drug and will be treated with BI 655130 1200mg i.v. or placebo every 4 weeks (week 12, week 16 and week 20) as shown in figure 3.1:3. Such patients originally assigned to placebo will thus stay on placebo.

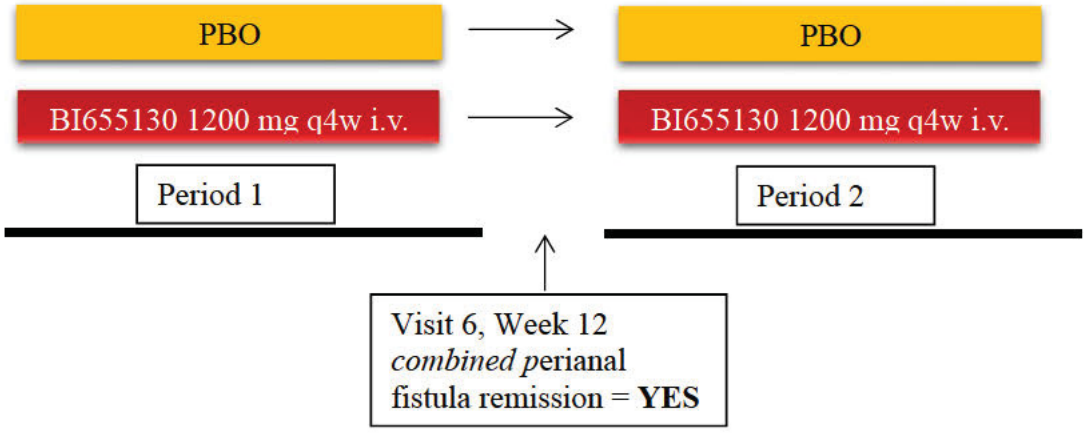


Figure 3.1:3 schematic overview treatment decision responders

- Patients *without combined perianal fistula remission* (irrespective of period 1 treatment) will be treated with BI 655130 1200 mg i.v. every 4 weeks (week 12, week 16 and week 20) as shown in figure 3.1:4. Such patients originally assigned to placebo will thus switch to active drug.

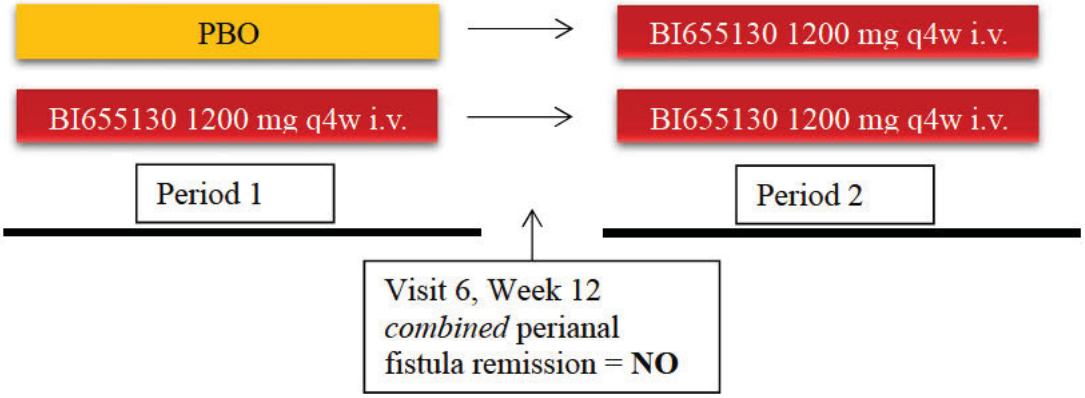


Figure 3.1:4 schematic overview treatment decision non-responders

Follow-up period:
Patients who terminate study drug early or do not enrol into the subsequent long-term extension study 1368-0007, will continue safety follow up until 16 weeks after last study drug

administration. These patients, who drop out of the study, will receive standard of care treatment per investigator´s discretion.
Patients who complete the EOT visit (visit 9, week 24) in period 2 of this study and who have individual clinical benefit may enter the long-term extension study 1368-0007, which offers open label active treatment with subcutaneous BI 655130.

Background therapy for underlying CD with conventional immunosuppressants or anti-TNF α compounds (provided that is allowed (cf. section 4.2.1).

Individual patient participation is concluded when the patient has completed the last planned visit.
The end of the trial is defined as “last patient out”, i.e. last scheduled visit completed by last patient.

An interim analysis of the Study Cohort is planned, please refer to section 7.4

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

Table 3.1:1 Study definitions

Rescue Medication	New or increase in dose of any medication applied to treat new or persisting symptoms related to CD
Disease worsening	Worsening of clinical status or symptoms of CD requiring administration of rescue medication in the investigator`s opinion – in patients without a clinical response

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

This trial is a 2-part exploratory trial. The initial *Screening Cohort* will determine, whether identical pro-inflammatory and pro-fibrotic mediators and pathomechanisms are active in tissue samples collected from the fistula canal (via curettage) or from the inner orifice (via biopsy), where fistula generation is believed to start with the emergence of epithelial-mesenchymal transition (EMT) and tissue invasion. Based on the outcome of this cohort, feasibility criteria for *Study Cohort* may have to be adapted (via substantial amendment) to exclude patients where for technical reasons a sufficient biopsy of the inner orifice cannot be obtained. Patients in the *Screening Cohort* will only receive standard of care (SOC) for their disease, without subsequent randomization to IMP or PBO.
The *Study cohort* is designed as a randomized, double-blind and placebo-controlled phase IIa study. The placebo controlled period 1 of 12 weeks will be followed by additional 12 weeks of blinded treatment with active drug or placebo. Treatment in period 2 will depend on the original treatment group and the achievement of a strict combined fistula remission outcome at week 12: all patients in the original BI 655130 group and non-remitters from the original

placebo group will be treated with BI 655130 from week 12 to 24. Remitters to placebo at week 12, will continue placebo till week 24. The double blinding will be kept by IRT assigning active or placebo based on these decision criteria. The total treatment duration is up to 24 weeks; after that time all patients having derived an individual benefit will be offered to roll-over into a long-term open label extension study (1368-0007).

The double blind and placebo controlled induction period 1 of the *Study Cohort* allows to compare gene and biomarker expression in patients with perianal fistulizing CD under conditions of placebo treatment or IL36R inhibition. The results will be critical to longitudinally characterize the mechanisms of disease involved in the evolution of fistulas, and assess the MoA in the active treatment group. The short period of placebo treatment is justified due to the previous failure of the selected patients to approved standard of care treatments, the subsequent cross-over to double blind treatment with active drug in case there is no perianal fistula remission at week 12, and the expected group benefit for patients with perianal fistulizing CD resulting from an improved understanding of the pathophysiology of this disease and the MoA of a new treatment candidate. The placebo group will also serve as appropriate comparator to investigate clinical effect size and safety/tolerability of BI 655130 in this disease. Placebo patients not achieving a strictly defined combined perianal fistula remission (which is unlikely to occur on PBO) will be switched to active drug.
Patients experiencing disease worsening during the treatment period can be discontinued from treatment at any time at the investigator`s discretion. Responders to induction treatment, in contrast, are expected to benefit from maintenance treatment, e.g. by the achievement of luminal and/or fistula remission or mucosal healing, and by prevention of relapses. All patients completing the 24 weeks course of the study with an individually perceived clinical benefit will be offered to roll-over into an open label long-term study offering continued BI 655130 treatment for up to additional 7 years.

Since a PoC for BI 655130 is not yet available in CD, the chance of an individual benefit for study participants is difficult to estimate, and thus sample size and treatment duration were limited to a minimum and based on practical feasibility to achieve the study objectives.

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 5-8 patients will be enrolled in the Screening Cohort at approximately 3 sites (approx. 2 patients per site).
Approximately 20 patients will be randomised in the Study Cohort at approx. 20 sites (approx. 1 patient per site). A sufficient number of patients will be screened to meet this randomisation target. Screening of patients for this trial is competitive. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Screening of patients for Study Cohort may stay open until approximately 15 patients have valid baseline and post treatment biopsies for primary endpoint analysis.

Participation of Women of childbearing potential (WOCBP): Please refer to section 4.2.2.4 for acceptable methods of birth control.

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 previously treatment-resistant perianal fistulizing CD with clinical indication for seton drainage.

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

3.3.2 Inclusion criteria for Screening Cohort and Study Cohort

Each patient of *Screening Cohort* and *Study Cohort* must meet all of the following inclusion criteria to be included into the trial:

1. 18-75 years at date of signing informed consent
2. Male or female patients. Women of childbearing potential (WOCBP)[1] must be ready and able 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 are provided in section 4.2.2.4 Restrictions regarding women of childbearing potential. Restrictions regarding contraception for female patients are not applicable for Screening Cohort.
3. Diagnosis of clinical Crohn´s Disease ≥ 3 months prior to screening by clinical and endoscopic evidence and corroborated by a histopathology report
4. Has ≥ 1 **perianal active* fistula(s)** with clinical indication for seton drainage (≥ 4 weeks duration before enrolment, as a complication of CD) **.
   * Criteria for Active Fistula: As per clinical evaluation: P*resence of spontaneous drainage or drainage after gentle finger compression at the external openings* **&** as confirmed by radiological (MRI) exploration .

   ** Patients who are screened with a seton drainage in place are eligible provided the drainage has not been in place for > 3 months and the patient meets the rest of the eligibility criteria
5. Additional enterocutaneous or abdominal fistulas are permitted (except rectovaginal fistulas)

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

6. Absent, mild or moderate clinical activity with CDAI ≤ 250. CDAI is not applicable for Screening Cohort.
7. Demonstrated in the past inadequate fistula response or loss of response or have had unacceptable side effects with approved doses of at least one of the following compounds: Immunesuppressive agents (e.g. thiopurines, methotrexate), TNFα antagonists (e.g. infliximab, adalimumab, certolizumab pegol; or respective biosimilars), vedolizumab, ustekinumab, azathioprine and / or antibiotics (cf. section 10.7)
8. Patients with family history of colorectal cancer or personal history of increased colorectal cancer risk must have had a negative ileocolorectal cancer screening within <1 year prior to screening per local guidance
9. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

3.3.3.1 Screening Cohort

No exclusion criteria are applicable for the *Screening Cohort*.

3.3.3.2 Study Cohort

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

3.3.3.2.1 Gastrointestinal Exclusion Criteria

1. Complications of Crohn's Disease such as symptomatic strictures, functional stenosis distal from fistula(s), short gut syndrome, or any other manifestation that might require surgery, could preclude the use of the PDAI and CDAI to assess response to therapy, or would possibly confound the evaluation of benefit from treatment with BI 655130
2. Rectovaginal fistulas
3. Anticipated to require surgical intervention for CD including any fistula surgical procedures (except seton drainage). See Table 4.2.2.2:1 for a detailed list of restricted interventions
4. Has an abscess that the investigator feels requires drainage beyond fistula drainage with a seton (based on either clinical assessment or MRI)
5. Any kind of bowel resection or diversion within 6 months or any other intraabdominal surgery within 3 months prior to screening.
6. Ileostomy, colostomy or known fixed symptomatic stenosis of the intestine at screening.
7. Positive stool examinations for C. difficile or other intestinal pathogens < 30 days prior to screening
8. Evidence of colonic mucosal dysplasia or colonic adenomas, unless properly removed (properly according to the investigator's assessment)
9. Faecal Microbiota transplant (FMT) within 6 months prior to randomization
10. Treatment with (See table 4.2.2.1:1 for a detailed list of restricted treatments):

- any non-biologic medication (incl. cyclosporine, JAK inhibitors such as tofacitinib, tacrolimus, sirolimus, mycophenolate mofetile, S1P modulators, SMAD7 antisense inhibitors such as mongersen), other than those allowed per chapter 4.2.1 within 30 days prior to randomisation unless these patients show an undetectable plasma concentration
- any biologic treatment approved for CD other than anti-TNFα inhibitors within 8 weeks prior to randomization unless these patients show an undetectable plasma concentration
- any investigational or non-approved biologic for CD (including but not limited to IL-23 inhibitors) within 12 weeks prior to randomisation or etrolizumab within 8 weeks prior to randomization unless these patients show an undetectable plasma concentration
- rectal 5-ASA, rectal Tacrolimus, parenteral or rectal corticosteroids (incl. budesonide) within 2 weeks prior to randomisation
- any antibiotics within 1 week prior to randomisation
- any prior autologous or allogeneic, haematopoietic (HSC) or mesenchymal stem cell (MSC) therapy any prior exposure to BI 655130
- any chronic use of NSAID within 2 weeks prior to randomisation (occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc., and daily use of baby or low dose (81-162.5mg) aspirin for cardiovascular prophylaxis are permitted)
- any life-attenuated vaccines within 6 weeks prior to randomization

3.3.3.2.2 Infectious Disease Exclusion Criteria

11. Increased risk of infectious complications (e.g. due to past organ or stem cell transplantation)
12. Live or attenuated vaccination within 6 weeks prior to randomization
13. Patients with a positive QuantiFERON TB test during screening are excluded, unless:
    - Patient had previous diagnosis of active or latent TB and has completed appropriate treatment per local practice/guidelines within the last 3 years and at least 6 months before first administration of trial medication under this protocol (patients may be re-screened once to meet this criterion)
    - Patients with suspected false positive or indeterminate QuantiFERON TB result may be re-tested once
    - If Quantiferon not available or providing indeterminate results after repeat testing : A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent)
14. Relevant chronic or acute infections including active tuberculosis, human immunodeficiency virus (HIV) infection or viral hepatitis. A patient can be re-screened if the patient was treated and is cured from the acute infection.

3.3.3.2.3 General Exclusion Criteria

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

16. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned during study conduct, e.g. hip replacement.
17. Pathological safety lab parameters: haemoglobin < 8 g/dL, total white blood count (WBC) < 3000 cells/µl, neutrophils < 1000 cells/µl, thrombocytes < 100.000/µl, creatinine ≥ 2 mg/dL, total bilirubin > 2 x ULN with ratio of direct/indirect >1 (patients with Gilbert's syndrome are not excluded), Alkaline Phosphatase >3 x ULN.
18. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
19. Previous enrolment in this trial (exception: patients of screening cohort may be enrolled in study cohort)
20. Currently enrolled in another investigational device or drug trial. Specific restrictions for patients who have participated recently in another drug trial are listed in section 4.2.2
21. Women who are pregnant, nursing, or who plan to become pregnant in the trial
22. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than crohn´s disease, surgical procedure, medical examination finding (including vital signs and electrocardiogram (ECG)), or laboratory value at the screening visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data
23. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients or to contrast media.

3.3.4 Withdrawal of patients from therapy or assessments

Patients may discontinue trial treatment (not applicable for Screening Cohort) or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.
Every effort should be made to keep the patients in the trial: if possible on treatment (not applicable for Screening Cohort), or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment (not applicable for Screening Cohort) or withdraw consent to trial participation and the reason must be documented in the patient files and CRF.
If the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

3.3.4.1 Discontinuation of trial treatment

Not applicable for *Screening Cohort*. Applicable for *Study Cohort*, only.

An individual patient will discontinue trial treatment if:
- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The investigator clinical judgement advises for it.

- 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 adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment. Please refer to the section 4.2.2 for restricted medications.
- The patient needs surgical interventions for CD including any fistula surgical procedures (except seton drainage, see section 4.2.2.2)
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- For individual stopping rules related to specific adverse events, please see section 4.2.1

In case of a temporary reason, trial treatment should be restarted if medically justified, please see section 4.1.4.

Even if the trial treatment is discontinued, the patient remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart B and C and section 6.2.2.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation (not applicable for Screening Cohort) and withdrawal of consent to trial participation, as well as explain the options for continued follow up after trial treatment discontinuation, please see section 3.3.4.1 above.

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

Patients in *Screening Cohort* will not be treated with trial medication. For this reason, the chapter 4.1 is not applicable for *Screening Cohort*.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Description of test product BI 655130 i.v.

Substance:	BI 655130
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	60mg/ml
Posology	Study Cohort: 1200mg every 4 week • Period 1: at week 0, 4, 8 • Period 2: at week 12, 16, 20
Route of administration:	Intravenous (i.v.)
Duration of use	24 weeks

Table 4.1.1: 2 Description of test product placebo matching to BI 655130 i.v.

Substance:	Placebo matching to BI 655130
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable

Table 4.1.1: 2 Description of test product placebo matching to BI 655130 i.v. cont.

Posology	Study Cohort: 0 mg (placebo) every 4 week • Period 1: at week 0, 4, 8 • Period 2: at week 12, 16, 20
Route of administration:	Intravenous (i.v.)
Duration of use	24 weeks

4.1.2 Selection of doses in the trial

The aim of this small exploratory study is to provide the highest likelihood to study the mechanism of BI 655130 in CD [redacted] Based on other effective anti-cytokine drugs in IBD and pre-clinical assays for IL-36 inhibition, a monotonic rather than a bell-shaped dose-response curve is expected. Thus, the highest tolerated dose (1200 mg i.v. q4w) should provide the highest likelihood to achieve this objective. This dose is also expected to provide the best chance to induce clinical remissions in CD patients. Whether lower doses will be sufficient to achieve maximum efficacy will be subject of subsequent studies. This dose regimen is the highest covered by current healthy volunteer PK and safety data for individuals.
Currently approved or investigational biologics (e.g. TNFi, vedolizumab, ustekinumab) have established 4-8 weeks duration of induction treatment in CD; a longer induction period of 12 weeks (patients on placebo in period 1) or 24 weeks (patients on BI 655130 in period 1) was selected to allow assessment of the response kinetics for BI 655130, which represents a new and clinically non-validated MoA.
The dosing interval of once every 4 weeks is supported by the long half-life of BI 655130.

4.1.3 Method of assigning patients to treatment groups

Study Cohort, Period 1: Double blind
During visit 2 eligible patients in Study Cohort will be randomised to receive 12 weeks of treatment (i.e. three administrations) with BI 655130 1200mg i.v. every 4 weeks or matching placebo in a 1:1 ratio according to a randomization plan. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).
Study Cohort, Period 2: Double blind
Treatment in period 2 starting in visit 6 (BI 655130 1200mg i.v. every 4 weeks or placebo) will be determined by the outcome at week 12 (cf. section 3.1). The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

Details regarding the use of the IRT are described in the site-user manual available in the ISF.

4.1.4 Drug assignment and administration of doses for each patient

Patients in Study Cohort will be treated with BI 655130 as indicated in the Flow Chart and section 3.1.

The medication will be assigned via IRT for period 1 and 2.

Detailed instructions for the preparation of the solution for infusion, the volume to be administered and the infusion rate (BI 655130 i.v.) are provided in the ISF.

The administration of the trial medication 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 so-called 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.

During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may discuss with BI to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations.

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, including but not limited to slowing down the infusion rate, interrupting the infusion and - provided no further safety concern exist - restarting at a slower rate. Further, based on [redacted] medical judgment he/she will provide medications such as steroids, etc., as needed (cf. section 4.2.1 for handling of infusion reactions). Detailed instructions for handling of infusion reactions are also provided in the ISF.

Dose modifications or adjustments are not permitted. In exceptional cases of missed or delayed visits, study drug of the following visit should not be administered within 14 days of the prior dose. 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

Study Cohort, Period 1 and 2: Double blind
Patients and investigators (including the research staff at the trial site) will remain blinded with regard to the randomized treatment assignments until the final database lock for the final trial analysis.
The interim analysis, which is the primary analysis of the trial will be performed once all randomized patients have completed through 12 weeks of trial treatment. At this time, a preliminary database lock will be done and treatment will be unblinded. In order to confirm the integrity of the treatment blind while the trial continues through to completion, a logistics plan will be developed to describe the mechanisms that are to be put in place to assure that

the patients and investigators remain blinded to both individual patient data, as well to the primary analysis results. The blind status of trial and project team members at this time will also be clarified. The logistics plan will be finalized prior to the treatment unblind for the primary analysis.

The randomization code will be kept secret by Clinical Trial Support and will not be accessible prior to the preliminary database lock for the interim analysis by anyone else involved in the trial with two exceptions. The bioanalytical laboratory will receive the randomization code during the trial conduct in order to avoid testing of placebo patient samples for PK and ADA. The bioanalytical laboratory can be regarded as totally independent from the trial team. After the last patient completes the Week 12 visit the random plan will be released to the bioinformatics group. The bioinformatics group will receive the randomisation code in order to start with the pre-processing of gene expression data (using limma packages).
Bioinformatics groups and the analytical laboratory will not disclose the randomization code until the trial is officially unblinded.

A fully external DMC will perform an un-blinded safety and efficacy assessment at specified intervals in order to ensure that patients are protected from potential harm, please refer to Section 7.4 for further details.

4.1.5.2 Unblinding and breaking the code

Study Cohort, Period 1 and 2:
Emergency unblinding will be available to the investigator / pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI' s Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

Treatment unblinding will be performed prior to each DMC meeting as a prerequisite for generation of the applicable DMC summaries required.

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 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.

IMP will only be prepared for infusion just prior to the administration.

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,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators 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

Section 4.2.1 is applicable for the *Study Cohort* and not for the *Screening Cohort*.

Patients in this trial may be on conventional **immunosuppressants** or anti-TNFα biologic treatment for CD.**These** may consist of one or more of the following drugs (cf. Section 4.2.2.1 for restrictions), which are therefore permitted concomitant medications:

- Oral 5-ASA compounds, provided that dose has been stable for ≥ 2 weeks prior to randomisation, and/or
- Oral corticosteroids (≤ 20 mg per day of prednisone or equivalent), provided that dose has been stable for ≥ 2 weeks prior to randomisation, and/or
- Oral budesonide (≤ 9 mg per day), provided that dose has been stable for ≥ 2 weeks prior to randomisation, and/or
- Azathioprine, 6-MP, 6-TG or methotrexate, provided that dose has been stable for ≥ 8 weeks prior to randomisation
- Approved anti-TNFα (e.g. infliximab, adalimumab, certolizumab pegol; or respective biosimilars) provided that
    i. dose has been stable for at least 6 months prior to screening and
    ii. Rest of eligibility criteria are met (i.e activity of the fistula based on clinical and MRI assessment at screening, see inclusion criterion 4).
- Probiotics (e.g. S. boulardii) provided that dose has been stable for ≥ 4 weeks prior to randomisation
- Regular use of anti-diarrheals

Dose has to be stable throughout the trial. The only exceptions are anti-diarrheals, which may be adjusted to current symptoms, and steroid *reduction,* which is allowed after week 12 to a minimum dose of 10 mg/d (budesonide: 6 mg/d) according to local standard of care.

Peri-OP antibiotics
Peri-OP antibiotics at the day before until the day after fistula preparation visits (visit 1c and 4) are allowed if required according to standard of care.

In the event that a patient experiences a disease worsening of CD, as deemed by the investigator, during the course of the trial, the decision whether or not to discontinue treatment and start rescue treatment should be taken in the discretion of the investigator and in discussion with the CTM. Rescue treatment may be any new medication for treatment of CD or any increase in dose of a baseline CD medication.

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation (cf. Section 3.3) are permissible. All concomitant medications should be carefully evaluated by the investigator and the CTM should be contacted when there are questions regarding concomitant medications.

For further information regarding concomitant therapies and restrictions, see table 4.2.2.1:1.

Details of all concomitant medication will be recorded in the eCRF, along with the main reason for prescription. In addition, all prior treatment for CD at Visit 1a will be recorded including information on reason for discontinuation.

Management of Adverse Events:

Infusion reactions including anaphylactic reaction

- In case of infusion reactions including anaphylactic reaction emerging during or after infusion of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to
- Immediately interrupt the infusion
- Treat with systemic anti-histamines, 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 (ISF). Consider also the evaluation of histamine, serum tryptase, and complement components.

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

In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.8 R11-4890) suspected to be caused by the trial medication, the investigator should discontinue treatment with trial medication permanently.

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.

Severe infections (according to RCTC grading in Appendix 10.9), serious infections, opportunistic or mycobacterium tuberculosis infections

- 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 has resolved. Treatment with trial medication may be restarted when the patient has recovered according to investigator's assessment.

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 trial medication. Diagnostics and treatment have to be initiated according to local standard of care.

4.2.2 Restrictions

Section 4.2.2 is applicable for the *Study Cohort* and not for the *Screening Cohort*.

4.2.2.1 Restrictions regarding concomitant treatment

Restrictions regarding previous and concomitant treatment are summarized in table 4.2.2.1: 1

Table 4.2.2.1:1 Restrictions regarding previous and concomitant treatment

Medication or class of medications	**Restriction**
Any non-biologic medication (incl. cyclosporine, JAK inhibitors such as tofacitinib, tacrolimus, sirolimus, mycophenolate mofetile, S1P modulators, SMAD7 antisense inhibitors such as mongersen), other than those allowed per chapter 4.2.1	Not allowed from 30 days prior to randomisation , unless undetectable plasma concentration, until end of the trial For use as rescue medication, refer to Section 4.2.1.
Any biologic treatment *approved for CD other than anti-TNF α* (vedolizumab or ustekinumab)	Not allowed from 8 weeks prior to randomisation, unless undetectable plasma concentration, until end of the trial For use as rescue medication, refer to Section 4.2.1. Pre-requisites for anti-TNF α treatment, please refer to Section 4.2.1.

Table 4.2.2.1:1 Restrictions regarding previous and concomitant treatment (cont.)

Any *investigational or non-approved* biologic for CD (incl. but not limited to IL-23 inhibitors, etrolizumab)	Not allowed from 12 weeks prior to randomisation, unless these patients show an undetectable plasma concentration, until end of the trial. Etrolizumab: Not allowed from 8 weeks prior to randomisation, unless undetectable plasma concentration, until end of the trial. For use as rescue medication, refer to Section 4.2.1.
Any immunomodulator allowed per chapter 4.2.1 (azathioprine, 6-mercaptopurine, 6-TG or methotrexate)	Only allowed during the trial, if dose is stable for at least 8 weeks prior to randomisation until end of the trial For use as rescue medication, refer to Section 4.2.1.
Autologous or allogeneic, haematopoietic (HSC) or mesenchymal stem cell (MSC) therapy	Any prior exposure is not allowed
Faecal Microbiota transplant (FMT)	Not allowed from 6 months prior to randomization until the end of the trial
BI 655130	Any prior exposure is prohibited
5-ASA	*Oral administration:* Only allowed during the trial, if dose is stable for at least 2 weeks prior to randomisation until end of the trial *Rectal route of administration (5-ASA):* Not allowed from 2 weeks prior to randomisation up to end of the trial For use as rescue medication, refer to Section 4.2.1.

Table 4.2.2.1:1 Restrictions regarding previous and concomitant treatment (cont.)

Rectal Tacrolimus	Not allowed from 2 weeks prior to randomisation up to end of the trial
Corticosteroids (incl. budesonide)	*Oral administration:* Oral budesonide only allowed at a dose of ≤ 9 mg per day, and with stable dose for at least 2 weeks prior to randomisation and throughout the trial. Oral steroids only allowed at a dose of ≤ 20 mg per day of prednisone or equivalent and with stable dose for at least 2 weeks prior to randomisation and throughout the trial. *Note:* Steroids may be reduced after week 12 to a min. dose of 10mg/d (budesonide: 6 mg/d) – see section 4.2.1. *Parenteral administration:* Not allowed from 2 weeks prior to randomisation up to end of the trial. Note: parenteral steroids dosed for less than 24 hours as treatment of infusion or anaphylactic reactions are permitted. *Rectal administration:* Not allowed from 2 weeks prior to randomisation up to end of the trial For use of steroids as rescue medication, refer to Section 4.2.1.
NSAID	Chronic use not allowed from 2 weeks prior to randomisation up to end of the trial (Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc., and daily use of baby or low dose (81-162.5mg) aspirin for cardiovascular prophylaxis are permitted.)
Life-attenuated vaccines	Not allowed from 6 weeks prior to randomisation up to end of the trial

Table 4.2.2.1:1 Restrictions regarding previous and concomitant treatment (cont.)

Probiotics (e.g. S. boulardii)	Probiotics only allowed if dose is stable for at least 4 weeks prior to randomization until end of the trial
Antibiotics for IBD	Not allowed from 1 week prior to randomisation up to end of the trial. Peri-OP antibiotics at the day before until the day after fistula preparation visits (visit 1c and 4) are allowed if required according to standard of care.
Anti-diarrheals	No restrictions

4.2.2.2 Restricted fistula interventions

Surgical interventions for CD are not allowed during the trial.
Any surgical intervention or procedure for perianal and enterocutaneous fistulas (except seton drainage) are also not allowed (patient shall be discontinued) since they would interfere with the clinical endpoints of the trial. These are summarized in table 4.2.2.2:1. (no exhaustive list).

Table 4.2.2.2:1 Restrictions regarding procedures for perianal and enterocutaneous fistulas

Procedure for perianal and enterocutaneous fistulas	**Restriction**
- Cutting of fistulas - Shortening of fistulas - Splitting of fistulas - Fibrin glue	Not allowed from start of screening (screening visit 1a) until end of the trial

4.2.2.3 Restrictions on diet and life style

No specific restrictions on diet or life style of the patients are required.

4.2.2.4 Restrictions regarding women of childbearing potential

Female patients of child bearing potential must maintain adequate contraception throughout the course of the trial and up to 16 weeks after the last study drug administration.

Women of childbearing potential must use highly effective contraception methods described below:

- Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation.
- Progestogen-only hormonal birth control associated with inhibition of ovulation.
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS).
- Bilateral Tubal occlusion (blocking of the fallopian tubes).

- Vasectomy of sexual partner (proven effective by absence of sperm on the ejaculation).
- Complete sexual abstinence (not to have male-female vaginal sex)*.

*Refraining from heterosexual intercourse during the entire trial. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient

As monoclonal antibodies can be secreted in milk, women should refrain from breastfeeding once they receive the study drug and up to 16 weeks after, i.e. until BI 655130 is eliminated. They can start nursing again after this period.

4.3 TREATMENT COMPLIANCE

Study medication will be administered in accordance with the protocol by authorised study personnel (e.g. study nurse).

[redacted]

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Screening Cohort

[redacted]

5.1.2 Study Cohort

Perianal fistula activity

The Perianal fistula activity will be evaluated using the following definitions:

- *Perianal fistula remission*
  A *perianal* fistula remission is defined as closure of all external openings, no drainage / discharge despite gentle finger compression of fistulas, that were draining at baseline and without new emerging fistulas as assessed by physical examination by investigator(s) on site
- *Perianal fistula response*
  A *perianal* fistula response is defined as closure at least 50% of external openings, no drainage / discharge despite gentle finger compression of fistulas, that were draining at baseline and without new emerging fistulas as assessed by physical examination by investigator(s) on site
- *Combined perianal fistula remission:*
  The achievement o*f combined perianal* fistula remission drives the decision for treatment allocation at the start of period 2.
  A *combined perianal* fistula remission is defined as closure of all external openings, no drainage / discharge despite gentle finger compression of fistulas, that were draining at baseline and without new emerging fistulas, AND absence of collections >2 cm, confirmed by MRI in at least two of three dimensions – blinded and centrally read.
  The treatment allocation decision from Week 12 onwards is based on physical examination performed by investigator(s) on site and MRI reading (no central reading needed for treatment allocation decision at week 12, central reading will be mandatory only for efficacy assessment purposes) .

Fistula Preparation Visit (FPV)

The FPV with examination of anus and rectum using the endoscope as well as examination and drainage of fistula via curettage (if required) may need to be done in anesthesia or narcosis at the investigator`s discretion according to local standard of care.
Tissue will be taken from all perianal fistulas drained by a seton placed at visit 1c (cf. section 3.1).

[redacted]

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Physical examination
- Vital signs
- Clinical laboratory values (haematology, clinical chemistry, coagulation and urinalysis), not applicable for Screening Cohort
- 12-lead ECG, not applicable for Screening Cohort
- Adverse events
- Serious adverse events (SAEs)
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to ISF for details)

5.2.1 Physical examination

A *complete physical examination* will be performed at the time points specified in the flowchart. It includes 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 laboratory abnormalities.

Measurement of height and body weight will be performed at the time points specified in the flowchart.

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, prior to blood sampling.

This includes temperature, pulse rate (electronically or by palpation count for 1 minute), systolic/diastolic blood pressure and respiratory rate in a seated position after at least 5 minutes of rest.

Study Cohort:
At dosing visits vital signs evaluations will be performed *pre-dose* and additional evaluation will be taken at approximately *10 minutes and 1 hour post-dose*.

Monitoring for hypersensitivity reactions:
Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately *2 hours* after the *first dose* administered at visit 2 and *1 hour* following all *other doses* of study drug. Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further infusions might be considered and will be agreed on between investigator and BI clinical monitor.

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

5.2.3 Safety laboratory parameters

The safety laboratory samples will be taken for the *Screening Cohort* according to their local standard of care. No specific parameters are requested.
Section 5.2.3 is applicable for the *Study Cohort*, only.

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1 and 5.2.3:2. For the sampling time points please see the Flow Chart. More frequent blood sampling may be done whenever the investigator deems necessary. Unscheduled safety laboratory examinations will be reported in the CRF along with the results.

All safety laboratory analyses will be performed by a local laboratory.

It is preferred but the patients do not have to be fasted for the blood sampling for the safety laboratory.

It is the responsibility of the investigator to evaluate the laboratory results from the local laboratory.
Clinically relevant abnormal findings as judged by the investigator will be reported as baseline conditions or adverse events (please refer to Section 5.2.6).
A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed 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 Exclusionary testing

Category	**Test name**
Infection testing	Hepatitis B Surface Antigen (qualitative)[1] Hepatitis B core Antibody[1] HBV-DNA (quantitative PCR)[2] Hepatitis C Antibodies (qualitative)[1] HIV-1, and HIV-2 Antibody (qualitative)[1]
TB screening	QuantiFERON®-TB[3, 4]
Serum Pregnancy test (only for female patients of childbearing potential) 1)	Human Serum Chorionic Gonadotropin
Stool studies to evaluate for enteric pathogens 1)	Salmonella Shigella Yersinia Campylobacter E. coli Clostridia difficile toxin Enteric parasites and their ova (including Cryptosporidia)

[1] At screening only (visit 1)
[2] A HBV-DNA should be conducted if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative (definition of occult HBV infection: B core Antibody is positive, Hepatitis B Surface Antigen is negative; HBV DNA detectable).
[3] There is the trial site option to perform a PPD skin test
[4] If the 1st QuantiFERON®-TB test result is undetermined, a re-test should be performed. If the re-test QuantiFERON-TB test result is undetermined, a PPD skin test should be performed.

Table 5.2.3: 2 Laboratory tests

Category	Test name
Haematology	Haematocrit (Hct) Haemoglobin (Hb) Glycosylated Hbc (HbA1c) (only at screening) 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
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) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol

Table 5.2.3: 2 Laboratory tests (cont.)

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 (only at screening)	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)
Infections screening	HBV-DNA (quantitative) at EOT Visit[2]
QuantiFERON-TB test	QuantiFERON®-TB at EOT visit [3, 4]

[1]Only in case of allergic reaction
[2] HBV-DNA in case of occult HBV infection (for definition see Table 5.2.3: 1 footnote 2)
[3] There is the trial site option to perform a PPD skin test
[4] If the 1st QuantiFERON®-TB test result is undetermined, a re-test should be performed. If the QuantiFERON-TB re-test result is undetermined, a PPD skin test should be performed.

5.2.4 Electrocardiogram

12-lead ECGs are performed for the *Screening Cohort* according to their local standard of care. No specific parameters are requested.
Section 5.2.4 is applicable for the *Study Cohort*, only.

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 either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

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 (cf section 3.3.3).

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:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
  or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Planned hospitalizations which may be required for administrative reasons to make the conduct of visits feasible (e.g. fistula preparation visits 1c and 4) need not to be reported as SAEs.
Patients may be hospitalized for administrative reasons during the trial, including hospitalization for respite care. These as well as hospitalizations/surgical procedures which were planned before the patient signed informed consent need not be reported as SAEs if they

have been documented at or before signing of the informed consent and have been performed as planned (the condition requiring hospitalization/surgical procedure has not changed/worsened after signing the informed consent).

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in 5.2.6.2, 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 concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.

The following are considered as AESIs:

- Infusion reactions including anaphylactic reaction (study cohort, only)
    - 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 10.8 R11-4890).
- Severe infections (according to RCTC grading in Appendix 10.9)
- Opportunistic and mycobacterium tuberculosis infections
    - These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leukoencephalopathy, 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 (study cohort, only)
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity (severity) of AEs
The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by [redacted] 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.
Investigator´s causality assessment should be provided as requested on the appropriate CRF(s) and on the SAE form (if applicable).

Arguments that may suggest that there is a reasonable possibility of a causal relationship to drug 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 to drug 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:

For patients *without* roll-over from study cohort to subsequent long-term extension study 1368-0007:

- From signing the informed consent onwards until individual patient's end of trial:
  - all AEs (non-serious and serious) and all AESIs.
- After the individual patient's end of the trial:
  - the investigator does not need to actively monitor the patient for new AEs but should 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 chapter "AE reporting to sponsor and timelines"), but not on the CRF.

For patients *who roll-over* from study cohort to subsequent long-term extension study 1368-0007:

- From signing the informed consent (1368-0008) onwards until the first dose of trial medication in 1368-0007:
  - all AEs (non-serious and serious) and all AESIs.
    (updates to concomitant therapy should also be included until first dose of trial medication in 1368-0007)

AE reporting to sponsor and timelines
The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in sections 5.1 and 5.2.

In the *Screening Cohort* biomarkers from various biopsies including inner fistula orifice, curettage at the fistula canal, outer fistula orifice, and rectal luminal biopsies will be analyzed (cf. Flow Chart A).

For the *Study Cohort* blood samples (serum), [redacted] will be collected at time points indicated in the Flow Chart B and C for the analysis of biomarkers.

All remaining samples will be destroyed no later than one year after end of the trial.

[redacted]

[redacted]

[redacted]

[redacted]

5.6 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements in CD 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

Screening Cohort:
All patients from Screening Cohort are to adhere to the visit schedule as specified in the Flow Chart A. Visit windows are defined in the Flow Chart.

Study Cohort:
All patients from Study Cohort are to adhere to the visit schedule as specified in the Flow Chart B (visit 1 to 5) and Flow Chart C (visit 6 to 10).
Visit windows are defined in the Flow Chart.
Each visit data (with its window) up to EOS is to be counted from Day 1 (Visit 2). If any of these visits has to be rescheduled, the date of subsequent visits should be calculated from the date of visit 2.
Follow-up visit (EOS, visit 10) refers to the last dose administration of BI 655130 at visit 8 (Week 20) and is applicable for patients only who will not join the roll-over long-term extension study 1368-0007.
Regarding instructions for drug administration at missed or delayed visits please refer to Section 4.1.4.

Screening Cohort and Study Cohort:
Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

This trial is devided into two cohorts (cf.section 3.1)

The *Screening Cohort* is designed as a non-randomized screening cohort in patients with perianal fistulizing CD. Based on the outcome of this cohort, feasibility criteria for the Study cohort may have to be amended (via substantial amendment) to exclude patients where for technical reasons a sufficient biopsy of the inner orifice cannot be obtained.
The patients will not be treated with trial medication.

Study Cohort is designed as a randomized, double-blind and placebo-controlled, parallel-group phase IIa study of BI 655130, an anti IL-36R antibody, in patients with perianal fistulizing CD. The double-blind period 1 of 12 weeks (plus 5 weeks screening and fistula preparation) will be followed by a double blind period of 12 weeks treatment.

6.2.1 Screening Cohort

6.2.1.1 Screening visit (visit 1)

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 the patient has consented, the patient is considered to be enrolled in the trial. The patient should be recorded on the subject enrolment log as a screened patient. Patient will be assigned a patient number and enrolment must be recorded in the eCRF page.

The Screening visit (Visit 1) should normally take place not more than 28 days before Visit 2 and be complete 1 day prior to visit 2.
At this visit, information will be collected for evaluation of trial eligibility as indicated in the Flow Chart A.

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 CD) will be reported on the baseline condition eCRF page.

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

Medical and Surgical History
Information on clinically significant previous and concomitant illnesses, other than CD, 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 CD, a detailed history of the disease, including date of diagnosis, disease location, behaviour and severity, surgeries, hospitalizations, and extraintestinal manifestations will be collected.
Also, previous and concomitant treatment for CD will be recorded.

Physical examination and vital signs
Please refer to section 5.2.1 and 5.2.2.

[redacted]

Safety laboratory
Safety laboratory for patients in the Screening Cohort will be done according to their local standard of care. No specific parameters are requested.

If the time window for Visit 1 is other than is specified in the Flow Chart, this should be agreed at the discretion of the PI, in alignment with the trial monitor on a case by case basis. Re-screening will be allowed.

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

6.2.1.2 Fistula preparation and seton placement visit (Visit 2)

The Visit 2 should normally take place at day 1.

Rectoscopy / Proctoscopy
A rectoscopy and proctoscopy will be performed according to standard of care at this visit.

Biopsies
During the fistula preparation visit 2, fistula(s) will be drained and a seton will be placed.

The following tissue samples will be collected from all perianal fistulas drained by a seton:

- Biopsy at the inner fistula orifice
- Curettage of the fistula canal
- Biopsy at the outer fistula orifice, if clinically indicated
- Rectal luminal biopsy (endoscopic)
  2 pairs of biopsies: inflamed region and non-inflamed region

Approximately 5-8 patients with perianal fistulizing CD and a clinical indication for seton drainage will be included in the Screening Cohort. The final sample size will be driven by the availability of tissue samples not only from curettage but also inner fistula orifice biopsy. Enrolment will be stopped once both tissues have been obtained from at least 5 patients.

Refer to Section 15 of the ISF for details.

Physical examination and vital signs
Please refer to section 5.2.1 and 5.2.2.

Safety laboratory
Safety laboratory for patients in the Screening Cohort will be done according to their local standard of care. No specific parameters are requested.

For a detailed description of the trial procedures at Visit 2, please refer to the Flow Chart A.

6.2.1.3 Follow up period (Visit 3)

The Visit 3 should normally take place at day 21 (± 7 days)

Physical examination and vital signs
Please refer to section 5.2.1 and 5.2.2.

[redacted]

Safety laboratory
Safety laboratory for patients in the Screening Cohort will be done according to their local standard of care. No specific parameters are requested.

For a detailed description of the trial procedures at Visit 3, please refer to the Flow Chart A.

Further treatment after the follow-up period of the screening cohort
After the follow-up period of the screening cohort, patients will be treated for their CD at the discretion of the investigator, according to local CD guidelines.

6.2.2 **Study Cohort**

[redacted]

Blood sampling for safety lab
Blood sampling for safety lab should be done prior to study drug infusion and prior to endoscopy , if applicable.
It is preferred but patients do not have to be fasted for the blood sampling for the safety laboratory. Nonetheless,if a patient comes in a non-fasted condition this should be documented.

[redacted] drug infusion.
For further details, please refer to the lab manual (ISF).

Pregnancy testing
Urine pregnancy testing for all women of child-bearing potential will be conducted on-site at screening visit 1a and baseline visit 2 and afterwards approximately every four weeks and must be negative to continue treatment. The pregnancy testing should be done prior to study drug administration, if applicable. A positive urine test must be confirmed with a serum pregnancy test.

6.2.2.1 Screening visits (Visit 1a and Visit 1b)

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 the patient has consented, the patient is considered to be enrolled in the trial. The patient should be recorded on the subject enrolment log and be registered in IRT as a screened patient. Patient will be assigned a patient number and enrolment must be recorded in the eCRF page.

The screening visits 1a and 1b will be scheduled according to Flow Chart B.
At these visits, information will be collected for evaluation of trial eligibility as indicated in the Flow Chart B.

[redacted]

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 CD) will be reported on the baseline condition eCRF page.

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

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

Medical and Surgical History
Information on clinically significant previous and concomitant illnesses, other than CD, 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 CD, a detailed history of the disease, including date of diagnosis, disease location, behaviour and severity, surgeries, hospitalizations, and extraintestinal manifestations will be collected.
Also, previous and concomitant treatment for CD will be recorded.

Physical examination and vital signs
Please refer to section 5.2.1 and 5.2.2.

Imaging: MRI [redacted]
MRI will be performed as described in the Flow Chart B.
Decision on eligibility of patients is based on assessment by investigator(s) on site.
MRI will be read by independent assessor(s) who determine the [redacted]
for efficacy outcome measures purposes, cf. section 5.1.
MRI results to be reviewed PRIOR to surgical procedures at visit 1c.

[redacted]

Blood sampling
Blood samples will be taken for safety laboratory, and infection screening according to Flow Chart B.
For women of childbearing potential, a serum pregnancy test will be performed.
For further details, please refer to the lab manual (ISF).

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

If the time window for Screening Visits 1a and 1b is other than is specified in the Flow Chart, this should be agreed at the discretion of the PI, in alignment with the trial monitor on a case by case basis.
Re-screening will be allowed.

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

6.2.2.2 Fistula preparation visit 1c and visit 4

The Visit 1c should take place 3 weeks (-21 days + 4 days) *prior* to Visit 2.
The visit 4 should take place 4 weeks (29 days ± 4 days) *after* visit 2

In- and Exclusion criteria to be checked prior to performing the surgical visit.

[redacted]

[redacted]

Biopsies

During the fistula preparation visit 1c, the fistula(s) will be drained and a *seton will be placed*.

Based on the outcome of the Screening Cohort (gene expression analysis by RNAseq), it will be decided whether eligibility criteria have to be amended for Study Cohort.

- If only the tissue from the inner orifice but not the fistula canal allows assessing gene expression changes the eligibility criteria for Study Cohort will be amended to require the availability of an inner orifice biopsy during the baseline FPV.
  The following samples will be collected at visit 1c and 4 from all perianal fistulas drained by a seton:
  - Biopsy at the inner fistula orifice, *mandatory*
  - Curettage of the fistula canal
  - [redacted]

- If both tissue sources (inner orifice and fistula canal) allow assessing gene expression changes, the eligibility in study cohort will not need to limit the study population to patients where both tissues are available from the baseline FPV.
  The following samples will be collected at visit 1c and 4 from all perianal fistulas drained by a seton:
  - Biopsy at the inner fistula orifice, *optional*
  - Curettage of the fistula canal
  - [redacted]

Screening Cohort tissue analyses have shown that all tissue sources allow assessing gene expression. However, they have also shown differences in gene expression depending on the tissue location. (inner / outer fistula orifice and curettage). Thus, it has been decided:

1. Not to change the eligibility criteria: No need to limit the study population to patients where both, tissue from the inner orifice and fistula canal, are available
2. To keep the tissue sampling approach as stated in the screening cohort and described below:
   The following samples will be collected at visit 1c and 4 from all perianal fistulas drained by a seton placed at visit 1c:
   - Biopsy at the inner fistula orifice
   - Curettage of the fistula canal
   - [redacted]

- [redacted]

During the fistula preparation visit 4, the *seton will be removed*.

Results from the biopsies at visit 1c and 4 will be used for primary endpoint analysis.

Refer to Section 15 of the ISF for details.

Please refer to section 4.2.2.2 for surgical restrictions.

[redacted]

[redacted]

Physical examination and vital signs
Please refer to section 5.2.1 and 5.2.2.

Blood sampling
Blood samples will be collected according to Flow Chart B. For further details, please refer to the lab manual (ISF).

Stool sampling
Stool samples will be collected according to Flow Chart B. For further details, please refer to the lab manual (ISF).

For a detailed description of the trial procedures at Visits 1c and 4, please refer to the Flow Chart B.

6.2.2.3 Treatment period(s): Visit 2, Visit 3 and Visit 5 to End of Treatment (EoT) Visit

All procedures from visit 2, visit 3 and visit 5 to End of Treatment (EoT) Visit are displayed in this chapter since all visits have nearly the same structure.

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

[redacted]

[redacted]

Imaging: MRI and [redacted]
MRI will be performed as described in the Flow Chart B and Flow Chart C.
Decision on progress of patients is based on assessment by investigator(s) on site.
MRI will be read by independent assessor(s) who determine the [redacted] for efficacy outcome measures purposes, cf. section 5.1.
Visit 6:
MRI to be performed in a time window of 2 weeks PRIOR to visit 6. MRI result to be available at visit 6 for the evaluation of combined perianal fistula remission.
The treatment decision for period 2 is based on the evaluation of combined perianal fistula remission performed by investigator(s) on site (cf. chapter 3.1 and 5.1).

[redacted]

Physical examination and vital signs
Please refer to section 5.2.1 and 5.2.2.

Blood sampling
Blood samples will be collected according to Flow Chart B and C. For further details, please refer to the lab manual (ISF).

Stool sampling
Stool samples will be collected according to Flow Chart B and C. For further details, please refer to the lab manual (ISF).

Roll-over to open label long-term extension study 1368-0007
All patients of study cohort completing week 24 of the study and having an individual clinical benefit may be offered to enter open label long-term extension study 1368-0007, which offers open label active treatment with subcutaneous BI .
Patient information for trial 1368-0007 (for patients to whom the roll-over trial 1368-0007 will be offered) may be performed during visit 8 since visit 9 is coinciding with the first visit for trial 1368-0007 in most cases.

Unscheduled visits
The patient may be called in for additional unscheduled visits due to safety reason at the discretion of the investigator or the sponsor, unless the patient has withdrawn his/her consent.
The patient may also contact the site due to safety reason for an unscheduled visit.

The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the investigator such as laboratory samples, ECGs, or other procedures which were missed at a previous visit.
All unscheduled visits should be described (including the reason for the visit) and documented in the medical/source record, and in the eCRF.

6.2.2.4 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, ie at week 36 for those discontinuing after completing 24 weeks of treatment.

All patients of study cohort completing week 24 of the study and having an individual clinical benefit may be offered to enter open label long-term extension study 1368-0007, which offers open label active treatment with subcutaneous BI 655130. These patients are not requested to complete the follow up visit (V 10). They will have their last study visit at visit V09, probably co-inciding with the first visit in 1368-0007. For AE and concomitant therapy reporting the end of study participation is defined as the day of first administration of study drug in 1368-0007.

Early treatment discontinuation
Patients of study cohort who terminate study drug early should be encouraged to follow all study procedures per the Flow Chart until week 24, but not receive any more study drug at the respective visits. Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.2.3.

Further treatment after the end of the trial
At the end of the trial, patients will be treated for their CD at the discretion of the investigator, according to local CD guidelines.

Trial completion
Trial completion is defined as a patient having reached the EOS visit or day of the first administration of Spesolimab in 1368-0007. EOS visit will be at week 36 (Visit 10) for patients who will not enter subsequent maintenance trial.
Last visit will be at week 24 (Visit 9) for patients rolling-over into subsequent maintenance trial. But individual patient's end of trial is defined as the day of first administration of Spesolimab in 1368-0007.

Regarding instructions for drug administration at missed or delayed visits, please refer to Section 4.1.4.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This section is only applicable for the Study Cohort. Planned analyses for the Screening Cohort will be defined in the TSAP. These will be separate from the analyses for the Study Cohort and will comprise the analysis of disposition, AEs and [redacted].

7.1 STATISTICAL DESIGN - MODEL

The trial objectives and endpoints are stated in section 2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in a confirmatory sense.

The results including confidence intervals and (adjusted) p-values will be discussed and interpreted in the perspective of the exploratory character of the study.

7.3 PLANNED ANALYSES

All individual data will be listed.

The statistical analysis of the Screening Cohort will be based on the following analysis sets:

- Enrolled set (ES – Screening Cohort)
  This patient set includes all patients of the Screening Cohort who signed informed consent.
  It will be used for analyses of patient disposition.
- Entered set (ENTS – Screening Cohort)
  The entered set includes all patients of the Study Cohort who entered the trial.

The statistical analysis of the Study Cohort will be based on the following analysis sets:

- Enrolled set (ES – Study Cohort)
  This patient set includes all patients of the Study Cohort who signed informed consent.
  It will be used for analyses of patient disposition.
- Randomised set (RS): The randomised set includes all randomised patients, whether treated or not.
  Since patients in the Screening Cohort will not be randomised, RS only contains patients of the Study Cohort.
- Safety set (SAF): The safety set includes all patients who were randomised and treated with any amount of study drug. The treatment assignment will be determined based on the actual treatment the patient received.
  Since patients in the Screening Cohort will not be randomised, SAF only contains patients of the Study Cohort.
- Full analysis set (FAS)
  The full analysis set includes all patients of the Study Cohort who provided a baseline value and at least one post-baseline value for at least one secondary endpoint or

further efficacy endpoint. Following the intent-to-treat principle, patients will be analysed according to the treatment they were assigned to at randomisation.

- RNA sequencing set (RSS): This patient set includes all patients in the safety set who provide a valid baseline and at least one valid post-baseline observation for at least one gene expression variable of biopsy. This patient set will be used for analyses related to RNA sequencing.
  By definition of the safety set, RSS only contains patients of the Study Cohort.

In the TSAP, the FAS definition may be updated, and further analysis data sets may be defined.

The following analyses of this trial protocol, in chronological order, are planned:

Week 12 Primary Analysis
The primary analysis of the trial will be performed once all randomised patients have completed the first 12 weeks of the trial, and a preliminary database lock will be done. Details of the analysis to be performed will be described in the TSAP which is planned to be finalized prior to achieving database lock for this primary analysis. Treatment will be unblinded at this time.
For further details regarding the maintenance and protection of the blind through the continuing trial subsequent to performance of the primary analysis, refer to Section 4.1.5.1.

Final Trial Analysis
The final analysis of the trial will be performed once all randomised patients have completed the trial. At this time, the treatment will be officially unblinded.

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol deviations (IPDs) will be identified in an initial version of the TSAP and will be updated no later than in the Report Planning Meeting and will be provided in the final Trial Statistical Analysis Plan (TSAP).

The handling of patients who received a wrong treatment will be described in the TSAP.

7.3.1 Primary endpoint analyses

Primary analysis

The analysis of the gene expression values will be based on the RSS and will be conducted for biopsy location inner orifice and curettage. The analyses will be done by ‘actual treatment’.

All analyses will be performed using the raw read counts for gene expression. This gene expression analysis is conducted for biopsy.

The RNA expression analysis will initially include all genes and all determined read counts. This means, if no gene expression values have to be excluded due to technical or other reasons, there is one read count value per person, per gene and per time point.
To get interpretable results several pre-processing steps are needed to correct e.g. for different sequencing depth. The following steps are conducted:

- Lowly expressed genes are filtered:
    - Genes for which at least 5 samples display a cpm ≥1 are used in the subsequent analyses.
    - normalization factors to scale the samples based on the raw library sizes are calculated using the weighted trimmed mean of M-values (TMM) method using the default parameters of edgeR's calcNormFactors function (R18-2554).

After these pre-processing steps the $\log_2$ counts per million along with associated weights for each observation are then calculated based on the normalized library sizes from the previous step using limma's voom function [R15-5383]. Correlations between paired measurements per patient are estimated by the duplicateCorrelation function. For each gene, a repeated measures linear regression model will be utilized with treatment (BI 655130 or Placebo), visit (baseline, week 4), treatment by visit interaction as fixed effect and patient as a blocking factor. Hereby the weights for each observation are taken into account (13). This will be implemented using the lmFit function of the limma package.
Estimates for the mean $\log_2$ fold change ratio for BI 655130 vs. Placebo at Week 4 will be calculated as

$$\log_2 FC_{BIvsPBO} = (\log_2 BI_{Week\ 4} - \log_2 BI_{BL}) - (\log_2 PBO_{Week\ 4} - \log_2 PBO_{BL}),$$

where baseline is the measurement at Visit V1c.

Changes will be quantified by $\log_2$ fold changes (FC) and associated FDR adjusted p-values. Genes will be considered deregulated if they fulfil the following criteria:

- FDR adjusted p-value ≤ 0.05
- |fold change| ≥ 1.5 (|log2 fold change| ≥ 0.58)
- genes can be annotated with Ensembl identifiers (version 84 or later)

The total number of deregulated genes at Week 4 will be reported.

[redacted]

[redacted]

[redacted]

7.3.2 Secondary endpoint analyses

The analysis of efficacy endpoints will be based on the FAS and will be done by 'planned treatment'.

The secondary efficacy endpoints regarding proportions of patients will be described descriptively. 95% confidence intervals for the rate difference will be provided, if feasible.

7.3.4 Safety analyses

Safety will be assessed based on the assessments listed in Section 5.2. All treated patients (that is, all patients who received at least one dose of study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

The analyses will be done by 'actual treatment'.

Measurements (such as vital signs, or laboratory parameters) or AEs will be assigned to a treatment sequence ('Pbo – Pbo', 'Pbo – BI', 'BI – BI'), based on the treatments the subject

received, and furthermore to a treatment (BI or placebo, see Section 4.1) based on the actual treatment at the recorded time of the measurement or the recorded time of AE onset (concept of treatment emergent AEs).

For assignment based on the actual treatment, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to 'screening'. For subjects who switch treatment during the trial, measurements or AEs starting or worsening between first trial medication intake of the first treatment until first trial medication intake of the second period will be assigned to the first treatment period, while AEs starting or worsening between first trial medication intake of the second period and end of the residual effect period (a period of trial medication intake, see Section 1.2.3) will be assigned to the second treatment period. For subjects who do not switch treatment during the trial, measurements or AEs starting or worsening between first trial medication intake until end of the residual effect period (see Section 1.2.3) will be assigned to the treatment period. Events after the residual effect period will be summarised as 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Please note that AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment emergent'.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals or periods without treatment effects (such as screening).

AEs will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA. In the same way, summaries will be prepared for SAEs and for the frequency of AEs by intensity (according to RCTC).

Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline will be evaluated.

For vital signs, the differences from baseline will be evaluated.

Relevant ECG findings will be reported as AEs.

[redacted]

[redacted]

7.4 INTERIM ANALYSES

The primary analysis of the efficacy and safety data collected up to week 12 will be performed once all randomised patients have completed the first 12 weeks of the treatment period (through visit 6). At that time point, a preliminary database lock will be done. Since the patients will be treated for another 12 weeks, the patients and the investigators (as well as the research staff at the trial site) must remain blinded. A logistics plan will be developed in order to describe the processes to be implemented for protecting the blinding (with regards to the patients and the investigators) and the integrity of the ongoing trial until the final database lock. Details of the analyses to be performed for the primary analysis, as well as for the final analysis after trial completion (through 36 weeks), will be described in the trial statistical analysis plan. Both the TSAP and the logistics plan will be finalized prior to the preliminary database lock for the primary analysis.

The primary analysis and final analysis may be performed as a single analysis (at the time of trial completion), if, prior to the time of the primary analysis, the trial team agrees that the expected time interval between the planned analyses is insufficient to justify the performance of separate analyses.

Further, a fully external DMC will be in place in order to ensure that patients are protected from potential harm, specific tasks are described in Section 8.7.

7.5 HANDLING OF MISSING DATA

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

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

For disease specific [redacted] the following handling of data below or above the limit of quantification will be applied:

- BLQ data will be replaced by 0.5 times the LLOQ
- ALQ data will be replaced by ULOQ, if ULOQs are available. Otherwise, ALQ data will be excluded from the analysis.

7.6 RANDOMISATION

No randomisation is performed in the Screening Cohort.

In the Study Cohort, patients will be randomised in blocks to double-blind treatment. Approximately equal numbers of patients will be randomised to each treatment group using a 1:1 allocation ratio.
BI will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of approximately 5-8 patients in the Screening Cohort and approximately 20 patients in the Study Cohort of this trial. The number of patients is not based on a power calculation but on feasibility, coordinating investigator's experience with regard to recruitment and practical considerations.

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

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).

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains 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 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. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial 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

- 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, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- 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
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

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 'individual patient's end of the trial of the last patient in the whole trial ("Last Patient Out"). The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.
The **"Individual patient´s end of the trial"** is defined as:

- Patients who do *not* roll-over to 1368-0007: Follow up visit 10
- Patients who roll-over to 1368-0007: Day of first administration of Spesolimab in 1368-0007**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 **"Last Patient Completes Week 12"** date is defined as the date on which the last patient in the whole trial attends Visit 6.

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 Data Monitoring Committee (DMC) will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.
The DMC will evaluate safety and efficacy data. The DMC will receive urgent significant safety concerns for immediate evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

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 Clinical Trial Manager (CTM), 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 will be done by BI according to BI SOPs.
Statistical Evaluation will be done by BI or by a Contract Research Organisation (CRO) 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, central reading service for blinded reading of MRI and an IRT vendor will be used in this trial.
Details will be provided in the IRT Manual, MRI Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R00-0812 Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, Hogezand RA van, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, Deventer SJH van
Infliximab for the treatment of fistulas in patients with Crohn's disease.
N Engl J Med 340 (18), 1398 - 1405 (1999)

R04-0551 Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, Deventer SJ van
Infliximab maintenance therapy for fistulizing Crohn's disease.
N Engl J Med 350 (9), 876 - 885 (2004)

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

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)

R13-2231 Baumgart DC, Sandborn WJCrohn's disease.
Lancet 380, 1590 - 1605 (2012)

R13-2232 Latella G, Papi C
Crucial steps in the natural history of infammatory bowel disease.
World J Gastroenterol 18 (29), 3790 - 3799 (2012)

R13-2233 Cosnes J, Gower-Rousseau C, Seksik P, Cortot A
Epidemiology and natural history of inflammatory bowel diseases.
Gastroenterology 140 (6), 1785 - 1794 (2011)

R13-2269 Sandborn WJ
State-of-the-art: immunosuppression and biologic therapy.
Dig Dis 28, 536 - 542 (2010)

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)

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

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

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

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

R15-5253 Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, Rolleri RL, Bortey E, Paterson C, Forbes WP, Levesque BG
[redacted]
Aliment Pharmacol Ther 41, 77 - 86 (2015)

R15-5383 Law CW, Chen Y, Shi W, Smyth G
Voom: precision weights unlock linear model analysis tools for RNA-seq read counts.
Genome Biol 15, R29 (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 [redacted] in inflammatory bowel disease in Germany.
Inflamm Bowel Dis 16 (1), 42 - 51 (2010)

R16-0177 Khanna R, Bouguen G, Feagan BG, D'Haens G, Sandborn WJ, Dubcenco E, Baker KA, Levesque BG
A systematic review of measurement of endoscopic disease activity and mucosal healing in Crohn's disease: recommendations for clinical trial design.
Inflamm Bowel Dis 20 (10), 1850 - 1861 (2014)

R16-0240 Irvine EJ
Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients

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)

R16-1923 Hovde O, Moum BA Epidemiology and clinical course of Crohn's disease: results from observational studies. World J Gastroenterol 18 (15), 1723 - 1731 (2012)

R16-2299 Russell SE, Horan RM, Stefanska AM, Carey A, Leon G, Aguilera M, et al
IL-36alpha expression is elevated in ulcerative colitis and promotes colonic inflammation.
Mucosal Immunol, (2016)

R17-2217 Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al, OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators
Tofacitinib as induction and maintenance therapy for ulcerative colitis.
N Engl J Med 376 (18), 1723 - 1736 (2017)

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.
Am J Gastroenterol 102, 794 - 802 (2007)

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)

R17-2617 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)

R17-3555 Scharl M, Rogler G, Biedermann L
Fistulizing Crohn's disease.
Clin Transl Gastroenterol 8 (7), e106 (2017)

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)

R17-4040 Khanna R, Zou G, Stitt L, Feagan BG, Sandborn WJ, Rutgeerts P, et al
Responsiveness of endoscopic indices of disease activity for Crohn's disease.
Am J Gastroenterol 112, 1584 - 1592 (2017)

R17-4068 Irvine EJ, McMaster IBD Study Group
Usual therapy improves perianal Crohn's disease as measured by a new disease activity index.
J Clin Gastroenterol 20 (1), 27 - 32 (1995)

R17-4073 Samaan MA, Puylaert CAJ, Levesque BG, Zou GY, Stitt L, Taylor SA, et al
The development of a magnetic resonance imaging index for fistulising Crohn's disease.
Aliment Pharmacol Ther 46, 516 - 528 (2017)

R17-4076 Losco A, Vigano C, Conte D, Cesana BM, Basilisco G
Assessing the activity of perianal Crohn's disease: comparison of clinical indices and computer-assisted anal ultrasound.
Inflamm Bowel Dis 15 (5), 742 - 749 (2009)

R17-4245 Walsham NE, Sherwood RA
Fecal calprotectin in inflammatory bowel disease.
Clin Exp Gastroenterol 9, 21 - 29 (2016)

R17-4246 Chang S, Malter L, Hudesman D
Disease monitoring in inflammatory bowel disease.
World J Gastroenterol 21 (40), 11246 - 11259 (2015)

R18-0017 Panes J, Rimola J
Perianal fistulizing Crohn's disease: pathogenesis, diagnosis and therapy.
Nat Rev Gastroenterol Hepatol 14 (11), 652 - 664 (2017)

R18-2555 Panes J, Garcia-Olmo D, Assche G van, Colombel JF, Reinisch W, Baumgart DC, et al, ADMIRE CD Study Group Collaborators
Long-term efficacy and safety of stem cell therapy (Cx601) for complex perianal fistulas in patients with Crohn's disease.
Gastroenterology 154 (5), 1334 - 1342 (2018)

R18-2554 Robinson MD, Oshlack A
A scaling normalization method for differential expression analysis of RNA-seq data.
Genome Biol 11, R25 (2010)

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)

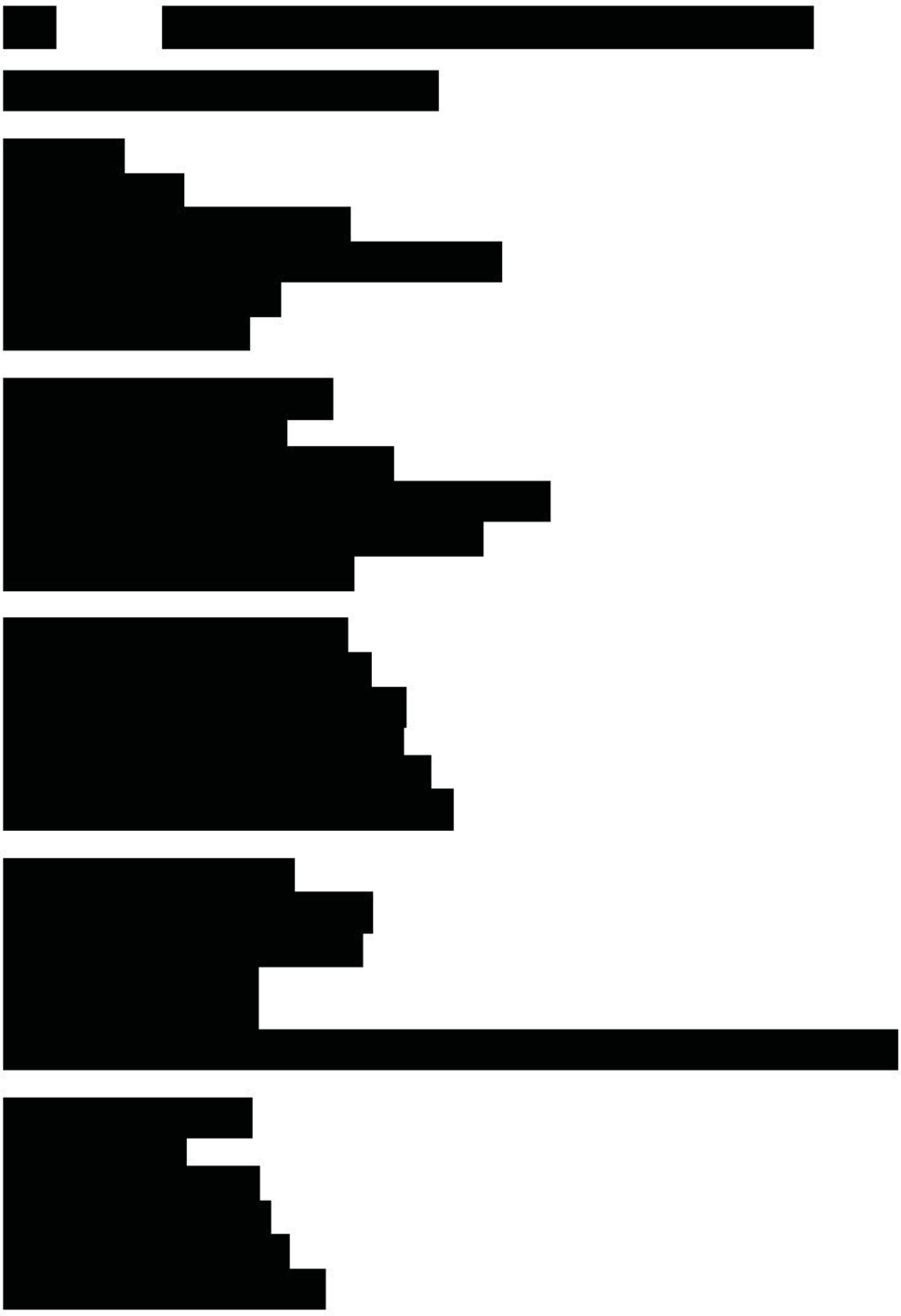
R97-3569 Jain A, Buist NRM, Kennaway NG, Powell BR, Auld PAM, Martensson J
Effect of ascorbate of N-acetylcysteine treatment in a patient with hereditary glutathione synthetase deficiency.
J Pediatr 124, 229 - 233 (1994)

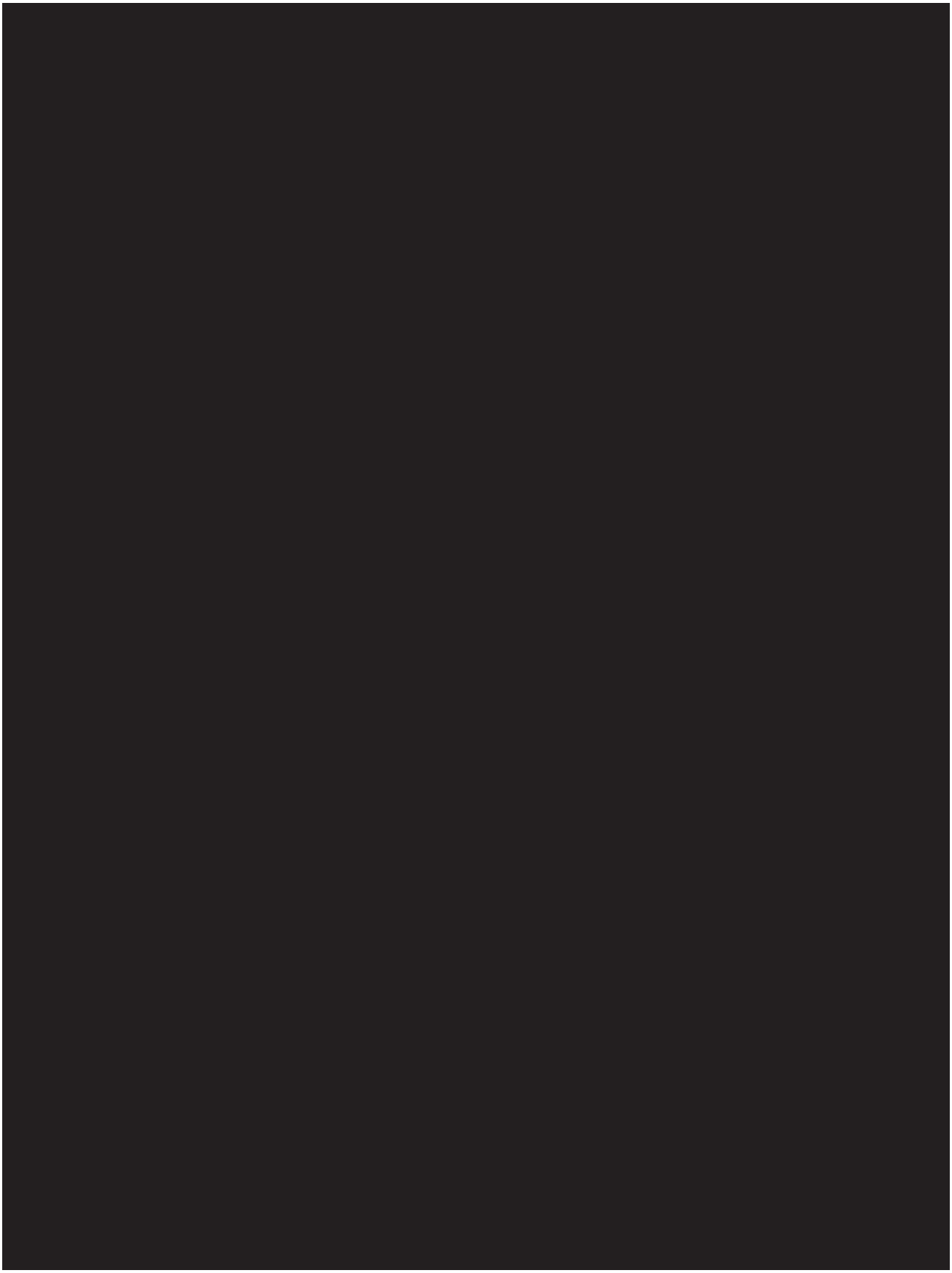
9.2 UNPUBLISHED REFERENCES

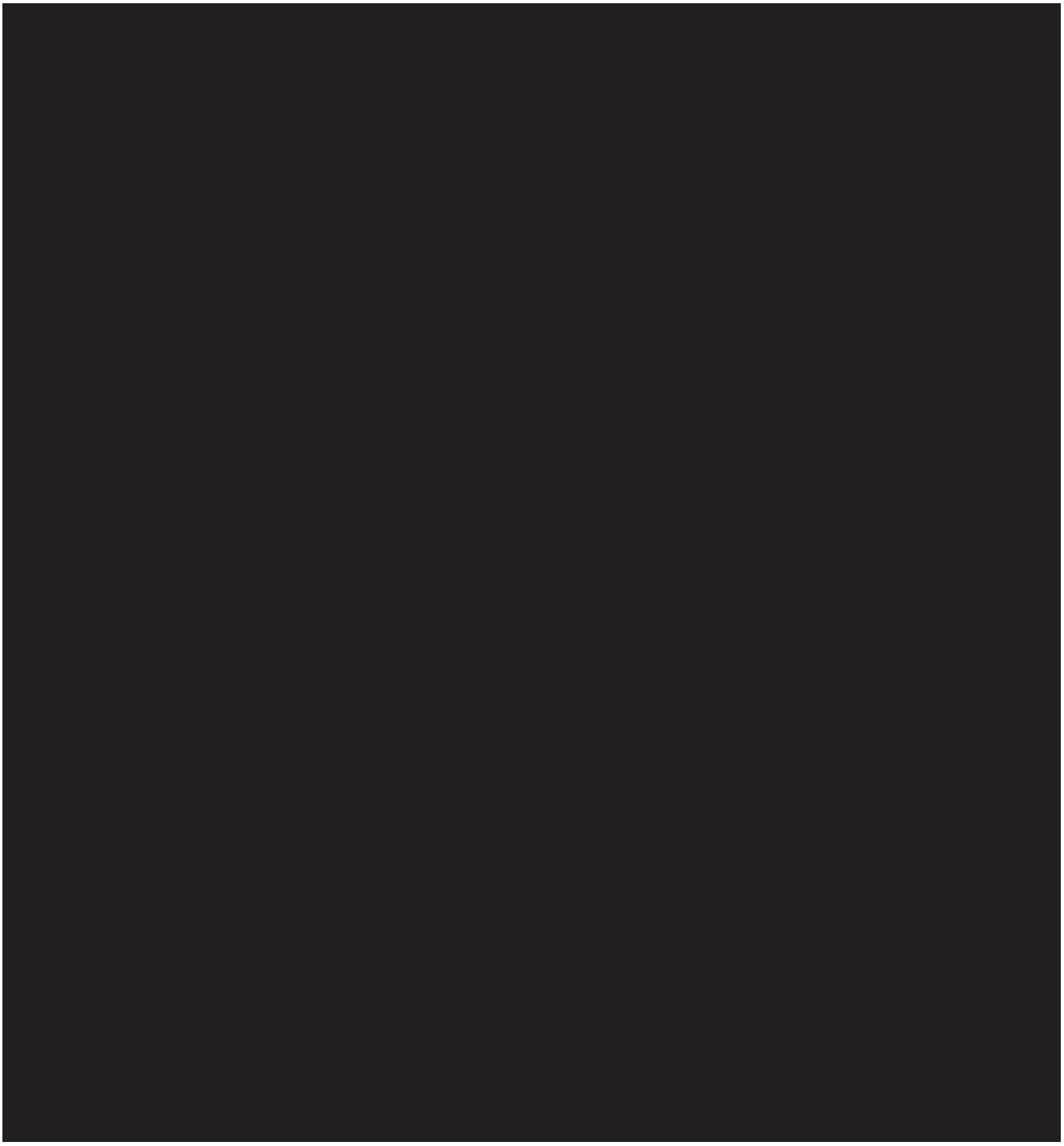
c03320877 IL36R antibody in Ulcerative Colitis, Crohn's Disease, Palmoplantar Pustulosis, Pustular Psoriasis and Atopic Dermatitis

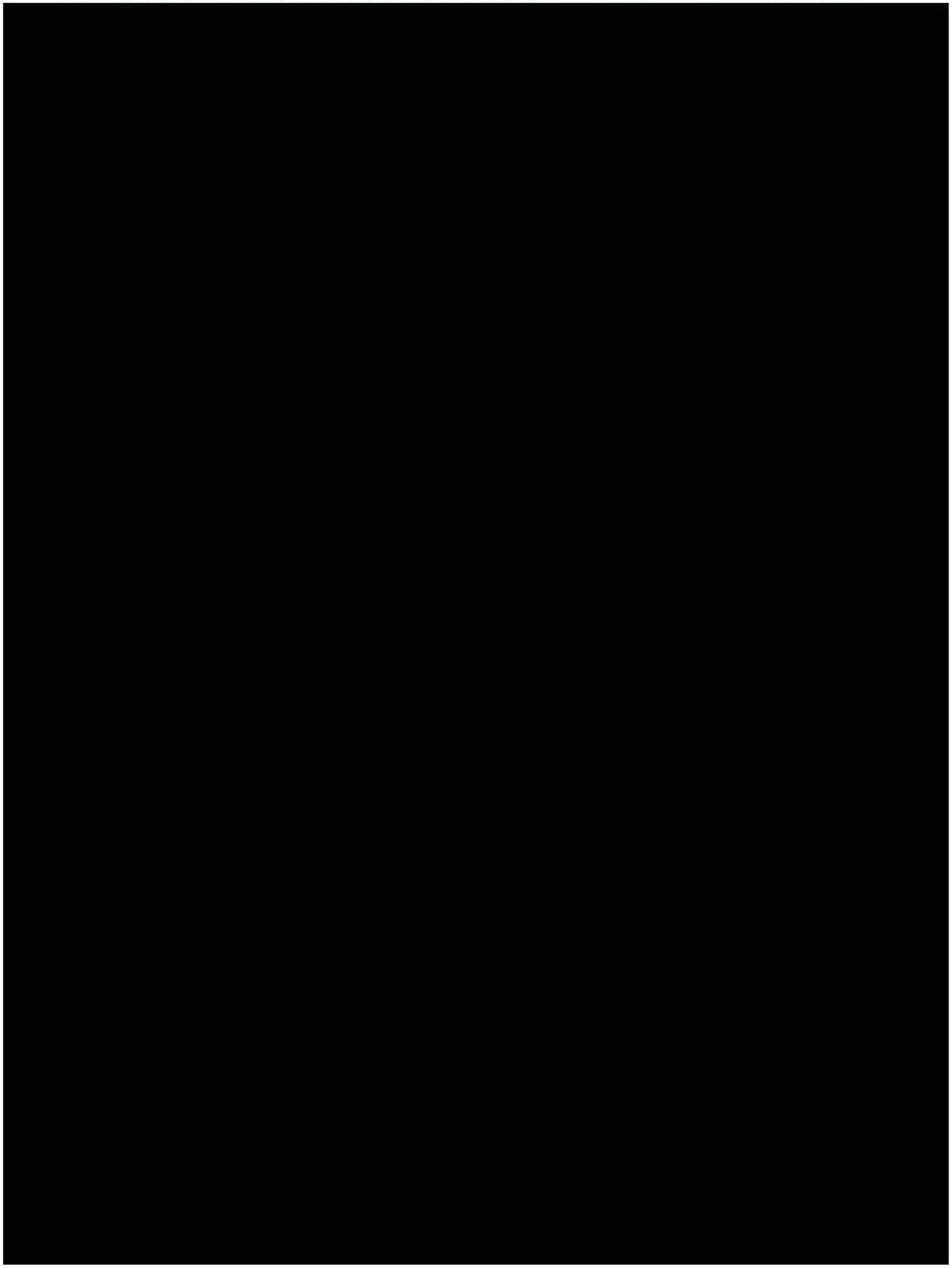
c03361085-07 [redacted] Single-blind, partially randomised, placebo-controlled Phase I study to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising intravenous doses of BI 655130 in healthy male volunteers, 1368.1, 27 Jan 2016.

10. APPENDICES









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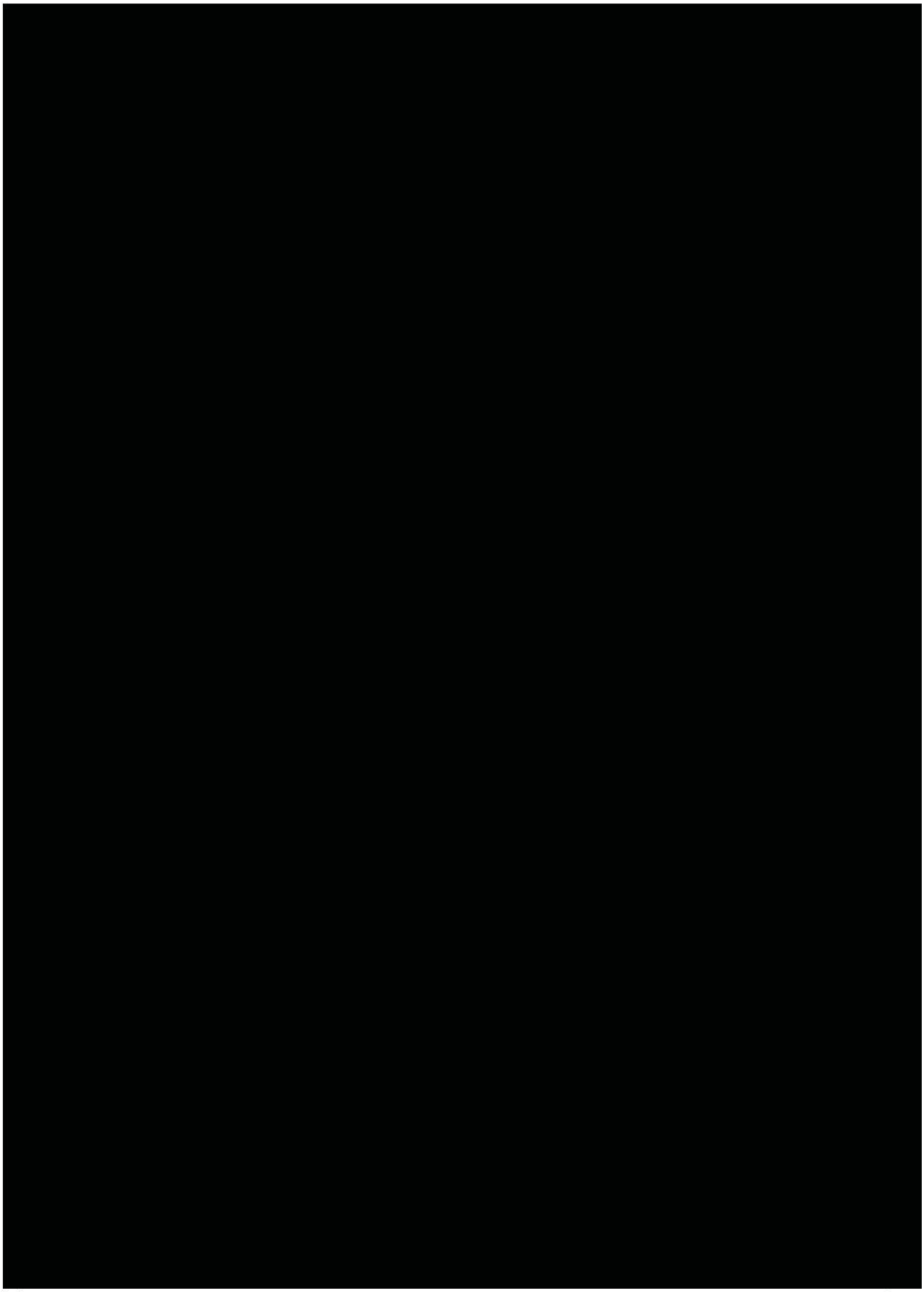

10.5 EQUIVALENT DOSES OF CORTICOSTEROIDS

Table 10.5:1 Equivalent Doses of Corticosterodis

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

[redacted]

[redacted]

10.7 DEFINITION OF PRIMARY, SECONDARY NONRESPONSE OR INTOLERANCE TO PREVIOUS BIOLOGICS THERAPY

The criteria for primary non-response (inadequate initial response), secondary non response (response followed by loss of response), or intolerance to immunesuppressive agents (e.g. thiopurines, methotrexate), TNFα antagonists (e.g. infliximab, adalimumab, certolizumab pegol; or respective biosimilars) and / or vedolizumab and / or ustekinumab and / or azathioprine and / or antibiotics are described below.

I. **Primary nonresponse** (inadequate initial response)

Eligible patients must have received approved doses of at least one of the above immunesuppressive agents, biologics and/or antibiotics for at least 12 weeks

AND

did not respond to this treatment as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of fistulas:

- Lack of improvement or worsening in draining fistulas,
- Recurring drainage from a previously non-draining fistula or development of a new draining fistula.

II. **Secondary nonresponse** (initial response followed by loss of response)

Eligible patients must have received approved doses of at least one of the above immunesuppressive agents, biologics and/or antibiotics for at least 12 weeks,

AND

have responded to this therapy as evidenced by improvement in the number of initially draining fistulas without recurring drainage from a previously non-draining fistula or development of a new draining fistula,

AND

have subsequently developed a recurring drainage from a previously non-draining fistula or developed a new draining fistula during ongoing treatment.

III. **Current or prior intolerance**

Eligible patients must have had an adverse reaction that meets 1 of the following criteria:
1. Significant acute infusion/administration reaction;
2. Significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum-sickness like reaction);
3. Other adverse reaction thought to be related to this drug and leading to its discontinuation.

10.8 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.

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

Excerpt out of the publication, cf. **R13-3515**

	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<24 h 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 autoimmun	Evidence of autoimmune reaction involving a	Reversible autoimmune reaction involving	Causes major organ dysfunction, or progressive, not

	e reaction but patient asymptomatic: all organ function normal and no treatment is required (e.g., vitiligo)	non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g., hypothyroidism)	function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g., transient colitis or anemia)	reversible, or requires long term administration of high dose immunosuppressive therapy
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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		17. September 2019
EudraCT number **EU number**		2017-003090-34
BI Trial number		1368-0008
BI Investigational Product(s)		BI 655130
Title of protocol		Mechanism of Action and Clinical Effect of BI 655130 in Patients with fistulizing Crohn's Disease
Global Amendment due to urgent safety reason		☐
Global Amendment		☒
Section to be changed		Clinical Trial Protocol Synopsis, Section 2
Description of change		Secondary endpoints (changes highlighted in bold): • Proportion of patients with perianal fistula response at week 12 (defined as closure of at least 50% of external openings, no drainage / discharge despite gentle finger compression **of fistulas** that were draining at baseline **and without new emerging fistulas**) • Proportion of patients with perianal fistula remission at week 12 (defined as closure of all external openings, no drainage / discharge despite gentle finger compression **of fistulas** that were draining at baseline **and without new emerging fistulas**) • Proportion of patients with combined perianal fistula remission at week 12 (defined as closure of all external openings, no drainage / discharge despite gentle finger compression **of fistulas** that were draining at baseline **and without new emerging fistulas**, AND absence collections of >2 cm, confirmed by MRI in at least two of three dimensions – blinded and centrally read) Same for further endpoints "perianal fistula response", "perianal fistula remission", and "combined perianal fistula remission" analysed at

		different time points.
Rationale for change		Clarification of definitions “Response”, “Remission” and “Combined Remission” in order to describe that we are evaluating perianal fistulas that were draining at the study entry.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		Flow Chart C
Description of change		Visit window of EOT visit 9 extended to 7 days
Rationale for change		Give more flexibility for scheduling the investigations (i.E. endoscopy and MRI)
Section to be changed		Flow Chart C, Section 3.1, 5.1.2, 6.2.2, 8.7
Description of change		Endoscopy at EOT visit 9: Distinguish between patients who roll-over / do not roll-over to maintenance trial 1368-0007: • Patients who NOT roll-over to long-term extension study 1368-0007: A rectoscopy OR proctoscopy is sufficient and [redacted] by segment will be performed. • Patients who roll-over to long-term extension study 1368-0007 which mandates a full ileocolonoscopy at baseline: Will NOT need to undergo the recto/proctoscopy and instead a full ileocolonoscopy is mandatory and SES-CD will be performed. Ileocolonoscopy images will be centrally read by an external independent assessor(s); management of images will be performed

		by an external vendor.
Rationale for change		Reduce the efforts for the patients. Patients who roll-over to 1368-0007 should not do a procto/rectoscopy AND a full ileocolonoscopy in a short period of time (EOT 1368-0008 and baseline 1368-0007). Instead, the baseline endoscopy for the maintenance trial 1368-0007 will be done at EOT visit of 1368-0008.
Section to be changed		Flow Chart C, 3.1, 6.2.2.4
Description of change		Clarify that all patients completing week 24 of the study and having an individual clinical benefit may be offered to enter open label long-term extension study 1368-0007.
Rationale for change		Clarification
Section to be changed		Section 3.1; Flow Chart B
Description of change		Based on the outcome of the Screening Cohort it has been decided to keep the tissue sampling approach as described in the current CTP version 1. The following tissue samples are required during fistula preparation visits: • Biopsy at the inner fistula orifice, optional • Curettage of the fistula canal • Biopsy at the outer fistula orifice, if clinically indicated • Rectal luminal biopsy (endoscopic): 2 pairs of biopsies: inflamed region and non-inflamed region
Rationale for change		Outcome of the screening cohort added and clarification which samples are required during fistula preparation visits.
Section to be changed		Section 3.3
Description of change		Screening of patients for Study Cohort may stay open until approximately 15 patients have valid baseline and post treatment biopsies for primary endpoint analysis.
Rationale for change		Minimum of approx. 15 patients may be needed for primary endpoint analysis.
Section to be changed		Section 3.3.4.1
Description of change		Add the following bullet point for discontinuation from trial treatment: The investigator clinical judgement advises for it.
Rationale for change		Clarify that based on the judgement of the investigator, patients may be discontinued from trial treatment.
Section to be changed		Section 4.2.1
Description of change		Updated wording of steroid tapering in order to

		allow steroid tapering schedule according to standard of care.
Rationale for change		Give more flexibility to investigators for steroid tapering
Section to be changed		Sections 4.2.1, 4.2.2
Description of change		Peri-OP antibiotics at the day of the fistula preparation visits (visit 1c and 4) are allowed if required according to standard of care.
Rationale for change		Clarification in respective chapters (already described in figure 3.1:1)
Section to be changed		Section 5.2.3
Description of change		Clarification in table 5.2.3:1 (exclusionary testing) and 5.2.3:2 (removal of calprotectin from local safety laboratory)
Rationale for change		Clarification exclusionary testing: HBV-DNA and QuantiFERON®-TB will be repeated at EOT; Calprotectin will be analysed by central laboratory, no additional testing by local laboratory necessary
Section to be changed		Section 5.2.6.2
Description of change		AE reporting: Distinguish between patients who roll-over to maintenance trial 1368-0007 and who not roll-over. Patients who roll-over to 1368-0007 AE reporting will be done from signing the informed consent (1368-0008) onwards until the first dose of trial medication in 1368-0007.
Rationale for change		Harmonization of AE reporting with trial 1368-0007.
Section to be changed		Appendix 10.4
Description of change		Add weighting to [redacted]
Rationale for change		Clarification
Section to be changed		Several chapters
Description of change		Minor editorial changes were done across the protocol
Rationale for change		Clarification

11.2 GLOBAL AMENDMENT 2

Date of amendment		02 Apr 2020
EudraCT number **EU number**		2017-003090-34
BI Trial number		1368-0008
BI Investigational Product(s)		BI 655130
Title of protocol		Mechanism of Action and Clinical Effect of BI 655130 in Patients with fistulizing Crohn's Disease
Global Amendment due to urgent safety reason		☐
Global Amendment		☒
Section to be changed		Clinical Trial Synopsis, Section 3.3.2
Description of change		Inclusion criterion 4: Has ≥ 1 perianal fistula(s) (≥ 4 weeks duration before enrolment, as a complication of CD, confirmed by MRI at screening*) actively draining with clinical indication for seton drainage **. ***A historical MRI** might be sufficient if all these conditions are met: a) the MRI is performed within ≤ 4 weeks prior to screening visit 1a b) the patient has not experienced any clinical significant changes regarding its perianal CD which may induce suspicion of newer complications since the historical MRI was done (in this case a new MRI at screening is mandatory) c) the historical MRI meets quality and technical imaging requirements described in the Imaging Acquisition Guideline in the ISF d) the patient meets the rest of the eligibility criteria ****This also applies to patients who currently have or had in recent past a seton in place, provided these conditions are met:** **a) no seton(s) in place for ≥2 weeks prior to the first fistula preparation visit 1c** **b) fistula(s) are actively draining (as assessed per clinical exploration) during screening**
Rationale for change		- Clarification added for patients who at the time of screening have or had in recent past a seton in place.

		- Accept historical MRIs for described conditions in order to facilitate screening visits.
Section to be changed		Section 3.3.2
Description of change		Inclusion criterion 7: Reference to section 10.7 added
Rationale for change		Clarification
Section to be changed		Section 3.3.2
Description of change		Inclusion criterion 8: Cancer screening during endoscopy at screening removed.
Rationale for change		Ileocolonoscopy during screening no longer mandatory. Please refer to the description below.
Section to be changed		Synopsis, Section 3.3.3.2.1, Section 4.2.2
Description of change		Exclusion criterion 9: Faecal **Microbiota** transplant **(FMT) within** 6 months **prior to randomization**
Rationale for change		Clarification
Section to be changed		Synopsis, Section 3.3.3.2.1, 4.2.2
Description of change		Exclusion criterion 10: Allow undetectable plasma concentration for: - previous non-biologic medication - previous biologic treatment approved for CD - previous investigational non-approved biologic for CD. Exclude patients with prior stem cell therapy (HSC, MSC).
Rationale for change		- In case of undetectable plasma concentration of the described prior therapy, the wash out period can be disregarded which should ease the recruitment. - Prior stem cell therapy could have an impact on the gene expression and therefore on the primary endpoint.
Section to be changed		Section 3.3.3.2.3
Description of change		Exclusion criterion 20 amended: Currently enrolled in another investigational device or drug trial**. Specific restrictions for patients who have participated recently in another drug trial are listed in section 4.2.2**
Rationale for change		Refer to section 4.2.2.1 for restriction on prior therapies.
Section to be changed		Flow Chart B, Section 6.2.2
Description of change		- Expand visit window of visit 1b:-35 to -21 - Expand visit window of visit 1a: -35 to -22 - (Re)check in-/exclusion criteria during visit 1c instead of visit 2

Rationale for change		To give more flexibility to the investigators, but make sure that the eligibility of patients is checked prior to the surgical visit 1c.
Section to be changed		Flow Chart B
Description of change		Remove physical examination at visit 1b
Rationale for change		Same visit window for visits 1a and 1b, therefore these investigations do not need to be repeated
Section to be changed		Flow Chart B, C, section 1.4, Section 3.1, Section, 5.1.2, Section 5.4.3, Section 6.2.2, Section 8.7
Description of change		Ileocolonoscopy not mandatory for baseline and visits 6 and 9. Instead, recto- or proctoscopy requested for visits 1c, 4, 6 and 9 for [redacted] No central reading of endoscopy at visit 9 as baseline for 1368-0007 requested.
Rationale for change		[redacted] due to the aimed population (low luminal inflammation as per eligibility criteria) there is very low chance (no power) for this trial to pick up this potential spesolimab effect. Therefore, no justification to force a full ileocolonoscopy or a colonoscopy to these patients unless it is clinically indicated as per trial physician The ileocolonoscopy is not used for eligibility purposes nor for the assessment of perianal activity.
Section to be changed		Flow Chart B and C
Description of change		[redacted]
Rationale for change		Clarification
Section to be changed		Flow Chart B
Description of change		[redacted]

		order to check eligibility PRIOR to surgical procedures at visit 1c; no additional diary completion prior to visit 2 requested
Section to be changed		Flow Chart B and C
Description of change		[redacted]
Rationale for change		Clarification
Section to be changed		Flow Chart B, Footnote 5, Section 6.2.2
Description of change		Accept historical MRIs for described conditions; MRI results to be reviewed prior to surgical procedures at visit 1c
Rationale for change		On the one hand, facilitate screening visits. On the other hand, make sure that MRI will be reviewed with regards to eligibility prior to surgical procedures at visit 1c.
Section to be changed		Flow Chart B and C, section 5.4, section 6.2.2 and section 7
Description of change		- Blood sampling for immune cell phenotyping (flow cytometry) and gene expression analysis removed - corresponding chapter 5.4, 6.2.2 and 7 amended
Rationale for change		Reduce efforts for patients and focus on mainly important samples for the trial
Section to be changed		Section 5.4
Description of change		Staged approach for biomarker sample analysis
Rationale for change		This is due to the exploratory nature of the mechanism being tested and the timing of effect on candidate biomarkers in the study
Section to be changed		Flow Chart B and C and section 5.4.2
Description of change		Characterization of stool microbiome and stool miRNA instead of 16S rDNA sequencing
Rationale for change		Clarification
Section to be changed		Flow Chart B, footnote 9
Description of change		If collection of stool sample for enteric pathogens is not possible at visit 1a, stool sample has to be collected at (prior to) **visit 1c**
Rationale for change		Eligibility to be checked prior to surgical visit 1c
Section to be changed		Flow Chart B and C
Description of change		Flow Chart B and C: Footnote 14 (FC B) 12 (FC C) I.v. administration **and related procedures** may be done within max. of 3 days after other investigations / procedures…
Rationale for change		Due to logistical reasons on site, it may be challenging to schedule all investigations according to the given time windows in the flow

		charts. Therefore, i.v. administration and related procedures like vital signs may be done in the expanded time window.
Section to be changed		Section 3.1, Section 6.2.2; Section 5.1.2
Description of change		Fistula preparation visit - Decision on biopsies during fistula preparation visits and eligibility criteria, taking screening cohort results into account: Screening Cohort tissue analyses have shown that all tissue sources allow assessing gene expression. However, they have also shown differences in gene expression depending on the tissue location. (inner / outer fistula orifice and curettage). Thus, it has been decided: **1.** Not to change the eligibility criteria: No need to limit the study population to patients where both, tissue from the inner orifice and fistula canal, are available **2.** To keep the tissue sampling approach as stated in the screening cohort from all perianal fistulas drained by a seton **placed at visit 1c**
Rationale for change		Describe decision, based on screening cohort results, on biopsies to be taken during fistula preparation visits and eligibility criteria. Clarification from which fistulas the biopsies will be taken.
Section to be changed		Section 3.1
Description of change		No interim analysis ~~of efficacy and safety data~~ of the Study Cohort is planned.
Rationale for change		Clarification that no interim analysis will be done in a broaden sense
Section to be changed		Section 3.3
Description of change		Increased number of sites
Rationale for change		Update
Section to be changed		Section 4.1.5
Description of change		Release of random plan to bioanalytical laboratory (changes highlighted in bold): After the last patient completes the Week 12 visit the random plan will be released to the bioinformatics group **and the bioanalytical laboratory**. The bioinformatics group will receive the randomisation code in order to start with the pre-processing of gene expression data (using limma packages). **The bioanalytical laboratory will receive the randomization code in order to**

		[redacted] Bioinformatics groups **and the analytical laboratory** will not disclose the randomization code until the trial is officially unblinded.
Rationale for change		Avoid testing of placebo patient samples for PK and ADA.
Section to be changed		Section 5.1.2
Description of change		Definitions for perianal fistula activity amended: - Perianal fistula remission and response: Physical assessment by investigator(s) on site - Combined perianal fistula remission Physical assessment by investigator(s) on site and MRI reading on site
Rationale for change		- Ilecolonoscopy not needed for combined perianal fistula remission assessment - Clarify, that assessment of perianal fistula remission / response / combined remission is performed by investigator(s) on site. Central reading will be used for efficacy assessment purposes.
Section to be changed		Section 5.1.2
Description of change		Wording Fistula Preparation Visit and Clinical CD activity amended
Rationale for change		Clarification
Section to be changed		Section 5.1.2
Description of change		[redacted]
Rationale for change		See above, ileocolonoscopy not mandatory and recto-or proctoscopy requested instead
Section to be changed		Section 5.2.3
Description of change		- Vibrio removed from exclusionary testing - Type of E. coli removed (O157/H7) - CRP: high density analysis not required
Rationale for change		Analysis not needed for safety profile of BI 655130
Section to be changed		Section 5.2.6.2
Description of change		Concomitant therapy reporting for patients who roll-over to 1368-0007: updates to concomitant therapy should also be included until first dose of trial medication in

		1368-0008
Rationale for change		clarification
Section to be changed		Section 5.3.1
Description of change		PK data may be incorporated into a population pharmacokinetic analysis if feasible
Rationale for change		Clarification that PK data from 1368-0008 may still be considered via a population pharmacokinetic approach
Section to be changed		Section 6.2.2
Description of change		Blood sampling for safety laboratory: - Ileocolonoscopy removed, see above - It is preferred but patients do not have to be fasted for the blood sampling for the safety laboratory (documentation of fasting condition requested)
Rationale for change		Clarification
Section to be changed		Section 6.2.2.1
Description of change		Stool sampling prior to **visit 1c**
Rationale for change		Allow more flexibility on site and check eligibility prior to surgical visit 1c
Section to be changed		Section 6.2.2.2
Description of change		Description which biopsies will be taken during fistula preparation visit based on results from screening cohort
Rationale for change		Clarification
Section to be changed		Section 6.2.2.2
Description of change		Stool sampling for visit 1c and 4 described
Rationale for change		Clarification according to Flow Chart B
Section to be changed		Section 6.2.2.3
Description of change		Procedures for roll-over to trial 1368-0007 described (patient information)
Rationale for change		Clarification
Section to be changed		Several chapters
Description of change		Minor editorial changes were done across the protocol
Rationale for change		Clarification

11.3 GLOBAL AMENDMENT 3

Date of amendment		23 Oct 2020
EudraCT number **EU number**		2017-003090-34
BI Trial number		1368-0008
BI Investigational Product(s)		BI 655130
Title of protocol		Mechanism of Action and Clinical Effect of BI 655130 in Patients with fistulizing Crohn's Disease
Global Amendment due to urgent safety reason		☐
Global Amendment		☒
Section to be changed		Clinical Trial Synopsis, Flow Chart B, Section 3.3.2, 6.2.2
Description of change		**Inclusion criterion 4:** Requirement on removing the seton 2 weeks before fistula preparation visit (V1c) for patients who present with seton drainage at screening HAS BEEN REMOVED- Thus Criterion 4 is now: Has ≥ 1 perianal active* fistula(s) with clinical indication for seton drainage (≥ 4 weeks duration before enrolment, as a complication of CD). **. **ADDED:** * Criteria for Active Fistula: As per clinical evaluation: Presence of spontaneous drainage or drainage after gentle finger compression at the external openings & as confirmed by radiological (MRI) exploration . ** Patients who are screened with a seton drainage are eligible if the patient meets the rest of the eligibility criteria. **REMOVED**: Historical MRI for baseline assessment is no longer allowed (important for evaluation of criteria for active fistula)
Rationale for change		Need to remove seton drainage 2 weeks until 1st surgical visit is not accepted by patients and doctors and is endangering trial feasibility. Therefore, this requirement has been removed **provided fistula is actively draining**. Criteria for **active** fistula were added to ensure primary endpoint of the trial is no compromised.

Section to be changed		Synopsis, Section 3.3.2
Description of change		**Inclusion criterion 7:** Demonstrated in the past inadequate **fistula** response or loss of response or have had unacceptable side effects with approved doses of at least one of the following compounds: …
Rationale for change		Clarification
Section to be changed		Synopsis, Section 3.3.3, 3.3.4.1, 4.2.2.2, 6.2.2.2
Description of change		Clarification that **surgical procedures to treat fistulas** (other than interventions requested for visits 1c and 4 according to CTP) are not allowed after randomization. Section 3.3.3 (Exclusion criterion 3): Anticipated to require surgical intervention for CD **including any fistula surgical procedures** (except seton **drainage**). **See Table 4.2.2.2:1 for a detailed list of restricted interventions** Section 3.3.4.1: • The patient needs surgical interventions for CD including any fistula surgical procedures (except seton drainage, see section 4.2.2.2) Section 4.2.2.2: Surgical interventions for CD are not allowed during the trial. Any surgical intervention or procedure for perianal and enterocutaneous fistulas (except seton drainage) are also not allowed (patient shall be discontinued) since they would interfere with the clinical endpoints of the trial. These are summarized in table 4.2.2.2:1 (no exhaustive list). Table 4.2.2.2:1 was added. Section 6.2.2.2: Please refer to section 4.2.2.2 for surgical restrictions.
Rationale for change		Clarification to investigators that previously restricted surgical procedures INCLUDE procedures to treat perianal and / or enterocutaeous fistulas since these would confound efficacy endpoints
Section to be changed		Synopsis, Section 1.4, 3.1, 3.3.3 & 4.2.1 & 4.2.2
Description of change		**Exclusion criterion 10:** Patients may continue pre-existing anti-TNF treatment as defined in Sections 4.2.1 and 4.2.2.1. Corresponding wording updated in sections 1.4 and 3.1.
Rationale for change		Need to discontinue anti-TNF therapy (SOC for

		luminal inflammatory activity control in CD patients) is not possible on most of target population due to the need to ensure controlled luminal activity throughout the study. Therefore, this requirement has been removed provided anti-TNFα (e.g. infliximab, adalimumab, certolizumab pegol; or respective biosimilars) dose has been stable for at least 6 months prior to screening and rest of eligibility criteria are met (i.e activity of the fistula based on clinical and MRE assessment at screening). Criteria for active fistula was added to ensure primary endpoint of the trial is not compromised
Section to be changed		Section 1.3, 1.4
Description of change		Update of development program of Spesolimab. The respective wording was updated in the sections mentioned above.
Rationale for change		BI has decided to discontinue the development of spesolimab in UC. The decision is based on available results of the phase II clinical trials (1368-0004, 1368-0005, 1368-0010, and 1368-0017) conducted in patients with UC which show a lower than expected efficacy on clinical endpoints. The decision is not related to or triggered by any safety findings. Data from ongoing and completed clinical trials in UC and other conditions show a good safety and tolerability profile of spesolimab with no evidence of any new safety risks. The anticipated benefit and the safety data obtained thus far support the continuation of the spesolimab clinical development programme in all other indications under study.
Section to be changed		Section 1.4
Description of change		Benefit-Risk Assessment in context of COVID-19 pandemic added
Rationale for change		Clarification
Section to be changed		Section, 3.1, 4.1.5, 7.3, 7.4
Description of change		Introduction of interim analysis once all randomised patients have completed the first 12 weeks of the treatment period (through visit 6). Blinding procedures were amended accordingly.
Rationale for change		At visit 6, all patients will have completed the randomized treatment part of the trial and the primary and secondary endpoint data will be available. At that time point, a preliminary

		database lock will be carried out to have the results available for further planning.
Section to be changed		Section 4.1.4
Description of change		During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may discuss with BI to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations.
Rationale for change		Challenges due to covid-19 are acknowledged and the flexibility should be given to administer the trial medication at home taken the requirements described above into account.
Section to be changed		Flow Chart C, Section 6.2.2.4, 8.6
Description of change		Amended definition for "individuals patients end", "end of the trial" and clarification on AE/CT reporting timeline for patients who roll-over to 1368-0007.
Rationale for change		Clarification
Section to be changed		Flow Chart C
Description of change		Removal of infection testing for EOT visit in Flow Chart C
Rationale for change		Correction, in order to harmonize the Flow Chart C with table 5.2.3:1 which states that infection testing is required for screening, only.
Section to be changed		Section 5.3.2
Description of change		[redacted]
Rationale for change		Correction to align with Laboratory Manual.
Section to be changed		Section 6.2.2.3
Description of change		Amended wording for patients who roll-over to 1368-0007 (patient information).
Rationale for change		Clarification, avoid inconsistences with CTP 1368-0007
Section to be changed		Section 7.3
Description of change		The FAS will follow the intent-to-treat principle and the handling of patients who received a wrong treatment will be described in the TSAP.
Rationale for change		Added additional information for clarification
Section to be changed		Several chapters
Description of change		Minor editorial changes were done across the protocol

Rationale for change		Clarification
Section to be changed		4.2.1
Description of change		Peri-OP antibiotics **at the day before until the day after** fistula preparation visits (visit 1c and 4) are allowed if required according to standard of care.
Rationale for change		Allow more flexibility in order to address local standard of care

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

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Author-Clinical Trial Leader	[redacted]	26 Oct 2020 13:19 CET
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