Clinical Trial Protocol

	Document Number: **c34096215-03**
EudraCT No.	2020-005770-99
BI Trial No.	1368-0059
BI Investigational Medicinal Product(s)	Spesolimab (BI 655130)
Title	Multi-center, double-blind, randomized, placebo-controlled, phase IIa trial to evaluate spesolimab (BI 655130) efficacy in patients with fibrostenotic Crohn's Disease
Lay Title	A study to test whether spesolimab helps people with Crohn's disease who have symptoms of bowel obstruction
Clinical Phase	Phase IIa
Clinical Trial Leader	[redacted] Phone: +[redacted], Fax: +[redacted]
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Current Version and Date	Version 3.0, 20 Oct 2021
Original Protocol Date	08 Feb 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	08 Feb 2021
Revision date	20 Oct 2021
BI trial number	1368-0059
Title of trial	Multi-center, double-blind, randomized, placebo-controlled, phase IIa trial to evaluate spesolimab (BI 655130) efficacy in patients with fibrostenotic Crohn's Disease
	[redacted]
Trial site(s)	Multi-center trial conducted in approximately 30 countries
Clinical phase	IIa
Trial rationale	Proof of Clinical Concept (PoCC)
Trial objective(s)	To demonstrate that spesolimab is effective in maintaining Symptomatic Stenosis Response and / or inducing Radiographic Stenosis Response in patients with symptomatic Crohn's Disease (CD)-related small bowel stenosis, who have achieved Symptomatic Stenosis Response after standard medical therapy.
Trial endpoints	<u>Primary endpoints:</u> Spesolimab superiority vs. placebo on one of the following • Proportion of patients with maintained Symptomatic Stenosis Response at Week 48 • Proportion of patients with Radiographic Stenosis Response at Week 48 <u>Secondary endpoints:</u> • Proportion of patients with maintained Symptomatic Stenosis Response at Week 24 • Proportion of patients with Radiographic Stenosis Response at Week 24
Trial design	This is a randomized, double-blind, placebo-controlled, parallel-design trial testing one active dose versus placebo.
Total number of patients randomized	100
Number of patients per treatment group	50
Diagnosis	Fibrostenotic Crohn's Disease

Main inclusion criteria	• Male and female patients, 18 to 75 years when signing informed consent at screening • Established diagnosis of clinical CD prior to screening • Suspicion of symptomatic small bowel stenosis • Presence of abdominal pain after eating or limitation in amount or types of food at screening • 1 or 2 naïve or anastomotic stenoses in the terminal ileum at screening, confirmed by MRE at randomization • Have achieved Symptomatic Stenosis Response before randomization (i.e. 7 day average scores <2 for diary questions on the abdominal pain after eating AND on the limitation in amount or types of food) • Endoscopic activity defined by Colonic Simple Endoscopic Score in CD (SES-CD) ≤12 after Lead-in Period, at the time of randomization
Main exclusion criteria	• No stenosis in reach of ileocolonoscopy • Systemic corticosteroid treatment of current obstructive symptoms for >1 week prior to screening • Endoscopic balloon dilation (EBD) or surgical treatment of the same small bowel stenosis within the last 6 months prior to screening Visit 1 • More than 2 small intestinal stenoses • Patients who require immediate EBD or surgical intervention as per the investigator´s discretion • Failure of >2 different biological drug classes prior to screening (e.g. TNF inhibitors, Integrin Receptor antagonists and IL-12 / IL-23 antagonists) • Current complications of CD at screening Visit 1 and randomization (Day 1) that would possibly confound the evaluation of benefit from treatment with spesolimab • Current stenosis in the colon • Previous strictureplasty on current stricture • Current ileostomy or colostomy • Any kind of bowel resection or diversion within 6 months of screening Visit 1 • Any other intra-abdominal surgery (except for abscess drainage) within 3 months prior to screening Visit 1 • Colorectal cancer (CRC) present and past (<5 years) history
Test product(s)	Spesolimab (BI 655130)
dose	1200 mg every 4 weeks (Day 1 to Week 8), then 1200 mg every 8 weeks until Week 40 (last trial drug administration)
mode of administration	intravenous (i.v.)
Comparator product(s)	Placebo
dose	Placebo every 4 weeks (Day 1 to Week 8), then Placebo every

	8 weeks until Week 40 (last administration)
mode of administration	intravenous (i.v.)
Duration of treatment	48 weeks
Statistical methods	The primary analysis will be performed for the full analysis Set (FAS) which is based on the intent-to-treat principle. The primary analysis of the unadjusted absolute rate difference versus placebo, once all patients have completed through week 48, will be calculated simply as the difference in the observed proportion of patients with maintained Symptomatic Stenosis Response / Radiographic Stenosis Response, based on FAS. A 95% Newcombe confidence interval around the difference will also be provided. An interim analysis will be conducted when 100% of the patients have completed at least 24 weeks of treatment.

FLOW CHART

Trial Periods	**Lead-in Period**[1]		**Randomized Blinded Treatment Period**								**FUP**[2]
	Screening										
Visit	**1**	**2**[1]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 EoT**[24]	**11 EoS**[2]
Week	(-14 to) -12	(-13 to) -10		4	8	16	24	32	40	48	56
Day	(-98 to) -84	(-91 to) -70	1[3]	29 ±7	57 ±7	113 ±7	169 ±7	225 ±7	281 ±7	337 ±7	393 +7
Informed Consent	X										
Demographics	X										
Baseline Condition, Medical History and CD history[4]	X										
Review of in-/exclusion criteria	X		X								
Physical examination[5]	X^C	X^T	X^C	X^T	X^T	X^T	X^C	X^T	X^T	X^C	X^C
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X
Smoking status	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[7]	Xs	Xu,(s)	Xu,(s)	Xu,(s)	Xu,(s)	Xu,(s)	Xu,(s)	Xu,(s)	Xu,(s)	Xu,(s)	Xu,(s)
Safety laboratory[8]	X	X	X[8]	X	X	X	X	X	X	X	X
Stool sampling (enteric pathogens)	X										
Therapeutic drug monitoring (pre-screening biological therapy)[9]	X										
Infections testing[10]	X									X	
S-PRO[11]	X	X	X	X	X	X	X	X	X	X	
IBDQ, SF-36, and PGI-S scales[12]	X[12]	X	X	X	X	X	X	X	X	X	
CGI-S and CGI-C scales[13]	X[13]	X	X	X	X	X	X	X	X	X	
CDAI (Crohn's Disease Activity Index)[14]	X[14]	X	X	X	X	X	X	X	X	X	
Schedule baseline MRE and endoscopy examinations		X[15, 16]									

Trial Periods	**Lead-in Period[1]**		**Randomized Blinded Treatment Period**								**FUP[2]**
	Screening										
Visit	**1**	**2[1]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 EoT[24]**	**11 EoS[2]**
Magnetic Resonance Enterography (MRE)[15]			X[15] (review results)				X			X	
Endoscopy (incl. SES-CD) + Biopsy[16]			X[16] (review results)				X			X	
IRT call[17]	X		X	X	X	X	X	X	X	X	
Randomization[18]			X								
Administer trial drug[19]			X	X	X	X	X	X	X		
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DNA-Banking (optional)[21]			X								
[redacted]			[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]			[redacted]				[redacted]			[redacted]	
[redacted] e			X			X	X			X	
All AEs / SAEs / AESIs[25]	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Study completion											X

1 The **Lead-in Period** starts with the Informed Consent at the Screening Visit (Visit 1). At Visit 1, the **corticosteroid treatment** as described in Section 4.2.1 is to be started and the blood sample for the therapeutic drug monitoring (TDM) of the anti-inflammatory biological therapy the patient was receiving prior to screening is to be taken. As soon as the TDM result is available, the **optimization of the anti-inflammatory biological treatment** is started (see Section 4.2.1) and takes (at least) 8 weeks. Please see also Flow Chart 2 for more details on the Lead-in Period.

2 FUP = Follow-Up Period for safety follow-up not earlier than 16 weeks after the last trial drug administration at Week 40. EoS = End of Study Visit.

An extension trial is planned to be offered to patients who have an individual benefit from their study drug at End of Treatment (EoT) visit at Week 48. These patients are not requested to complete follow up period and the Visit 10 is the last visit for this trial, probably co-inciding with the first visit in the extension trial. For adverse event (AE) and Concomitant therapy reporting the end of study participation is defined as the day of first administration of study drug in the extension trial (please see Section 6.2.3).

[3] Day of Randomization / Day of first administration of randomized trial medication with baseline assessments. Please refer to footnote 15 for the baseline Magnetic Resonance Enterography (MRE) and footnote 16 for the baseline endoscopy: These assessments are to be scheduled when 8 weeks of the optimization of the anti-inflammatory biological treatment are over and at least 2 weeks before the planned randomization at Day 1. Ideally, MRE is to be done first (at least 10 business days before Day 1) and endoscopy second (at least 7 business days before Day 1), and both examinations are not on the same day. This is both to ease the burden of the visit and to allow for proper central review of the data with eligibility information returned to the site.

[4] BC = Baseline Conditions, and Medical History including the Crohn's Disease history. For details please see Section 6.2.1.

[5] Physical examination; C = complete physical examination includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. T = targeted physical examination focuses on evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities. Measurement of body weight will be performed at every visit, height at Visit 1 only. For details please see Section 5.2.1.

[6] Vital signs include systolic and diastolic blood pressure and pulse rate, body temperature and respiratory rate. Measurements of vital signs should precede blood sampling. In addition, at dosing visits vital signs are to be done pre-dose, approximately 10 minutes and approximately 60 minutes after stop of the infusion. For details please see Section 5.2.2.

[7] Pregnancy testing is applicable only for women of childbearing potential (WOCBP); For the definition please refer to Section 3.3.3. s = serum pregnancy test (performed at screening). u = urine pregnancy tests will be performed at all other visits. Urine pregnancy testing must be done prior to administration of study drug. Trial drug must only be administered in case of a negative test result. (S) - in case of a positive urine pregnancy test, a serum pregnancy test will be done.

[8] Safety laboratory tests will be done at a central laboratory. The safety laboratory samples relevant for Day 1 are to be taken when the patient comes for the baseline MRE examination (10 business days before Day 1) in order to have the laboratory report available at Day 1. For details please see Section 5.2.3.

[9] TDM: A blood sample is drawn at screening Visit 1 to determine the plasma drug level and antidrug antibody (ADA) status for the patient´s previous anti-inflammatory biological treatment. As soon as the result is available (approximately after 5 to 10 business days), the optimization of the anti-inflammatory biological therapy is to be started at Visit 2 according to the algorithm provided in Section 4.2.1.1.

[10] For details on infections testing at baseline and EoT Visit (or in case of early trial discontinuation, if applicable) please refer to Tables 5.2.3: 1 and 5.2.3: 2.

[11] The Stenosis Patient Reported Outcome (S-PRO) tool is set up as an eDiary (named Stricturing Crohn´s Disease Questionnaire). It is important to start the completion of the S-PRO at the screening visit (Visit 1) or as soon as the patient´s situation allows during hospitalization (latest on the day of discharge). The patient will then complete the S-PRO daily during the entire duration of the Lead-in Period and on Day 1. After randomization, the patient will complete the S-PRO daily in the week preceding a scheduled visit and on the day of the scheduled visit. See Section 5.1.2 and Appendix 10.1.1. In case of worsening of CD symptoms the patient is requested to contact the site to make an appointment for an **unscheduled visit** including MRE and endoscopy examinations. The patient is asked to start the S-PRO completion immediately, daily, for (at least) 7 days before the unscheduled visit and on the day of the unscheduled visit. For details of such an unscheduled visit, please see Section 6.2.2.

[12] All patient reported outcomes (PROs) should be completed by the patient on his / her own in a quiet area / room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the site staff team. IBDQ = Inflammatory Bowel Disease Questionnaire; SF-36 = 36 question instrument to measure health-related quality of life. PGI-S = Patient´s Global Impression of Severity. There are four versions of PGI-S measuring: post-prandial abdominal pain, dietary restriction, stenosis symptoms overall and stenosis symptoms related impact in daily life. The PROs IBDQ, SF-36 and PGI-S have to be completed the first time at the time of the first S-PRO completion (see above, at Visit 1 or as soon as the patient´s situation allows). For IBDQ see Section 5.1.5 and Appendix 10.1.4. For SF-36 see Section 5.1.6 and Appendix 10.1.5. For PGI-S scales see Section 5.1.7 and Appendix 10.1.6.

[13] Clinician reported outcomes: CGI-C = Clinician's Global Impression of Change; CGI-S = Clinician's Global Impression of Severity. Those CGI versions focus on stenosis symptoms overall. CGI-S scale starts at Visit 1, the CGI-C scale starts only at Visit 2. For details see Section 5.1.8 and Appendix 10.1.7.

[14] The patient will have to complete the CDAI symptom score in an eDiary daily for the 7 days preceding a visit (scheduled and unscheduled). At Visit 1, the eDiary is dispensed only for completion of the CDAI symptom score data daily 7 days before Visit 2. For details see Section 5.1.4 and Appendix 10.1.3.

[15] The baseline MRE is to be performed after 8 weeks of the optimization of anti-inflammatory biological therapy when Symptomatic Stenosis Response is achieved and at least 10 business days before the planned Day 1. This 10-days-period is required to allow for central review and reporting of eligibility information (inclusion criterion 8) to the investigator. Please factor in the need for glomerular filtration rate (GFR) assessment (either done locally or via central laboratory) within 14 days before every MRE examination (scheduled and unscheduled). **Generally, the MRE examination should be done before the endoscopy examination and is not recommended on the same day (see footnote 16).**

[16] The baseline endoscopy is to be performed after 8 weeks of the optimization of anti-inflammatory biological therapy when Symptomatic Stenosis Response is achieved and at least 7 business days before the planned Day 1. This 7-days-period is required to allow for central review and reporting of eligibility information for colonic simple endoscopic score for Crohn's Disease (SES-CD) (inclusion criteria 10) to the investigator. **Generally, the endoscopy (ileocolonoscopy) examination should be done after the MRE examination and is not recommended on the same day (see footnote 15).**

[17] An Interactive Response Technology (IRT) call at the screening visit indicates that a patient is in screening. IRT calls at dosing visits assign medication numbers.

[18] An IRT call at Day 1 indicates the patient´s randomization, if all inclusion and none of the exclusion criteria are met.

[19] Intravenous administration of the study drug must be performed by a healthcare professional. Please note that the last trial drug administration takes place at Week 40, not at Week 48. For the sequence of procedures please see Section 6.2. For details see also Section 4.1.4.

[redacted]

[21] Deoxyribonucleic Acid (DNA) banking sample is optional and should be done at Visit 3 or any subsequent visit. This sampling is only possible, if the patient agreed by signing a separate informed consent. For details please see Section 5.5.

[redacted]

[24] Patients who discontinue trial treatment prematurely should still follow the trial schedule, if possible. Otherwise they should undergo the EoT Visit as soon as possible, and for safety follow-up the EoS Visit 112 days (16 weeks) thereafter.

[25] After the EoS visit (= individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial drug related SAEs and trial drug related AESIs of which the investigator may become aware and only via the BI SAE form, please see Section 5.2.6.2.1.
In case of an extension trial, this does not apply for patients rolling over into the extension trial.

FLOW CHART 2: LEAD-IN PERIOD LOGISTICS

Week	**W-12 (V1)**	**W-11**	**W-10 (V2)**	**W-9**	**W-8**	**W-7**	**W-6**	**W-5**	**W-4**	**W-3**	**W-2**	**W-1**	**Day 1 (V3)**	**W1**	**W2**	**W3**	**W4**
Corticosteroids (mg/d)	40	40[1]	35	30	25	20	15	10	7,5	5	2,5	0	**0**				
Therapeutic drug monitoring (TDM)[2]	X																
Anti-inflammatory biological treatment optimization[3]			X	X	X	X	X	X	X	X[4]							
S-PRO[4]	daily	daily	daily	daily	daily	daily	daily	daily	daily	**daily[4]**	daily	daily					Daily in the week before
MRE[5]											X						
Endoscopy[6]											X						
Trial drug administration[7]													**X**				X
IBDQ and SF-36[8]	X		X										X				
PGI-S scales[9]	X		X								x		X				
CGI-S and CGI-C scales[10]	X		X								x		X				
CDAI (Crohn's	X (dispen	X (fill 7	X									X (fill 7	X				

Disease Activity Index)[11]	sed)	days prior to V2)										days prior to V3)				

1 Corticosteroid treatment and tapering during the Lead-in Period are described in Section 4.2.1.1. Appendix 10.2 provides the equivalent doses of corticosteroids. The numbers given in this table are for prednisolone as an example.

2 Therapeutic Drug Monitoring, i.e. plasma drug level and antidrug antibody (ADA) testing for the patient´s anti-inflammatory biological CD treatment at the time of enrolment (Screening, Visit 1). The optimization of the anti-inflammatory biological therapy starts as soon as the laboratory results are available to the investigator. Ideally this is after 1 week (5 business days), however, this can also take 2 weeks (10 business days), depending on the laboratory performing this analysis.

3 Based on the patient´s CD treatment at enrolment, the anti-inflammatory biological treatment optimization is to be performed as mandated and described in Section 4.2.2.1. All treatments are to be used according to the label. The duration of this optimization must not be shorter than 8 weeks before the baseline Magnetic Resonance Enterography (MRE) and baseline endoscopy are assessed.

4 The S-PRO completion (Stricuring Crohn´s Disease Questionnaire) starts ideally at screening Visit 1 or as soon as the patient´s situation allows. It is done daily during the Lead-in Period to assess if Symptomatic Stenosis Response is achieved at the time of scheduling the baseline MRE (W-2). Hence, **the eigth week (= 7 days) of optimization of the anti-inflammatory biological treatment is relevant to assess with the score of 2 questions** out of the S-PRO tool **if the patient has achieved the Symptomatic Stenosis Response** which is prerequisite to perform the baseline MRE and endoscopy examinations.

5 The baseline MRE is to be scheduled after 8 weeks of optimization of the anti-inflammatory biological therapy and (at least) 2 weeks before the planned Day 1 with randomization and the first dose of trial drug. The central review will provide eligibility information to the site (inclusion criterion number 9).

6 The baseline endoscopy is to be scheduled after a period of 8 weeks of optimization of the anti-inflammatory biological therapy and (at least) 7 business days before the planned Day 1 with randomization and the first dose of trial drug. The central review will provide eligibility information to the site (inclusion criterion number 10). Given the different patient preparation needed for the MRE and endoscopy examinations, the MRE should be done first and the endoscopy second.

7 Trial drug administration takes place for eligible patients at Day 1 upon randomization (via IRT call).

8 The IBDQ and SF-36 have to be completed at the time of the first S-PRO completion, at V2 and at V3 (tablet at the site)

9 PGI-S scales are completed at W-2 for patients who have **NOT** achieved a Symptomatic Stenosis Response. PGI-S scales are completed at V3 for patients who have achieved a Symptomatic Stenosis Response

10 CGI-S scale starts at Visit 1, the CGI-C scale starts only at Visit 2.

11 The CDAI eDiary is dispensed only for completion 7 days before Visit 2 and before V3.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ADA	Antidrug Antibody
ADCC	Antibody-dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (classification system)
AtD	Atopic Dermatitis
AxMP	Auxiliary Medicinal Product
AZA	Azathioprine
BI	Boehringer Ingelheim
CA	Competent Authority
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDC	Complement-dependent Cytotoxicity
CGI-C	Clinician's Global Impression of Change
CGI-S	Clinician's Global Impression of Severity
clinROs	Clinician's Reported Outcomes
C_{max}	Maximum Plasma Concentration
CRA	Clinical Research Associate
CRC	Colorectal Cancer
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRO	Contract Research Organisation
CTE	Computed Tomography Enterography
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
COVID-19	Corona Virus Disease 2019
DBL	Database Lock
DILI	Drug Induced Liver Injury

DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EBD	Endoscopic Balloon Dilation
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoS	End of Study
EoT	End of Treatment
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FUP	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
GPP	Generalized Pustular Psoriasis
HA	Health Authority
HIV	Human Immunodeficiency Virus
HS	Hidradenitis Suppurativa
IGRA	Interferon Gamma Release Assay
IHC	Immunohistochemistry
Ig	Immunglobulin
IL	Interleukin
IL-36R	Interleukin 36 Receptor
INN	International Nonproprietary Names
IND	Investigational New Drug
i.v.	intravenous
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product

IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
KO	Knockout
LI	Lead-in
LPLT	Last Patient Last Treatment
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Drug Regulatory Activities
miRNA	Micro Ribonucleic Acid
MoA	Mode of Action
MRD	Multiple Rising Dose
MR(E)	Magnetic Resonance (Enterography)
MTX	Methotrexate
6-MP	6-Mercaptopurin
Nab	Neutralizing Antibody
NFKB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NSAID	Non-steroidal anti-inflammatory drugs
OPU	Operative Unit
PCS	Physical Component Summary
PGI-S	Patient´s Global Impression of Severity
PD	Pharmacodynamic
PK	Pharmacokinetics
PPD	Purified Protein Derivative
PPP	Palmoplantar Pustulosis
p.o.	per os (oral)
PoCC	Proof of clinical concept
PV	Pharmacovigilance
qw	Weekly
q4w	Every four weeks
q8w	Every eight weeks
RA	Regulatory Authority
RCTC	Rheumatology Common Toxicity Criteria

REP	Residual Effect Period
REML	Restricted Maximum Likelihood
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAF	Safety Set
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
SB	Small Bowel
SES-CD	Simple Endoscopic Score in Crohn's Disease
SF-36	36 question instrument to measure health-related quality of life
SOC	Standard of Care
SOP	Standard Operating Procedure
(S-)PRO	Stenosis Patient Reported Outcome
SRD	Single Rising Dose
[redacted]	
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
TEAEs	Treatment Emergent Adverse Events
TMF	Trial Master File
TNF	Tumor Necrosis Factor
TSAP	Trial Statistical Analysis Plan
TST	Tuberculin Skin Testing
UC	Ulcerative Colitis
ULN	Upper Level of Normal
(I)US	(Intestinal) Ultrasound
vs.	versus
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Crohn's disease (CD) is a chronic condition that manifests clinically as recurrent gut inflammatory episodes followed by periods of inflammatory remission and is one of the recognized subtypes of Inflammatory Bowel Disease (IBD).
Under normal physiologic conditions acute gut inflammation, e.g. viral or bacterial gastroenteritis, is followed by a complex tissue repairing or tissue remodelling response. This response aims to repair the damage caused by inflammation and to recover normal structure and function of the intestinal mucosa and rest of the layers of the gut wall. Tissue remodelling response includes among others activation of mesenchymal cells, which produce an extracellular matrix, mainly collagen and fibronectin, which leads to wound healing. However, in IBD patients, the chronic or recurrent activation of tissue remodelling responses leads to excessive accumulation of this extracellular matrix causing destruction of the interstitium and increased apposition of collagen or fibronectins, which leads to fibrosis, which manifest clinically as intestinal stenosis [R20-2041, R20-2042].

CD patients with small bowel stenosis typically present with acute or subacute episodes of symptoms of small bowel obstruction that are currently treated with intensified medical therapy, interventional endoscopy or surgery [R20-2037, P20-05765].
Most stenoses on a tissue level have a mixed inflammatory and fibrotic component. Since no antifibrotic treatments are currently available [P19-05294], patients are usually first treated with anti-inflammatory therapy. Corticosteroids associated to escalation of immune modulators or biologic drugs are currently used to induce remission of inflammatory flare in the stenotic area and thus, resolve obstruction and avoid surgery [R20-2037, P20-05766].
Patients who respond to intensified anti-inflammatory therapy during the acute phase are currently offered maintenance of the intensified anti-inflammatory regime to prevent further relapses. However, there is no evidence that maintenance of anti-inflammatory therapy prevents further relapses and after initial improvement of obstructive symptoms around 50% of the patients will still require interventional endoscopy or surgery within 1 year [P20-05766, R20-3943].

For patients unresponsive to intensified anti-inflammatory therapy, endoscopic intervention or surgery are the only currently available options. Endoscopic Balloon Dilation (EBD) is the most common endoscopic treatment modality. Short-term symptomatic relief rates after EBD have been reported to be as high as 80% in patients with short length stenosis. However, this treatment modality is only amenable for stenosis that are within reach of endoscopy, limited in number and is associated to major complications such as bleeding or perforation in around 2-3% of the cases [P20-05765]. Moreover, after initial symptomatic response, relapse is almost universal in these patients, 50% of which will finally require surgery [R20-2236, R20-2235, P20-06254, P20-06255]. Thus, EBD is considered as a temporary bridge to surgery and thus, surgical resection or strictureplasty are currently the only left option in patients with fibrotic stenosis. However, these are not curative and relapse will appear in the majority of patients. Strictureplasty is associated with high morbidity and recurrence rates of 50% within a year [R20-2251]. Alternatively, bowel resection is associated with high risk of short bowel

syndrome in patients with recurrent, extensive or multiple stenosis [R20-4176] and is associated with high rates of recurrence, being almost universal 3 years after surgery [R20-2234].

IL36 is a group of three cytokines that are overexpressed in the gut of IBD patients [R16-2300]. They bind to IL36-receptor (IL36R) activating NFKB as well as Mitogen Activated Protein Kinases, which leads to the activation of various inflammatory pathways. These cytokines have also been shown to strongly activate myofibroblasts, one of the main effector cells in intestinal fibrosis [R20-2093].

Recently, it has been shown that cells expressing IL36α, one of the IL36R ligands, are significantly increased in the gut mucosa from IBD patients with fibrostenosis compared to those without and these were found in close proximity with alpha-SMA+ fibroblasts, one of the key effectors of intestinal fibrosis [R19-0857]. The same study showed higher expression of IL36α, alpha-SMA+ fibroblasts and type VI collagen in stenotic regions of CD and Ulcerative Colitis (UC) patients.

Blockage of IL36R has also been shown to reduce fibrosis in two animal models of chronic colitis. Moreover, antagonizing IL36R in these animals was shown to significantly reverse already established fibrosis [R19-0857]. In totality, these data strongly suggest IL36 being a key player in the generation of intestinal fibrosis, which underlies the clinical complication of fibrostenostic bowel obstruction.

1.2 DRUG PROFILE

Mode of action (MoA)
BI 655130 (INN: spesolimab) is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signalling. Binding of spesolimab to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways in inflammatory skin and bowel diseases such as Generalized Pustular Psoriasis (GPP), Palmoplantar Pustulosis (PPP), Atopic Dermatitis (AtD), Hidradenitis Suppurativa (HS), and IBD. Thus, spesolimab may be unique in directly suppressing not only pro-inflammatory but also profibrotic mechanisms in these diseases.

Key pharmacokinetic characteristics
Pharmacokinetics (PK) analysis showed that exposure ($AUC_{0\text{-}tz}$ and C_{max}) to spesolimab increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. The effective half-life of spesolimab is approximately 4 to 5 weeks in the linear dose range in healthy volunteers and approximately 3 weeks in GPP patients. For details please see the Investigator's Brochure (IB) [c03320877].

Overall, PK data so far suggests target-mediated drug disposition kinetics for spesolimab.

Pharmacodynamic effects in this first in human Single Rising Dose (SRD) trial [c03361085-07] were assessed by indirect target engagement of Interleukin 36 Receptor (IL-36R) by spesolimab using an ex-vivo whole blood stimulation assay. Preliminary analyses indicate

that ≥94% peripheral IL-36R receptor occupancy is achieved with doses ≥0.05mg/kg from 30 minutes post infusion to 10 weeks.

Drug interactions
Currently there are no data available to suggest interactions of spesolimab.

Residual Effect Period
The Residual Effect Period (REP) of spesolimab is 16 weeks. This is the period after the last dose with measurable drug levels and / or pharmacodynamic effects still likely to be present. The consideration behind the REP derivation is that the half-life of ~4 weeks for spesolimab was observed in the healthy volunteer SRD study of 1368.1. However, in the patient trial 1368.11 where spesolimab was tested in GPP patients, the effective half-life was 23.9 days, ie. ~3.4 weeks. Therefore 16 weeks would correspond to approximately 5 half-lives in patients, after which time most drug will have been cleared and only less than 3.125% of spesolimab will still be available.

Data from non-clinical studies
Spesolimab binds to human IL36R with a binding avidity of less than 1 pM. Spesolimab 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. Spesolimab also inhibits IL8 release in primary human intestinal myofibroblasts and Interferon gamma (IFNγ) secretion in human Peripheral Blood Mononuclear Cell stimulated with IL36α, IL36β, or IL36γ combined with IL12.

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

Toxicology studies
Spesolimab does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with spesolimab. However, hazard identification studies of the 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 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, spesolimab stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1 mL injections of the subcutaneous formulation in rabbits.

These preclinical toxicology data support chronic spesolimab dosing in humans.

Data from clinical studies

Spesolimab or placebo 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 Serious Adverse Events (SAE).

Proof of Concept trial 1368.11 was performed in patients with an acute flare of GPP, a disease closely linked to loss-of-function mutations in the natural IL36R antagonist. Complete data from 1368.11 demonstrate that spesolimab treatment rapidly stops the flare and clears pustules, the primary lesions in GPP. Based on rapid clinical responses on pustules – the key feature of GPP in trial 1368.11, a placebo controlled Phase II trial (1368.15) has been conducted to investigate proof of concept of spesolimab also in patients with PPP, a neutrophilic dermatosis with sterile pustules on palms and soles. This trial also showed a benefit for patients with PPP, with a clinically relevant response and good safety and tolerability. Trial 1368.32 was a Phase IIa, randomized, double-blind, placebo-controlled proof-of-concept trial in patients with moderate to severe Atopic Dermatitis (AtD) were treated with either 600 mg spesolimab (33 patients) or placebo (18 patients) i.v. every 4 weeks over a period of 16 weeks (time point of primary analysis) the trial showed a meaningful treatment effect from Week 8 onwards. For details please see IB [c03320877].

Trial 1368.5 was a multinational, randomized, parallel-group, double-blind trial of spesolimab in patients with moderate-to-severely active UC [c31366073-01]. This trial investigated efficacy and safety of 12-week induction treatment with different dose regimens of spesolimab in patients who had failed previous biologic treatments in the past. Due to recruitment issues, the trial was discontinued in February 2020 after completing 61% of the planned recruitment (communication submitted to Investigational New Drug (IND) 127074 on February 14, 2020 (SEQ 0075). An unblinded analysis was conducted including 90 patients who had either completed or discontinued through Week 12 (data cut-off 31 Jan 2020). At time of trial discontinuation, 8 additional patients were ongoing and therefore not included in the interim analysis.
Although with the sample size achieved, the study was not adequately powered, the results of the interim analysis showed no clear efficacy of spesolimab over placebo in primary and secondary clinical endpoints, although a few patients in the higher dose groups (450 mg q4w and 1200 mg q4w) showed a treatment effect in the strictest endpoints [c31366073-01]. However, changes in the IL-36 inflammatory pathway genes were observed in spesolimab clinical responders which were not observed in the placebo clinical responders, suggesting target engagement and pathway specific effect of spesolimab linked to clinical outcomes in UC patients. !"" # $%&'&%(&)'&%"*+,-'/ 0'1'/,""2 ."" 3%"'/,3'$4

In trial 1368.13 in patients with GPP, spesolimab showed an acceptable safety profile. The overall rates of adverse events were generally comparable between treatment groups during

Week 1. The proportions of patients and incidence rates were balanced between the 2 treatment groups for most system organ classes (SOCs) except for infections. Time-adjusted adverse event incident rates in the spesolimab treatment group were lower at Week 12 than in both treatment groups at the end of Week 1. For details please see IB [c03320877].

In trial 1368.4 in patients with moderate to severe active UC (multi-centre, non-randomized, uncontrolled (single arm), open-label, exploratory trial which assessed biomarker changes in response to IL36 signalling blockade induced by treatment with spesolimab) spesolimab was generally well tolerated [c03320877].

In trial 1368.10 spesolimab was tested at a dose of 1200 mg iv q4w for 12 weeks followed by 24 weeks after the end of the treatment period in patients with mild to moderate UC in addition to a stable Tumor Necrosis Factor (TNF) inhibitor background therapy. Spesolimab was well tolerated and the safety profile was generally comparable with the safety profile of the placebo and no unexpected safety observations were identified [c03320877].

For a more detailed description of the spesolimab (BI 655130) profile, please refer to the IB [c03320877].
Selected drugs from Anatomical Therapeutic Chemical (ATC) (level 3) L04A "Immunosuppressants" are considered Auxiliary Medicinal Products (AxMP) in this trial. These are drugs that are authorised to be used in CD and include the TNF-alpha inhibitors adalimumab, certolizumab and infliximab, the integrin receptor antagonists natalizumab and vedolizumab, and the IL12/23 antagonist ustekinumab. Respective labelling of authorised drugs will be provided to sites in the Investigator Site File (ISF).

Summary
Spesolimab is an anti IL-36R antibody with a high clinical activity to block IL-36R signaling, as demonstrated in patients with GPP, PPP and AtD inflammatory skin diseases that share underlying uncontrolled IL36 activity. In addition, spesolimab has been tested in more than 180 healthy volunteers and 604 patients for up to 16 weeks. For specific information on risks please refer to Section 1.4.2.

Unlike CD, inflammatory damage in UC is limited to the gut mucosa and complications such as stenosis and fistulae related to aberrant tissue remodelling responses are uncommon. Although, spesolimab did not lead to significant clinical efficacy in UC patients, based on its unique antifibrotic mechanism of action it is expected to provide efficacy in reversing or delaying progression of fibrostenotic damage in CD subjects, in particular if combined with an optimized anti-inflammatory treatment, as investigated in this current study 1368-0059.

1.3 RATIONALE FOR PERFORMING THE TRIAL

CD incidence and prevalence are rising [R15-0886] and around 10% of newly diagnosed patients will present with clinically significant gut stenosis, most frequently in the ileum, at the time of diagnosis [R16-3819]. Remarkably, around 50% of overall CD patients will eventually develop stenosis despite successful anti-inflammatory treatment [R15-6125]. Currently there are several medical treatments available that are efficacious to induce and maintain mucosal inflammation remission in CD patients. However, there is no approved

therapeutic drug to arrest or reverse the chronically accumulated bowel damage in these patients, specifically stenosis [P19-05294].

Clinical trial 1368-0059 is the first prospective, randomized, well-controlled proof of clinical concept (PoCC) study to evaluate the effect of an antifibrotic drug on CD-associated small bowel fibrostenosis. Lack of previously validated endpoints and outcomes measures tools have prevented drug development in this indication until this moment.
Currently, the [redacted], a leading group of experts and institutions in this field, have set out to specifically develop new tools to measure clinical and structural (radiological and histological) outcomes in these patients. Thus, beyond evaluating spesolimab efficacy in fibrostenotic CD, this PoCC study aims to start the development and validation processes of these new tools.

The first is a Patient Reported Outcome tool (S-PRO), named Stricturing Crohn's Disease Questionnaire. This is a questionnaire which has been developed in accordance with current Food and Drug Administration (FDA) guidance in collaboration with national and international IBD societies to capture symptoms specific to stenotic complication in CD patients. Thus, S-PRO, together with other patient reported outcomes (PROs) tools will be used in this study to measure symptoms to explore if this instrument might be fit-for-purpose to measure symptomatic endpoints in this population.

Besides patient reported clinical symptoms, an 'objective' measurement of fibrostenosis status and change after treatment in this population is desirable. In CD patients with luminal inflammation phenotype, inflammation is currently objectively assessed by endoscopy and histological evaluation of samples obtained from the superficial mucosa. However, CD stenosis develop mostly in the small bowel, frequently in areas not accessible by endoscopy. Moreover, CD-associated fibrostenosis is a transmural process. In CD, fibrosis accumulates mainly in the submucosa of the gut wall [P20-10740]. Thus, currently available endoscopic techniques would not provide adequate sampling of the tissue of interest [R20-3944]. Hence, cross-sectional imaging is currently the standard to evaluate CD stenosis status in individual patients in the clinical setting. Three core imaging features such as prestenotic dilation, wall thickening and luminal narrowing have been proposed as the most relevant features to describe CD-related stenosis. However, there are no data on the different accuracies of applying three, two or one of these items for the diagnosis of CD-related stenosis and their relationship with patient clinical or symptomatic status [R20-2233].

Regarding the differentiation of inflammation and fibrosis within a specific stenosis, which might guide subsequent therapeutic decisions, available data are also not conclusive. Magnetic Resonance Enterography (MRE) is free of ionizing radiation and has been proposed as the most accurate and widest available technique to differentiate fibrosis from inflammation in CD-related stenosis [P09-14233, R20-3945, R20-3946, R20-3948]. Therefore, in this PoCC trial we propose to use MRE to diagnose and assess the stenosis status in the targeted population at baseline and after treatment in order to explore the radiological variables that might be more closely linked to relevant clinical outcomes in this population. These data might provide the basis to develop a standardized radiological endpoint to be used in future clinical development.

In addition, data on PK, antidrug antibodies (ADA) of spesolimab and biomarkers of tissue remodelling will be collected. A robust understanding of the PK / Pharmacodynamic (PD) response correlation might be achieved using a modelling approach and which might support dose selection for the subsequent adult and pediatric development program.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.4). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an Adverse Event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Currently no medical treatment is available with evidence based effect on reducing the relapse of an acute or subacute symptomatic stenosis episode after initial response to intensified medical therapy (i.e. corticosteroids and escalated immunomodulatory or biologic regime).

The potential benefits that may be demonstrated in this study include:

- Spesolimab may maintain Symptomatic Stenosis Response (as defined in Table 2.3: 1) and may prevent further fibrostenosis development or even induce reversal of stablished fibrostenosis (measured as Radiographic Stenosis Response, defined in Table 2.3: 1), thus reducing relapse and need for invasive interventions (potential for individual patient benefit).
- The addition of spesolimab on top of current Standard of Care (SOC) therapeutics would create an entirely new treatment paradigm for fibrostenosing CD. It would represent the first antifibrotic drug for treating a common and severe CD complication that remains a high, unmet medical need (potential group benefit).
- Beyond the objective of demonstrating PoCC for spesolimab in this disease, the study will help to develop the novel S-PRO and stenotic radiographic outcome, which might be used as key endpoints in future studies in this indication (see Section 7).

Only patients not requiring endoscopic or surgical intervention at the time of study start will be enrolled into the trial. Moreover, during the Lead-in Period all patients will receive high dose but short-term pulse of systemic corticosteroids, which usually leads to a symptomatic response in about 80% of patients, combined with optimization of anti-inflammatory therapy. This represents current SOC for treatment of acute or subacute symptoms of small bowel obstruction in non-surgical and no endoscopic candidates with fibrostenotic CD.

Only responders to the Lead-in Period SOC therapy described above will be randomized to either spesolimab or placebo on top of their individually optimized anti-inflammatory therapy during the Blinded Randomized Treatment Period. Thus, even placebo patients will receive

best available SOC during all study periods and no patient is withheld from current best practice treatment.

1.4.2 Risks

Preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of chronic IL36R inhibition in mice (see IB, Section 5.3, c03320877).

A recent publication has assessed the clinical phenotype and immune function in 12 healthy individuals harboring an IL36R knock-out polymorphism [R17-3632]. This study showed no specific diseases or conditions, in particular of recurrent, severe or opportunistic infections or malignancies, in the medical records of these subjects. Also, serological and in-vitro studies indicated normal levels of non-, tetanus- or varicella-specific immune globulins, and normal immune functions as compared to matched controls, indicating that IL36 blockade is likely to represent a safe and well tolerated therapeutic concept [R17-3632].

Spesolimab has been shown to be safe and well tolerated in more than 149 healthy volunteers exposed in phase I SRD and Multiple Rising Dose (MRD) studies to single or multiple doses of spesolimab up to dose levels of 20 mg/kg given once weekly (qw) for 4 weeks; (for details see IB, c03320877).

Besides preclinical profiles and clinical data from healthy volunteers, patient trials performed to date also suggest that spesolimab is safe and tolerable in patients suffering from different skin conditions [c03320877].

In 1368.4, 1368.5 and 1368.10 (patients with UC) trials as well as in 1368.11, 1368.13 (patients with GPP), 1368.15 (patients with PPP) and 1368.32 (patients with AtD) trials, overall, spesolimab was well tolerated [c03320877].

No other IL-36 receptor antagonist is currently approved, providing further information on identified risks in molecules of this class.

Despite the favourable safety profile so far, as with any immune modulating agent, spesolimab has the potential to impair immune function resulting in an increased risk of infection. The role of IL36 in tumor immunity is not well established at this time, but an increased risk of cancer from an IL36R antagonist, though considered small, cannot be excluded. These potential risks of an experimental combination treatment will be addressed by careful safety monitoring and risk mitigation measures, which will be implemented in this trial of a novel and 1st-in-class MoA: (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 reactions and anaphylactic reactions as adverse event of special interest (AESI); (c) selection of sites experienced in treatment of IBD patients with biologics; and (d) regular surveillance by an independent Data Monitoring Committee (DMC).

Table 1.4.2: 1 lists possible risks for spesolimab as well as theroretical risks derived from general safety considerations of immunomodulatory drugs and from this trial specific procedures.

Table 1.4.2:1 Overview of trial related risks

Investigational Medicinal Product spesolimab (BI 655130)		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Drug Induced Liver Injury (DILI)	Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, DILI is considered as a standard risk in all BI development programs.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. See also Section 5.2.6.1.4, adverse event of special interest. Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.

Table 1.4.2: 1 Overview of trial related risks (cont.)

Investigational Medicinal Product spesolimab (BI 655130)		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Systemic hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of immediate (such as anaphylaxis) or delayed (such as drug reaction with eosinophilia and systemic symptoms) adverse immune reactions.	Patients with a history of allergy / hypersensitivity to the systemically administered trial medication agent or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with severity of the reaction and local SOC of care to interrupt and treat the condition. Systemic hypersensitivity reaction is defined as AESI. It is subject to close monitoring and investigators are requested to assess these conditions using the criteria discussed in the statement paper from Sampson HA [R11-4890].

Table 1.4.2: 1 Overview of trial related risks (cont.)

Investigational Medicinal Product spesolimab (BI 655130)		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections. A recent characterisation of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition may not substantially compromise host defences [R17-3632]. In clinical trials with spesolimab, a higher proportion of patients with mild to moderate infections was seen in the spesolimab treatment group than in the placebo treatment group. Nevertheless, there was no indication of an increased frequency of patients with severe, serious, and opportunistic infections in association with spesolimab treatment.	Screening procedures for infections are established for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Severe infections and opportunistic infections are considered AESIs for this trial. These conditions and serious infections are subject to close monitoring.

Table 1.4.2: 1 Overview of trial related risks (cont.)

Investigational Medicinal Product spesolimab (BI 655130)		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Malignancies	Inhibition of the immune response with an immune-modulating biologic may potentially impair immune defences and thus theoretically decrease immune defense against malignancies. A recent characterisation of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defences [R17-3632].	Patients with a recent history of malignancy will be excluded from participation in this trial. In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with spesolimab. Diagnostics and treatment have to be initiated according to local SOC. Malignancies represent always serious adverse events and are subject to close monitoring.
Hematological laboratory abnormalities	Hematological laboratory abnormalities are not considered to present a risk due to spesolimab administration according to current clinical data for spesolimab. However, due to administration of spesolimab in combination with anti-inflammatory treatments theoretical risks with regards to combination treatment are taken into consideration.	Guidance on assessment and mitigation measures with regards to hematological laboratory abnormalities is included into current Clinical Trial Protocol (Section 4.2.1.4)

Table 1.4.2: 1 Overview of trial related risks (cont.)

Trial procedures		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Blood sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and / or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as • close clinical monitoring for AEs; • selection of experienced sites and site staff; • training.
Infusion of trial medication	There is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and / or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as • close clinical monitoring for AEs; • selection of experienced sites and site staff; • training.

Table 1.4.2: 1 Overview of trial related risks (cont.)

Trial procedures		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Magnetic Resonance Enterography (MRE)	Intravenously applied contrast media could cause allergic reactions. Additionally, contrast agents could cause problems in patients with significant kidney disease. MRE assessments could lead to peripheral muscle or nerve stimulation that may feel like a twitching sensitation. Heating of the body could be caused by the radiofrequency energy used during MRE scans. The MR environment presents in general unique safety hazards for patients with implants, external devices and accessory medical devices that interfer with the magnetic field. The limited space of MR scanners may cause claustrophobic distress in predispositioned patients.	The risks will be addressed by careful monitoring and mitigation measures such as • close clinical monitoring of AEs; • kidney functions will be measured before MRE assements and patients with glomerular filtration rate (GFR) <30 mL/min are excluded from the trial; • patients with contra-indications for MRE are exluded from the trial; • only clinical sites with extensive experience in MRE assessments and trained site staff will be selected.

Table 1.4.2: 1 Overview of trial related risks (cont.)

Trial procedures		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Ileocolonoscopy with biopsy	Diarrhea, abdominal pain, perforation, bleeding effects of anaesthetic medications, infection	Selection of sites experienced in taking care of IBD patients: These risks will be addressed by careful monitoring and risk mitigation measures such as • close clinical monitoring for AEs; • selection of sites with experienced site staff; • ileocolonoscopy will be done according to the standard local care procedures including local clinic / hospital consent authorizing this procedure; • training.

Table 1.4.2: 1 Overview of trial related risks (cont.)

Other risks		
Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Administration of placebo	If the patient is randomized to receive a placebo, the patient´s condition could get worse during the course of the trial.	Trial medication is adminsistered on top of optimized anti-inflammatory biological therapy. Thus, best active SOC treatment is not withhold from any patient.
Use of Auxiliary Medicinal Products (AxMPs): Selected drugs from ATC (Level 3) L04A "Immunosuppressants" are considered AxMPs	Examples of risks which might be associated with AxMPs use include: infections, malignancies and hypersensitivity reactions. No interactions between AxMPs and spesolimab are expected.	Diagnostics, treatment and monitoring have to be implemented according to local SOC.
Use of corticosteroids during the Lead-in Period	Examples of associated risks: infections, elevation of blood pressure, fluid and electrolyte disturbances.	Diagnostics, treatment and monitoring have to be implemented according to local SOC.

1.4.3 Discussion

Although no direct benefit for individual patients can be assumed, based on the provision of individually optimized CD treatment to all patients, the proof of concept achieved in GPP and the strong scientific rationale, there is a reasonable chance that spesolimab may prevent further fibrosis development or even reduce established fibrosis in patients with CD-related small bowel symptomatic stenosis. This would improve long-term outcomes in these patients, for whom currently there are limited effective non-surgical treatments.
Preclinical and clinical data gathered up to this moment strongly suggest that spesolimab is safe at the dose regimens proposed for this trial, even if given in combination with other immune-modulators or biological therapies.
The benefit-risk profile is thus considered acceptable for an investigational product at this stage of clinical development.

Benefit-Risk Assessment in context of COVID-19 pandemic:
Spesolimab 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 have not shown an increased frequency of patients with severe, serious and opportunistic infections with spesolimab treatment. However, higher proportion

of patients with mild to moderate infections was seen in the spesolimab treatment group than in the placebo treatment group.
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 (CTP).

As any other acute infection, a suspected or diagnosed Corona Virus Disease 2019 (COVID-19) infection should be treated according to the SOC and interruption of study medication should be considered. To date, there is no reliable evidence suggesting a link between Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) infections and the IL-36 pathway targeted by spesolimab. Further investigations are needed to elucidate the molecular mechanisms underlying their biological functions in COVID-19. Considering the current knowledge of COVID-19 and the implemented risk mitigation measures addressing the potential risk of infections, patients with indications in which spesolimab is investigated are not per se believed to be at higher risk of COVID-19. Protocol-defined procedures do not impose undue risk to study participants.

The benefit-risk assessment of spesolimab 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 spesolimab 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. Boehringer Ingelheim (BI) as the sponsor, where required, will support the investigator in their decision finding.

2. TRIAL OBJECTIVES AND ENDPOINTS

The overall aim of this trial is to proof the concept that spesolimab is effective and safe in the long-term treatment of symptomatic small bowel stenosis in patients with established CD.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

To demonstrate that spesolimab is effective in maintaining Symptomatic Stenosis Response and / or inducing Radiographic Stenosis Response (defined in Table 2.3: 1) in patients with symptomatic CD-related small bowel stenosis, who have achieved Symptomatic Stenosis Response after standard medical therapy.

2.1.2 Primary endpoint(s)

Spesolimab superiority vs. placebo on one of the following:

- Proportion of patients with maintained Symptomatic Stenosis Response (defined in Table 2.3: 1) at Week 48
- Proportion of patients with Radiographic Stenosis Response (defined in Table 2.3: 1) at Week 48

2.1.3 Secondary endpoint(s)

- Proportion of patients with maintained Symptomatic Stenosis Response (defined in Table 2.3: 1) at Week 24
- Proportion of patients with Radiographic Stenosis Response (defined in Table 2.3: 1) at Week 24

2.3 DEFINITION OF STUDY OUTCOMES

Definitions of **symptomatic** and **radiographic** study outcomes are provided Table 2.3: 1.

Table 2.3: 1 Definitions of Study Outcomes

Symptomatic Stenosis Response	7 days average score for abdominal pain after eating* <2 AND 7 days average score for amount or types of food limitation* <2 **See questions for symptomatic primary outcome and explanation on the scoring in the paragraph below this table.*
Maintained Symptomatic Stenosis Response	Symptomatic Stenosis Response with no confirmed Stenosis Relapse after Week 16 post-randomization
Symptomatic Stenosis Relapse	7 days average score for abdominal pain after eating* ≥2 AND 7 days average score for amount or types of food limitation* ≥2 **See questions for symptomatic primary outcome and explanation on the scoring in the paragraph below this table.*

Table 2.3: 1 Definitions of Study Outcomes (cont.)

Confirmed Stenosis Relapse	Symptomatic Stenosis Relapse AND radiographic confirmation of small bowel obstruction
Radiographic Stenosis Response	a) stricture length improvement (by 25%) + no worsening of pre-stenotic small bowel (SB) diameter* OR b) pre-stenotic SB diameter improvement (by 50%**) + no worsening of stricture length* AND + no new small bowel stenosis + no new pre-stenotic fistula + no new stenotic abscess *no worsening refers to radiographic stenosis no progression **50% improvement in pre-stenotic SB diameter refers to dilation over the 20 mm of normal SB diameter, i.e. 30 to 25 mm change: 50% improvement, 30 to 22.5 mm: 75% improvement
Radiographic Stenosis no progression	No worsening from baseline (change <10%) of: - stricture length OR - pre-stenotic SB diameter AND + no new small bowel stenosis + no new pre-stenotic fistula + no new stenotic abscess
CDAI response	CDAI decrease of ≥100 points from baseline, OR an absolute CDAI ≤150
CDAI remission	CDAI ≤150
Inflammatory flare	Increase in CDAI score by ≥100 points from baseline with an absolute CDAI >220
Confirmed inflammatory flare	Increase in CDAI score by ≥100 points from baseline with an absolute CDAI >220 + An absolute colonic SES-CD >12 + absence of enteric pathogens in stool

The Symptomatic Stenosis Response and the Symptomatic Stenosis Relapse are calculated automatically using 2 questions of the eDiary completed by the patient.
For both questions, a 7-day average score is calculated based on a scale from 0 to 3 as below.

First question:
During the last 24 hours, how often did you experience abdominal pain after eating? [*Score*]

☐ Never [0]
☐ Sometimes [1]
☐ Often [2]
☐ Every time I ate [3]

☐ Not Applicable: I could not eat in the last 24 hours because of my Crohn's symptoms [3]
☐ Not Applicable: I did not eat in the last 24 hours for other reasons [considered as missing data]

Second question:
During the last 24 hours, how limited were you in the amount or types of food you could eat because of your stricturing Crohn's disease? [*Score*]

☐ Not limited at all [0]
☐ A little limited [1]
☐ Moderately limited [2]
☐ Very limited [3]

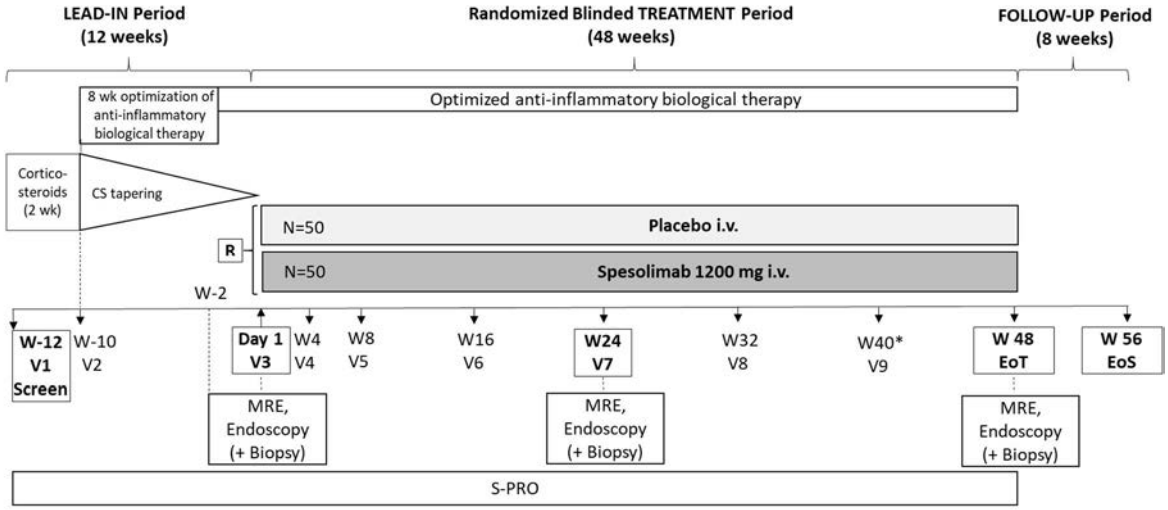
For scoring, average of 7 days information from the eDiary is used. A minimum of 4 days eDiary data is required for calculating the score.

In the Lead-in Period these data are collected daily. For eligibility (inclusion criterion number 8), the last 7 days of the 8 week optimization of anti-inflammatory biological treatment will be used to calculate the average score for these two items.
For primary and secondary endpoint assessment at Week 48 and Week 24, respectively, the average of 7 days eDiary data are used, collected the week immediately preceding the Week 48 and Week 24 visits.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-design trial testing one active dosage vs. placebo. The trial design is illustrated in Figure 3.1: 1.
Patients with obstructive symptoms due to confirmed CD related stenosis are screened for this trial, which includes three periods:
Lead-in Period, Randomized Blinded Treatment Period and Follow-up Period.



Abbreviations: CS = Corticosteroids, MRE = Magnetic Resonance Enterography,
R = Randomization, EoT = End of Treatment Visit, EoS = End of Study Visit, S-PRO = Stenosis Patient Reported Outcome
*last trial drug administration

Figure 3.1: 1: Trial design

Lead-in Period (12 weeks):
Patients with symptoms suggestive of bowel obstruction and with up to two CD-related small bowel stenoses (diagnosed by one of the following: Intestinal Ultrasoun (IUS), Computed Tomography (CT), Magnetic Resonance (MR), Computed Tomography Enterography (CTE), or Magnetic Resonance Enterography (MRE)) will be screened for enrolment into the trial. Patients who have indication of endoscopic balloon dilation or surgery are excluded from this trial. Only patients with clinical indication of anti-inflammatory treatment as per local SOC, are eligible for this trial.

Patients enrolled into the trial may be hospitalized or treated as outpatients and will receive standard medical treatment of their CD-stenosis-related obstructive symptoms, which includes:

- 2 weeks of corticosteroids which will be slowly tapered according to a standardized 8 week regimen (for details see Section 4.2.1)
  AND
- individual optimization of anti-inflammatory biological treatment as described in the algorithm included in Section 4.2.1.

Patient symptoms will be captured daily during the Lead-in Period using the S-PRO diary starting from the screening visit (Visit 1) or as soon as the patient´s situation allows during hospitalisation (latest on the day of discharge).

Patients who during the Lead-in Period, after the 2 weeks of corticosteroids or at any time thereafter need further testing or have indication of endoscopic balloon dilation or surgery as per investigator judgement, will be considered screening failures and will be discontinued from the study.

After 8 weeks of optimized biological anti-inflammatory therapy have been completed, only patients who have achieved a Symptomatic Stenosis Response (as defined in Table 2.3: 1) and an absent or mild-to-moderate colonic endoscopic activity (colonic SES-CD ≤12) will be eligible for randomization into the Blinded Treatment Period.

Patients not achieving Symptomatic Stenosis Response and / or the colonic SES-CD ≤12 eligibility criteria will be considered screening failures and discontinued from the study and undergo other diagnostic tests and treatments as per local guideline / practices.

Randomized Blinded Treatment Period (48 weeks):
Symptomatic stenosis responders to medical Lead-in treatment (as defined in Table 2.3: 1) will be randomized to receive either placebo or spesolimab for 48 weeks (with the last trial drug administration at Week 40) on top of their optimized biological anti-inflammatory therapy.

Randomization will be stratified by number of biologic classes failed prior to screening Visit 1 (0-1 versus >1) and stenotic length (≤ versus >5 cm) as measured by baseline MRE.

Patients need to maintain the biological treatment optimized during the Lead-in Period throughout the Randomized Blinded Treatment Period. After randomization, only 1 dose increase (strength and / or interval) of optimized biological anti-inflammatory therapy is allowed **until Week 16 after randomization.**

Rescue treatment: Any **dose escalation after Week 16 post-randomization or de-novo initiation** of any drug approved for treatment of moderate-to-severe CD during the whole length of the study (see Section 4.2.2.1 and Table 4.2.2.1: 1) **will be considered a rescue treatment.** Such patients will be considered as treatment failures in the primary efficacy analysis. However, the patient may continue the study as per CTP. This means visits and trial drug administration occur as scheduled.

Trial discontinuation: Patients experiencing worsening of stenosis symptoms during the Randomized Blinded Treatment Period that are not controlled by anti-inflammatory

medication and require endoscopic balloon dilation or surgery will be discontinued from the trial. Patients who experience any clinical complication that prevents continuation of the trial drug will be discontinued from the trial. Such patients will be considered as treatment failures in the primary efficacy analysis.

Follow-up Period:
Patient will undergo a safety follow-up monitoring until Week 56, which is not earlier than 16 weeks after the last dose of the trial drug at Week 40.

An extension trial might be offered to patients who present an individual clinical benefit from their trial drug (whether spesolimab or placebo).

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

3.2.1 Rationale for selected Trial Population

We will study the effect of spesolimab in patients with CD-related clinically significant intestinal stenosis. The selected population is representative of CD patients with symptomatic bowel obstruction referred to large referral centers, like those sites participating in this trial.

Current therapeutic options for the proposed population are unproven, limited or temporary efficacy. Escalated anti-inflammatory treatment may alleviate a stenosis with a predominantly inflammatory component. Corticosteroids [R20-2043] as well as anti-tumour necrosis factor alfa therapy have been shown to induce temporary improvement of obstructive symptoms in this population and thus represent the current SOC in many large IBD centers worldwide, though still around 50% of patients require endoscopic dilation therapy or surgery within 12 months [P20-05766].

To reduce and control part of the inherent heterogeneity of the general fibrostenotic CD population which may have different prior treatments and outcomes, history of previous stenosis, disease location and phenotype of stenosis as well as type and severity of symptoms randomization will be used and will be stratified based on variables known to impact outcomes (see Section 7.4). The population will be selected to ensure that only patients with the following disease characteristics are randomized:

1. minimum threshold of symptoms.
2. terminal ileum stenosis.
3. no severe colonic luminal disease.
4. fulfil standard radiographic criteria of CD-stenosis as published by the [redacted] [R20-3947].
5. Endoscopy and MRE central read confirmation of 3 and 4, respectively.
6. Response to a standardized duration and individually tailored optimization of biological anti-inflammatory treatment representative of SOC (see Section 4.2.1.1 and Flow Chart 2) during the Lead-in Period before randomization.

The targeted population is representative of patients with clinically significant fibrostenotic CD who are referred to large referral centers, like those sites participating in this trial, and with the highest but preventable risk of requiring invasive (endoscopic or surgical) treatment on the mid-term. Current therapeutic options for this population are unproven (maintenance of biological anti-inflammatory therapy) or have limited efficacy with universal relapse requiring EBD or surgical options, which are also associated to high morbidity and mortality rates [R20-2235, R20-2236, P20-06254, P20-06255] (see Appendix 10.4).

These measures are expected to increase the chances to demonstrate clinical efficacy while ensuring all patients will receive best available SOC.

3.2.2 Rationale for an Add-On Therapy and Placebo-controlled Trial

Intensified anti-inflammatory treatment may alleviate acute obstructive symptoms of stenosis with a predominantly inflammatory component [P19-05294, R20-2037, P20-05765] whereas, predominantly fibrotic stenoses are less responsive to available anti-inflammatory treatment [R20-2751] and therefore, the latter are currently treated by endoscopic balloon dilation, strictureplasty or segmental small bowel resection. However, there is at this time no imaging technology available to reliably distinguish between fibrotic- and inflammatory-dominant stenoses [R20-2233]. Moreover, there are no therapeutic agents available specifically targeting intestinal fibrosis. Thus, current SOC includes optimization of anti-inflammatory treatment, which is maintained in responders until patient relapses [R20-2037, P20-05766]. Spesolimab is an antibody that blocks the IL36R in humans. *In vivo* studies in IL36R knockout mice have shown reduced emergence of intestinal fibrosis resulting from chronic inflammation, and also reversal of already established intestinal fibrosis in wild type animals after treatment with an IL36R antibody [R19-0857]. In humans, IL-36 has been shown to be a key driver in the cross-talk between macrophages and fibroblasts, a central pathway that leads to collagen VI production in the gut of IBD patients [R19-0857].

We therefore propose to add spesolimab due to its putative predominantly antifibrotic effects as an add-on therapy to optimized anti-inflammatory treatment to test its clinical efficacy to prevent relapses of symptomatic stenosis in patients with clinically significant stenotic CD who present with acute symptoms of bowel obstruction and have responded to intensified anti-inflammatory treatment. Combination treatment of 12 weeks with the same spesolimab dose regimen on top of anti-TNF inhibitors was found safe and well tolerated in a pilot study (N= 22) in mild to moderate UC (see Section 1.4.2). The combination of both, anti-inflammatory and antifibrotic agents should have a synergistic effect and thus show improved efficacy over monotherapy.

The placebo comparator is required to demonstrate efficacy and safety of spesolimab, but the combination treatment design does not withhold the best active SOC treatment from any patient, and thus is ethically justified.

3.2.3 Rationale for a 48 week duration and for proposed endpoints

In absence of well-controlled prospective trials in this indication, there is sparse information on the actual rate of fibrostenotic progression and clinical relapses with SOC treatment in these patients. The largest published cohort study in a similar population treated with

adalimumab suggests that 50% of patients may relapse within 24 weeks [P20 05766]. However, in the mentioned cohort the relapse definition was based on clinical symptoms, using a non-validated score and without radiological confirmation.

The kinetics of symptomatic and structural responses of fibrotic stenoses is not understood at this time. While the inflammatory component of CD related stenoses may improve quite rapidly, as suggested by clinical response to corticosteroids within days, fibrosis regression may take months or longer, as suggested by fibrotic diseases in other organs [R11-4827, P16-11034].

Cross-sectional imaging is the most sensitive and specific way to quantitatively describe and monitor intestinal stenosis [R20-2233]. Emerging data from the [redacted] group using MRE indicate that imaging detection of structural changes in stenosis substantially lags behind the improvement of symptoms. Moreover, available data in fibrostenotic CD patients suggest that substantial numbers of symptomatic relapses accumulate over 6-12 months on anti-TNF treatment [P20-05766].

Therefore, a treatment period of 48 weeks is assumed to show the best discrimination between active and placebo treatment.

We propose to assess the effect of spesolimab treatment on CD-related stenosis by means of two primary endpoints assessing symptomatic and radiographic stenosis response.

The proposed endpoints have been developed in collaboration with the [redacted] and relevant experts in the IBD field.

The Symptomatic Stenosis Response and Relapse outcomes proposed (see Table 2.3: 1) are a composite of the reporting frequency of abdominal pain after eating and the grade of limitation of food amount and food type. Proposal is based on non-published data generated by [redacted] during the development of a new patient reported outcome questionnaire (S-PRO) in patients with CD-related symptomatic small bowel stenosis similar to our targeted population (for more details see Section 5.1.2). Abdominal pain is the most frequently reported symptom in this population, who also report limitation of types and amount of food intake as an adaptive mechanism to avoid symptoms. Those items are seen as the most specific and proximal to stenosis.

The Radiographic Stenosis Response and definition (see Table 2.3: 1) proposed are based on the CONSTRICT group recommendations and further supported by non-published data generated by [redacted] from a retrospective cohort analysis of 100 fibrostenotic CD patients who had MRE imaging at baseline and at 6 months follow-up while on standard biological anti-inflammatory therapy. Thus, stricture length and the maximal diameter of the proximal small bowel dilation as assessed by MRE show the highest reliability scores and sensitivity to change and were thus selected as the key imaging indicators for objective efficacy assessment in the present clinical trial. Fistulas developing in pre-stenotic small bowel have also been included in the definitions since these develop as the consequence of increased stenosis pressure.

3.3 SELECTION OF TRIAL POPULATION

A total of 100 patients will be randomized in a multicentre setting (at least 100 sites). A sufficient number of patients will be screened to meet this randomization 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. Patients already in screening at this time will be allowed to continue to randomization if eligible.

Participation of Woman of childbearing potential (WOCBP): Please refer to Section 4.2.2.3 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 irrespective of whether they have been treated with investigational drug or not.

If retrospectively it is found that a patient has been randomized in error (= did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

3.3.1 Main diagnosis for trial entry

Patients with symptomatic bowel obstruction due to fibrostenotic CD with a maximum of 2 terminal ileum stenoses (diagnosed by one of the following: IUS, CT, MR, CTE or MRE) and who have indication of biological anti-inflammatory therapy will be enrolled into the Lead-in Period of the trial. Patients requiring immediate endoscopic or surgical intervention to treat bowel obstruction will not be randomized into this trial.

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

At Screening:

1. Established diagnosis of clinical Crohn's Disease prior to screening by guideline supported criteria (e.g. clinical and endoscopic evidence, supported by a histopathology report)
2. Suspicion of symptomatic small bowel stenosis
3. Presence at screening visit (or at least 7 days before) of abdominal pain after eating (often, every time, not eat because of my Crohn's symptoms) or limitation in amount or types of food (moderately or very limited), assessed by investigator with patient by means of the two items used to define the Symptomatic Stenosis Response and Relapse (see Section 2.3)
4. **1 or 2 naïve or anastomotic stenoses in the terminal ileum** (as per IUS, CT, CTE, MR, or MRE imaging)**, with at least one being in reach of ileocolonoscopy** (i.e. a

portion of the stenosis is located within 15 cm of the ileocecal valve or ileocecal anastomosis) defined by CONSTRICT criteria [R20-3947]:

- localized luminal narrowing (luminal diameter reduction by ≥50% relative to normal adjacent bowel loop)
  AND
- bowel wall thickening (≥25% increase relative to adjacent non affected bowel)
  AND
- either:
  - prestenotic dilation (luminal diameter greater than 3 cm)
    OR
  - inability to pass an adult or pediatric colonoscope through the narrowed area (not older than 2 weeks) and unequivocal proximal small bowel dilation (but may be less than 3 cm)

5. 18 to 75 years of legal age (according to local legislation) at date of signing informed consent
6. 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 is provided in the patient information (and will be described in Section 4.2.2.3 of the CTP)
7. Signed and dated written informed consent, in accordance with Good Clinical Practice (GCP) and local legislation prior to admission into the trial

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.

At Randomization

8. Have achieved a **Symptomatic Stenosis Response** (average scores <2 for questions on abdominal pain after eating AND on limitation in amount or types of food during the 7 days after optimized biological anti-inflammatory therapy prior to randomization (see Flow Chart 2).
9. MRE confirmation of **1 or 2 naïve or anastomotic stenoses in the terminal ileum, with at least one being in reach of ileocolonoscopy** (i.e. a portion of the stenosis is located within 15 cm of the ileocecal valve or ileocecal anastomosis) defined by CONSTRICT criteria [R20-3947]:

- localized luminal narrowing (luminal diameter reduction by ≥50% relative to normal adjacent bowel loop)
  AND
- bowel wall thickening (≥25% increase relative to adjacent non affected bowel)
  AND
- either:
  - prestenotic dilation (luminal diameter greater than 3 cm)
    OR

- inability to pass an adult or pediatric colonoscope through the narrowed area (not older than 2 weeks) and unequivocal proximal small bowel dilation (but may be less than 3 cm)

10. Absent, mild or moderate endoscopic activity defined by Colonic Simple Endoscopic Score in Crohn's Disease (SES-CD) ≤12

3.3.3 Exclusion criteria

Gastrointestinal Exclusion Criteria

1. No stenosis is in reach of ileocolonoscopy
2. Systemic corticosteroids treatment of current obstructive symptoms for >1 week prior to screening
3. Endoscopic balloon dilation or surgical treatment of the same small bowel stenosis within the last 6 months prior to screening Visit 1
4. More than 2 small intestinal stenoses (where 2 stenoses within 3 cm are considered the same stenosis, a long segment with multiple areas of narrowing or multiple stenosis, that have inflammation between them is counted as 1 stenosis)
5. Patients who require immediate endoscopic balloon dilation or surgical intervention as per the investigator´s discretion
6. Failure of >2 different biological drug classes (mechanisms of action) prior to screening (e.g. TNF inhibitors, Integrin Receptor antagonists, and IL-12 / IL-23 antagonists)
7. 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
8. Current complications of Crohn's Disease such as enterocutaneous, internal or rectovaginal fistules, short gut syndrome, abscess, or any other manifestation that might require surgery or would possibly confound the evaluation of benefit from treatment with spesolimab at screening Visit 1 and randomization (Day 1)
9. Current stenosis in the colon (CONSTRICT criteria apply [R20-3947])
10. Previous strictureplasty on current stricture
11. Current ileostomy or colostomy
12. Any kind of bowel resection or diversion within 6 months of screening Visit 1
13. Any other intra-abdominal surgery (except for abscess drainage) within 3 months prior to screening Visit 1
14. Positive stool examinations for *clostridium difficile* or other intestinal pathogens <30 days prior to screening
15. Fecal transplant ≤6 months before screening

Infectious Disease Exclusion Criteria

16. Relevant chronic or acute infections including human immunodeficiency virus (HIV) and viral hepatitis
17. Active or latent tuberculosis:

- Patients with a positive QuantiFERON®-TB test at 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 with suspected false positive or indeterminate QuantiFERON®-TB result may be re-tested once
- If QuantiFERON®-TB test not available or providing indeterminate results after repeat testing: A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent)

General Exclusion Criteria

18. Contraindication to MRE or inability to undergo MRE (e.g. implanted medical devices that are contraindicated for MRI and cannot be removed (e.g. cardiac pacemaker, neurostimulation systems)), allergy to i.v. gadolinium based contrast agents, acute or chronic renal failure that precludes contrast administration (GFR <30 mL/min), severe claustrophobia)
19. Pathological safety laboratory parameters: hemoglobin <8 g/dL (<80 g/L), total white blood count (WBC) <3000 cells/µl (<$3x10^9$/L), neutrophils <1000 cells/µl (<$1x10^9$/L), thrombocytes <100.000/µl (<$100x10^9$/L), creatinine ≥2 mg/dL (≥176.80 µmol/L), total bilirubin >2 x ULN with ratio of direct / indirect >1 (patients with Gilbert's syndrome are not excluded), Alkaline Phosphatase >3 x ULN
20. 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. This includes colorectal cancer (CRC) present and past (<5 years) history
21. Major surgery (major according to the investigator's assessment, e.g. hip replacement) performed within 12 weeks prior to screening or planned until End of Treatment Visit
22. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant)
23. Previous enrolment in this trial
24. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s) at screening Visit 1, or receiving other investigational treatment(s)
25. History of allergy / hypersensitivity to the systemically administered trial medication agent or its excipients
26. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications (see Sections 3.3.4.1 and 3.3.4.2). If the patients agree, they should stay in the trial: even if continued trial treatment is not possible, they should attend further trial visits to ensure their safety and 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 or withdraw consent to trial participation and the reason must be documented in the patient files and Case Report Form (CRF). If applicable, consider the requirements for AE collection reporting (see Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

Ideally, the patient should attend all remaining visits. Should this not be feasible or should the patient not agree, direct patient contacts in accordance with local regulation should occur at the scheduled visit time points.
If all of the above is not possible, at least an End of Study (EoS) visit should be done (e.g. by phone contact or by other means in accordance with local regulations) to collect the most relevant information: safety, outcome events or last contact date in case of lost to follow-up.

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the patient cannot be guaranteed as he / she 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 safety of the Investigational Medicinal Product (IMP) or other trial treatment
- A hepatic injury alert (as defined in Section 5.2.6.1.4) is detected without identification of an alternative cause in the work-up according to the “DILI checklist”, the patient should not receive subsequent doses of trial treatment. Trial treatment can be restarted if:
  - Alternative cause is identified AND
  - Patient has recovered according to investigator assessment AND
  - After consultation with the sponsor
- The patient needs to undergo endoscopic balloon dilation or surgical intervention to treat the CD stenosisFor individual stopping rules related to specific adverse events, see Section 4.2.1If a patient experiences a moderate or severe opportunistic infection, or if a patient experiences any infection that meets serious adverse event (SAE) reporting criteria, the patient should be permanently discontinued from study drug
- The patient can no longer receive trial treatment for medical reasons such as surgery (see Section 5.2.6.1.4), other adverse events, other diseases, or pregnancy

In case of a temporary reason, trial treatment should be restarted with the next scheduled visit if medically justified, please see Section 4.1.4.

If new efficacy / safety information becomes available, BI will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to 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 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

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

- Failure to meet expected enrolment goals overall or at a particular trial site
- New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1
- Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further treatment and follow-up of patients affected will occur as described in Section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The IMP has been manufactured by BI Pharma GmbH & Co. KG. The spesolimab molecule is an anti-human IL-36 receptor monoclonal antibody heterodimer with a molecular weight of approximately 146 kDa.

4.1.1 Identity of the Investigational Medicinal Products

The investigational product (test product and matching placebo) is provided in vials of 5 mL.

Table 4.1.1: 1 Test product BI 655130 i.v.

Substance:	BI 655130, spesolimab
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	60 mg/mL
Posology:	1200 mg every 4 weeks (q4w) until Week 8 then 1200 mg every 8 weeks (q8w) until Week 40 (last trial drug administration)
Mode of administration:	Intravenous (i.v.) infusion

Table 4.1.1: 2 Test product Placebo matching BI 655130 i.v.

Substance:	Placebo matching BI 655130, spesolimab
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	Not applicable
Posology:	Placebo every 4 weeks (q4w) until Week 8 then Placebo every 8 weeks (q8w) until Week 40 (last trial drug administration)
Mode of administration:	Intravenous (i.v.) infusion

4.1.2 Selection of doses in the trial and dose modifications

The exposure in CD patients expected for the proposed dose regimen of 1200 mg i.v. q4w is lower than the highest exposure tested in healthy subjects in trial 1368.2, which was safe and well-tolerated (refer to current IB [c03320877]). Moreover, this regimen has been tested and found safe for 12–24 weeks in 85 patients with UC; and is currently being evaluated in an

exploratory study in up to 10 patients with perianal fistulizing CD. No dose dependent or dose limiting safety signal has been detected so far.
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. Therefore the highest tested and tolerated dose regimen should provide the highest likelihood to detect a positive effect. Whether lower doses might be sufficient to achieve maximum benefit / risk ratio in this particular population will be subject of subsequent studies.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomized to treatment groups according to a randomization plan in a 1:1 ratio at Visit 3 via Interactive Response Technology (IRT). The randomization will be stratified according to the number of previously failed biologic classes (0-1 vs >1) and stenosis length (≤5 cm vs >5 cm).
Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System). Each vial will have an individual medication number for dispensation.

4.1.4 Drug assignment and administration of doses for each patient

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 investigator or a designee at the site. For the monitoring of hypersensitivity reactions, please refer to Section 5.2.2. If available, a pharmacist should prepare the trial 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 (see 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

Patients, investigators, and central reviewers will remain blinded with regard to the randomized treatment assignments until after the Database Lock (DBL) for the final trial analysis.

An interim analysis is planned to be performed when all patients have completed Week 24 and the treatment information will be partially unblinded to selected members of the sponsor project team. In order to confirm the integrity of the treatment blind, a logistics plan will be set up to ensure that besides patients and investigators, relevant sponsor trial team members who are directly involved in the trial conduct remain blinded. The logistics plan will be finalized prior to the treatment unblind for the interim analysis.

An independent DMC will perform an unblinded safety and efficacy assessment at specified intervals in order to ensure that patients are protected from potential harm, please refer to Section 8.7 for further details.

The access to the randomization code will be kept restricted until its release for analysis. The randomization codes will be provided to bioanalytics before the last patient completed the trial to exclude placebo samples from the PK analysis. Bioanalytics will not disclose the randomization code or the results of their measurements until the DBL.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator 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.

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 randomization code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance (PV) representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated Contract Research Organisation (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 Clinical Research Associate (CRA) (as provided in the contact list of the ISF) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the CTP by the Institutional Review Board (IRB) / Ethics Committee (EC),
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site,
- Approval / Notification of the Regulatory Authority (RA), e.g. Competent Authority (CA),
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated CTP,
- Availability of the proof of a medical license for the Principal Investigator (if applicable),
- 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 or designee 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 medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and / or appointed CRO, the investigator or designee must verify that no remaining supplies (unsused or partcially used) are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.2.1.1 Lead-in anti-inflammatory treatment

CORTICOSTEROIDS

- Methylprednisolone 40 mg/d i.v. or 40 mg/d of oral prednisolone (or the equivalent dose of any systemic steroid formulation. Budesonide is not allowed)
- Patients receiving i.v. steroids should be switched to oral prednisolone when clinically justified, to complete 2 weeks of steroid treatment followed by a defined tapering regime
- Tapering Regime: Decrease by 5 mg/1wk until 10 mg and then decrease by 2.5 mg/1wk until 0 mg

OPTIMIZATION OF ANTI-INFLAMMATORY BIOLOGICAL TREATMENT
Anti-inflammatory biological treatment shall be individually optimized dependent on the prior (failed) treatment of each patient by introducing approved doses of TNF inhibitors (TNFi), vedolizumab, or ustekinumab following the algorithm below, optimization period of 8 weeks starts with the dose adaptation or treatment change as described and is restricted to locally approved dosing regimens of proposed agents:

If patient is anti-TNF naïve:
→ start anti-TNF

If patient is on first anti-TNF
- if plasma drug levels are below the therapeutic range and ADA negative
  → increase dose or shorten interval as locally approved for treatment of moderate-to-severe CD. If not applicable switch to second anti-TNF or switch to ustekinumab or vedolizumab
- if plasma drug levels are in the therapeutic range and ADA positive
  → switch to second anti-TNF or switch to ustekinumab
- if plasma drug levels are in the therapeutic range and ADA negative
  → switch to ustekinumab

If patient is on second anti-TNF (and has failed ≤1 anti-TNF prior)
- if plasma drug levels are below the therapeutic range and ADA negative
  → increase dose or shorten interval as locally approved for treatment of moderate-to-severe CD. If not applicable switch to ustekinumab or vedolizumab
- if plasma drug levels in the therapeutic range or ADA positive
  → switch to ustekinumab

If patient has failed ≥ 2 anti-TNF and is on vedolizumab
→ switch to ustekinumab

If patient has failed ≥ 2 anti-TNF and is on ustekinumab
→ switch to vedolizumab

4.2.1.2 Optimized anti-inflammatory treatment during the Blinded Randomized Treatment Period

After achievement of Symptomatic Stenosis Response patients need to maintain their optimized anti-inflammatory treatment initiated during the Lead-in Period after randomization and throughout the Blinded Randomized Treatment Period.

4.2.1.3 Concomitant Medication

All concomitant medications and the reason(s) for use will be documented throughout the course of the study. Concomitant therapies for other conditions, e.g. hypertension, diabetes, are allowed.

Allowed for CD treatment

Lead-in Period
The following CD therapies are allowed to be initiated or continued with dose optimization (as defined per protocol, see Section 4.2.1.1) during the Lead-in Period for anti-inflammatory biological treatment optimization. For the categorization of AxMPs, please refer to Section 1.2:

- TNF inhibitors, as locally approved for treatment of moderate-to-severe CD (infliximab, adalimumab, and certolizumab)
- Integrin Receptor antagonists as locally approved for treatment of moderate-to-severe CD
- Interleukin-12 and -23 antagonists as locally approved for treatment of moderate-to-severe CD (i.e. ustekinumab)
- Azathioprine, 6-mercaptopurin or methotrexate (are allowed in combination with TNF inhibitors) but need to be discontinued at least 14 days prior to the randomization with first trial drug administration
- Systemic Corticosteroids (p.o. or i.v.) (only during the Lead-in Period as defined per protocol, see Section 4.2.1.1)

After Randomization
In addition to the above mentioned medications, following CD therapies **are allowed** to be **continued without dose modifications:**

- Oral 5-ASA, stable dose for 4 weeks prior to randomization and throughout the study
- Probiotics (e.g. *Saccharomyces boulardii*), stable dose for 2 weeks prior to randomization and throughout the study

After randomization and prior to Week 16, only 1 dose increase (strength and / or interval) of optimized biological anti-inflammatory medication is allowed as locally approved for treatment of moderate-to-severe CD for that agent. No switch to a different agent is allowed.

If the patient needs further optimization and no dose increase is possible for that agent as per local label, patient can switch to a different agent. This will be considered rescue therapy as described below.

Any dose increase after Week 16 post-randomization, or de-novo initiation (switch) of any medication approved to treat moderate-to-severe CD throughout all the study period will be considered a rescue treatment. Such patients will be considered as treatment failures in the primary efficacy analysis. However, the patient may continue the study as per CTP. This includes the visit schedule and trial drug administration.

Antidiarrheals for control of chronic diarrhea (e.g. loperamide, diphenoxylate with atropine) are allowed at any time during this clinical trial.

4.2.1.4 Management of Adverse Events

Systemic hypersensitivity including infusion reaction and anaphylactic reaction
In case of systemic hypersensitivity including infusion reaction and anaphylactic reaction emerging during or after infusion of trial medication, the investigator should consider in accordance with severity of the reaction and local SOC to

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

Also draw a plasma sample for Immunglobulin (Ig) E and ADA as detailed in the Laboratory Manual (filed in the ISF). Also initiate the evaluation of histamine, serum tryptase, and complement components.

In case of infusion reaction / systemic hypersensitivity, based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate infusion reactions / systemic hypersensitivity (according to RCTC grading in Section 5 of the ISF) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of spesolimab / Placebo in the ISF. In any case, the total duration of infusion should not exceed 90 minutes (1.5 hours) provided that the maximum time between the start of preparation and completion of administration of the solution to the patient does not exceed 8 hours.

In case of anaphylactic reactions based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.3, [R11-4890]) suspected to be caused by the trial medication, the investigator should permanently discontinue treatment with the trial medication.

When a delayed hypersensitivity reaction is suspected, please draw a blood sample for laboratory assessment and evaluate for signs of extra-cutaneous organ involvement. The decision to discontinue treatment and/or restart treatment after resolution of the reaction should be based on reaction type and severity.

Severe infections (according to RCTC grading in Section 5 of the ISF), mild opportunistic or mycobacterium tuberculosis infections
Treatment of the infection should be initiated promptly according to local SOC. 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 SOC.

Severe hematological laboratory abnormalities (according to RCTC grading in Section 5 of the ISF)
No further trial medication should be administered in case of hematological laboratory abnormalities (leucopenia, neutropenia, lymphopenia, low platelets count, hemoglobin decrease) of Grade 3 or higher. Treatment with trial medication may be restarted when hematological laboratory abnormalities decrease below the level of Grade 3, patient has recovered based on investigator's assessment and after consultation with the sponsor.

4.2.2 Restrictions

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 Prohibited and restricted medications

Medications or class of medications	**Restriction duration**
Investigational products	Prohibited from 30 days or 5 half-lives (whichever is longer) prior to screening (Visit 1) and during the study. Wash-out of 30 days not needed if confirmed undetectable plasma concentration.
Biologic therapies aside from those used for the treatment of Crohn's disease	Prohibited during the study.
Any non-biologic medication (incl. cyclosporine, JAK inhibitors, S1P modulators, SMAD7 antisense inhibitors.	Not allowed from 30 days or 5 half-lives (whichever is longer) prior to screening and during the study. Wash-out of 30 days not needed if confirmed undetectable plasma concentration.
Azathioprine, 6-mercaptopurin or methotrexate (when given in combination with biologics)	Not allowed at least 14 days prior to randomization and during the study
Oral 5-ASA	Oral administration: Only allowed during the trial, if dose is stable for at least 4 weeks prior to randomization and during the study.
Probiotics (e.g. *Saccharomyces boulardii*)	Only allowed during the trial, if dose is stable for at least 2 weeks prior to randomization and during the study.

Table 4.2.2.1: 1 Prohibited and restricted medications (cont.)

Medications or class of medications	**Restriction duration**
Corticosteroids	Oral administration: i.v. and oral steroids are allowed per CTP during the Lead-in Period, refer to dosing and tapering schedule (Section 4.2.1). Rectal administration: Not allowed from 2 weeks prior to screening up to end of the trial. Allowed steroid treatments: Short-term use (<7 days) of systemic (oral or parenteral) corticosteroids for treatment of AE not related to the underlying CD, including treatment of infusion or anaphylactic reactions, are permitted throughout the study, both during the Lead-in Period and after randomization. Locally administered steroids as e.g. intra-articular, nasal inhalation or intra-ocular administration are allowed.
NSAID (Non-steroidal anti-inflammatory drugs)	Chronic use: Prohibited (Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc. and daily use of baby or low-dose [81-162.5 mg] aspirin for cardiovascular prophylaxis are permitted).
Live vaccines	Prohibited from 6 weeks prior to screening (Visit 1) and during the study.

4.2.2.2 Restrictions on diet and life style

On days with MRE, trial participants should have nothing by mouth 4 hours prior to this procedure.
On days with endoscopy, trial participants need to clean out the colon (colon preparation) by drinking a special solution for this procedure on the evening before.

4.2.2.3 Contraception requirements

WOCBP (for the definition please refer to Section 3.3.2) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly during the trial, and for a period of at least 16 weeks after the last study drug administration. Additional double barrier method of contraception is not required. A list of contraception methods meeting these criteria is also provided in the patient information.

Female Patients:
Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm

OR
Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable.

Male Patients:
Contraception of male trial participants and female partners of male trial participants are not required.

4.3 TREATMENT COMPLIANCE

Trial medication will be administered in accordance with the protocol under the supervision of the investigator or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

Any missed dose has to be documented and reported to the Clinical Trial Manager (CT Manager).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Efficacy will be assessed both on investigator (or designee) examinations and assessments and on Patient Reported Outcomes (PROs).
The MRE examination will be centrally reviewed to evaluate the Radiographic Stenosis Response.
The endoscopy (ileocolonoscopy) examination provides information on the inflammation status of the terminal ileum and colon. Endoscopy examinations will be centrally reviewed and assessed based on the SES-CD. Mucosal biopsies obtained from the terminal ileum and colon will serve the histopathology examination and exploration of disease and IL-36 pathway specific biomarkers.
Clinician's assessment of CDAI, and the clinician's reported outcomes (clinROs) CGI-C and CGI-S scales assess the status of both the inflammatory and stenotic portion of the fibrostenotic CD condition.
PROs include the newly developed S-PRO, as well as IBDQ, SF-36, and the PGI-S scales, and the diary portion of the CDAI.

5.1.1 Magnetic Resonance Enterography (MRE)

MRE is performed as indicated in the Flow Chart according to specifications detailed in the Central Imaging Vendor Manual (including documents describing image acquisition and image review) filed in the ISF. All scans on each patient are performed on scanners that were accredited for use by the Central Imaging Vendor. To achieve optimal image quality, patients should be nothing by mouth 4 hours prior the procedure. Additionally, MRE is conducted after oral ingestion of neutral enteric contrast medium and a spasmolytic agent is given immediately before the examination. During the MRE scan, an intravenous contrast medium is administered via a single dose. The detailed patient preparation procedure is outlined in the Central Imaging Vendor Manual.
Before undergoing MRE examinations, all patients must be checked for the GFR and meet the criterion of GFR ≥30 mL/min at screening Visit 2. Additionally, GFR values must be obtained before every MRE examination and must not be older than 14 days. Ideally these GFR assessments are done locally but can also be performed via central laboratory (reporting timelines are to be considered). Before beginning the MRE assessments, the scanning procedure should be explained carefully to the patient.

MRE is performed at timepoints given in the Flow Chart, and should be acquired at the discretion of the investigators at unscheduled visits in case of a Symptomatic Stenosis Relapse. If an unscheduled visit with MRE acquisition occurred within 4 weeks prior to the scheduled MRE visit depicted in the Flow Chart, the MRE must not be repeated at the planned scheduled visit. In case an MRE, both scheduled and unscheduled, was not performed according to the specifications detailed in the Central Imaging Vendor Manual, it needs to be repeated within 14 days after the visit.
All MRE scans are digitally transferred for central review within a pre-specified time period and the central review is conducted as outlined in the Central Imaging Vendor Manual. The evaluation of cross-sectional MRE data focuses on the morphological fibrostenotic

characteristics stricture length, pre-stenotic dilation of the bowel lumen and the manifestation of pre-stenotic fistulae. MRE images will be stored up to 15 years at the sponsor facilities or by an external vendor for future scientific research.
Additionally, non-patient MRE images have to be provided regularly for quality assurance purposes according to the Central Imaging Vendor Manual. Further information on MRE is provided in a separate manual filed in the ISF.

5.1.2 Stenosis Patient Reported Outcome (S-PRO) Tool

The [redacted], a leading group of experts and institutions in this field, have set out to specifically develop new tools to measure clinical and structural (radiological and histological) outcomes in these patients. The Stenosis Patient Reported Outcome tool (S-PRO) is developed following FDA guidance in collaboration with national and international IBD societies to capture symptoms related specifically to stenotic complication in CD patients. The S-PRO questionnaire (Stricturing Crohn's Disease Questionnaire) provides the data for the study outcomes such as Symptomatic Stenosis Response and Symptomatic Stenosis Relapse.
The S-PRO is set up as an eDiary and has a recall period of 24 hours. The S-PRO will be measured as indicated in the Flow Chart: Daily during the Lead-in Period and daily for 7 days preceding the scheduled site visits during the Randomized Blinded Treatment Period. Additionally, patients will be asked to contact the site at any time they feel a worsening of CD symptoms. An unscheduled visit will then be arranged and the patient will be asked to immediately start the S-PRO completion, daily, for (at least) 7 days before the unscheduled visit. The S-PRO is provided in Appendix 10.1.1.
A 7-day average score will be calculated; scoring method will be described in the Trial Statistical Analysis Plan (TSAP).

5.1.3 Ileocolonoscopy with Simple Endoscopic Score for Crohn's Disease (SES-CD)

The endoscopic CD activity will be assessed using the SES-CD score. The SES-CD is a numerical grading system generating a total score (0-56) composed of 4 variables (presence of ulcers, ulcerated surface, affected surface, and presence of narrowings), all of which are recorded in 5 segments: terminal ileum, right colon, transverse colon, left colon, and rectum [R16-0177].
The SES-CD will be measured at the timepoints noted in the Flow Chart. The SES-CD is provided in Appendix 10.1.2. Ileocolonoscopy videos will be done as described in the Endoscopy Video Instruction Manual filed in the ISF and digitally transferred for central review within a pre-specified time period and the central review is conducted as outlined in the Central Imaging Vendor Manual.

5.1.4 Crohn's Disease Activity Index (CDAI)

The clinical changes in luminal CD activity during the trial will be assessed using the Crohn's Disease Activity Index (CDAI) [R15-5253]. The patient will have to complete the CDAI symptom score data in an eDiary daily for 7 days before a visit (scheduled and unscheduled).

The CDAI will be calculated at the timepoints noted in the Flow Chart. The activity score for Crohn's Disease to calculate the CDAI is provided in Appendix 10.1.3.

5.1.5 IBDQ

The IBDQ [R97-3472] is a 32-item self-report questionnaire for patients with IBD to evaluate the patient reported outcomes across 4 dimensions:

- bowel symptoms (loose stools, abdominal pain)
- systemic symptoms (fatigue, altered sleep pattern)
- social function (work attendance, need to cancel social events), and
- emotional function (anger, depression, irritability)

Each question has graded response choices numbered from 1 to 7. Scores range from 32 to 224 with higher scores indicating better outcomes.
The IBDQ will be measured at the timepoints noted in the Flow Chart. The IBDQ has a 2-week recall period and is provided in Appendix 10.1.4.

5.1.6 SF-36

The SF-36 is a widely used instrument to measure health-related quality of life among healthy subjects and patients with acute and chronic conditions. It consists of 36 questions [R97-1093]. SF-36 scores can be compared across different populations of patients and healthy subjects.
Response options vary but are mostly a 5- or 3-item Likert scale. Subscales (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) are reported individually and summarised as Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (range: 0-100, with a score of 50±10 considered to reflect the US norm [R16-0032]). A 3 point difference is recommended as an minimal clinically important difference threshold for between-groups comparisons of the PCS and MCS [R16-0033].
SF-36 will be measured at the timepoints noted in the Flow Chart. The acute version of the SF-36 with a 1-week recall period will be used and is provided in Appendix 10.1.5.

5.1.7 Patient's Global Impression of Severity (PGI-S)

The PRO PGI-S scale has been developed for mental conditions, but has been used in several conditions.
There are four PGI-S versions measuring: post-prandial abdominal pain, dietary restriction, stenosis symptoms overall and stenosis symptoms related impact in daily life. The PGI-S scales will be measured at the timepoints noted in the Flow Chart. The PGI-S scales are provided in Appendix 10.1.6.

5.1.8 Clinician's Global Impression of Change (CGI-C) and Clinician's Global Impression of Severity (CGI-S)

The clinician's reported outcomes (clinROs) CGI-C and CGI-S have been developed for mental conditions, but have been used in several conditions [R19-1932]. Ideally, clinROs should be assessed always by the same physician.
The CGI-C is usually rated from trial medication start, in this trial the investigator is asked to recall the period since the patient started this study.
Those CGI versions focus on stenosis symptoms overall.
The CGI-C and CGI-S scales will be measured at the timepoints noted in the Flow Chart. The CGI-C and CGI-S scales are provided in Appendix 10.1.7.

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature, and respiratory rate)
- Safety laboratory values (hematology, clinical chemistry, coagulation, and urinalysis)
- 12-lead Electrocardiogram (ECG)
- Adverse events (AEs)
- Adverse events of special interest (AESIs)
- Serious adverse events (SAEs)
- Intensity of AEs will be assessed by RCTC version 2.0 (refer to ISF for details, and see Appendix 10.4)
- Immunogenicity (ADA/Nab)

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Targeted physical examination will include evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

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

Measurement of body weight will be performed at every visit, height at Visit 1 only.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart prior to blood sampling.
This includes body temperature, respiratory rate, systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute), and in a seated position after

approximately 5 minutes of rest. The results must be included in the source documents available at the site.

At dosing visits, vital sign evaluations will be performed pre-dose and additional evaluations will be taken post-dose, i.e. approximately 10 minutes and approximately 60 minutes after stop of the infusion.

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

Monitoring for hypersensitivity reactions:
Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose of trial drug administered at Day 1 (Visit 3) and 1 hour following all other doses of trial 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.

5.2.3 Safety laboratory parameters

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.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.
Patients do not have to be fasted for the blood sampling for the safety laboratory.
The safety laboratory samples relevant for Day 1 are to be taken when the patient comes for the baseline MRE examination (10 business days before Day 1) in order to have the laboratory report available at Day 1.

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

In case the criteria for Potential Severe DILI 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).
The amount of blood taken from the patient concerned will be increased due to this additional sampling.
The central laboratory will transfer the results of the analysis to the sponsor or delegate.

Table 5.2.3: 1 Safety laboratory tests

Category	**Test name**
Hematology	Hematocrit (Hct) Hemoglobin (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

Table 5.2.3: 1 Safety laboratory tests (cont.)

Category	Test name
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine eGFR (estimated by CKD-EPI formula) (only at screening Visit 2) 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
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), with microscopic examination if urine analysis abnormal	Color & Clarity Specific Gravity pH Protein Glucose Ketones Bilirubin Urobilinogen Nitrite Blood Leukocyte Esterase
Urinalysis	Urine Creatinine
Urine (only at screening)	Albumin (quantitative)
Infections Testing	HBV-DNA (quantitative) at EoT Visit[2]
QuantiFERON-TB test	QuantiFERON®-TB-Gold Plus 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: 2 footnote 2)

[3] There is the trial site option to perform a TST (PPD skin test)

[4] If the first QuantiFERON®-TB-Gold Plus test result is undetermined, a re-test should be performed. If the QuantiFERON®-TB-Gold Plus re-test result is undetermined, a PPD skin test should be performed.

Table 5.2.3: 2 Exclusionary laboratory tests

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-Gold Plus[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 test 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 TST (PPD skin test)
[4] If the 1st QuantiFERON®-TB-Gold Plus test result is undetermined, a re-test should be performed. If the re-test QuantiFERON-TB-Gold Plus test result is undetermined, a PPD skin test should be performed.

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a 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 AEs 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 (see Section 3.3.3). In case of an infusion reaction / systemic hypersensitivity, monitor the patient per SOC, grade the intensity of the reaction according to RCTC grading and proceed as described in Section 4.2.1.4.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

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

- Worsening of the underlying disease or of other pre-existing conditionsChanges in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the Electronic Case Report Form (eCRF) only.

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- 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 or which are indicated in the situation of acute of obstructive symptoms at the time of enrolment 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).

For Japan only: An event that possibly leads to disability will be handled as 'deemed serious for any other reason' and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.
The latest list of "Always Serious AEs" can be found in the Electronic Data Capture (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 in Section 5.2.6.2.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (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 5.2.6.2.2.

The following are considered as AESIs:

Infusion reaction and anaphylactic reaction
Any suspicion of severe infusion reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.3, [R11-4890]).

Severe infections (according to RCTC grading in Appendix 10.4 and filed in the ISF)

Opportunistic and mycobacterium tuberculosis infections
These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium / pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium,

salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617].

Potential Severe DILI
A potential severe DILI that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST (Aspartate Aminotransferase) and / or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other
  OR
- ALT and / or AST elevations ≥10-fold ULN.

In addition patients will be discontinued from study treatment if any of the following are observed:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Any ALT or AST value >3X ULN will be confirmed with a repeat test within 48 to 72 hours along with obtaining ALP and total bilirubin. If the elevated AST/ALT value is confirmed, close monitoring and evaluation for alternative causes of elevation of transaminases should be undertaken [P09-12413].

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.

5.2.6.1.5 Intensity (severity) of AEs

The intensity grading of AEs should be performed according to the RCTC Version 2.0 developed by [redacted] [R13-3515].
Refer to the ISF for intensity / severity classification.

Grade 1 mild

Grade 2 moderate
Grade 3 severe
Grade 4 life-threatening

5.2.6.1.6 Causal relationship of AEs

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

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the trial 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
- There is an 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

5.2.6.2.1 AE Collection

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

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

- From signing the informed consent onwards until the individual patient's end of trial (= the EoS Visit):
  all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial drug related SAEs and trial drug 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, but not on the CRF.
  In case of an extension trial, this does not apply for patients rolling over into the extension trial.

In case of extension trial, for patients, who roll-over:

- From signing the informed consent (1368-0059) onwards until the first dose of extension trial medication: all AEs (non-serious and serious) and all AESIs. Updates to concomitant therapy should also be included until the first dose of extension trial medication.

5.2.6.2.2 AE reporting to the 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 to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific process will be specified 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 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. 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.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Spesolimab concentrations will be reported descriptively. No PK parameters will be calculated. PK data will be incorporated into a larger pharmacometric analysis with other trials of the BI 655130 project. Also, ADAs will be measured and their impact on PK will be assessed. Samples that are confirmed positive may be further characterized using a validated neutralizing antibody (Nab) assay. The relationship between PK and selected efficacy endpoints, biomarkers and AEs may be assessed. PK and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation in accordance with sponsor's standard procedures.

Please refer to the Flow Chart for the time points of PK and ADA sample collection. Date and exact time of drug administration and PK and ADA sampling will be recorded on eCRFs. On visits with study medication dosing, PK and ADA samples should be collected prior to administration of study drug.

5.3.2 Methods of sample collection

5.3.2.1 Plasma sampling for PK analysis

For quantification of spesolimab plasma concentrations, blood will be taken from a forearm vein into a K2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flow Chart under plasma PK. Handling procedures can be found in the Laboratory Manual in the ISF. After completion of the trial, the plasma samples may be used for further methodological investigations, e.g. for stability testing. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

5.3.2.2 Plasma / Serum sampling for ADA and Nab assessment

For ADA assessment, blood will be taken from a forearm vein into a K2EDTA anticoagulant blood-drawing tube at the time points listed in the Flow Chart. For Nab assessment, blood will be taken from a forearm vein into a serum blood drawing tube at the time points listed in the Flow Chart. Refer to the Laboratory Manual in the ISF for further details.

The plasma / serum samples may be used for further methodological investigations, e.g. for stability testing. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

5.4 ASSESSMENT OF BIOMARKER(S)

Biomarkers associated with fibrostenotic CD and IL-36 pathway will be assessed in biopsies, peripheral blood and stool samples from patients both pre- and post-treatment with spesolimab.
Blood samples (serum), stool samples and biopsies will be collected at time points indicated in the Flow Chart for the analysis of biomarkers.
All remaining samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.
The statistical analysis results of the biomarker analyses may be reported in the Clinical Trial Report (CTR) or in a separate biomarker report.
The biomarker assay analysis will be performed in a staged approach. The initial analysis will focus on selected markers and time points (i.e. baseline, Week 24 and Week 48) and depending on these results a decision will be made about further analysis of all samples. This is due to the exploratory nature of the mechanism being tested and the timing of effect on candidate biomarkers in the study.

5.4.1 Biochemical and cellular biomarkers

Serum samples will be collected to assess changes in protein levels of disease specific IL-36 pathway specific biomarkers such as but not limited to Pro-C16 and C4M both pre and at various time points post treatment with spesolimab.
In addition, stool samples will be collected to assess changes in levels of inflammatory markers such as but not limited to calprotectin, haptoglobin, hemoglobin, MMP12, MPO, proteinase 3, resistin, serpin A4, PGRPS, properdin, chitinase 3L like 1, lipocalin 2, HMGB1 and neopterin pre and at various timepoints post-treatment with spesolimab. These biomarkers are considered exploratory biomarkers and respective assays will need to be qualified to meet the required performance criteria.

Mucosal biopsies for histology and immunohistochemistry (IHC) analyses both pre and post treatment with spesolimab will be performed at timepoints outlined in the Flow Chart on Day 1 (baseline), Week 24 and Week 48 (End of Treatment (EoT) visit). On Day 1 and Week 24, these should be collected prior to administration of study drug. Tissue samples will be assessed for the expression of markers such as but not limited to IL-36R by IHC.

5.4.2 Pharmacogenomic biomarkers

RNA Sequencing

Ribonucleic Acid (RNA) sequencing on mucosal biopsies both pre and post treatment with spesolimab will be performed at time points outlined in the Flow Chart on Day 1 (baseline), Week 24 and Week 48 (EoT visit). On Day 1 and Week 24, these should be collected prior to administration of study drug. Transcriptome-wide analysis using RNA sequencing is used to identify spesolimab modulated differential gene expression comparing placebo-corrected baseline, Week 24 and Week 48 timepoints.
Whole blood samples may be analyzed to assess changes in gene expression both pre and post treatment with spesolimab as specified in the Flow Chart. Therefore RNA may be isolated from peripheral blood and analyzed by RNA sequencing.

Characterization of stool microbiome and / or stool miRNA
Stool samples may be assessed for microbiome and Micro Ribonucleic Acid (miRNA) expression pre and and post treatment visits as specified in the Flow Chart.

5.4.3 Methods of sampling collection

Biomarkers sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK / PD data), including addition of samples and visits, as long as the total blood volume taken from each patient does not exceed 500 mL. Such changes would be implemented via CTP amendments.
In addition to biopsies from the strictured area, biopsies from ileum and / or colon / rectum will also be collected during ileocolonoscopy for RNA expression and / or IHC at baseline, Week 24 and Week 48.

For the assessment of RNA expression from whole blood, a maximum of 8 ml blood will be collected and stored at time points indicated in the Flow Chart for subsequent analysis.

For the assessment of soluble protein biomarkers in serum, blood will be collected from a forearm vein in a serum separation tube at time points indicated in the Flow Chart.

Detailed instructions for biopsies, biomarkers sampling (serum and stool), handling and shipment of samples are provided in the ISF or Laboratory Manual.

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

DNA banking
One blood sample will be used for DNA Banking if participation and the separate informed consent is agreed upon by the patient as noted below. The DNA Banking sample, derived from the original blood sample, will be stored at the sponsor. The stored DNA may retrospectively be analysed, e.g. to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions.

5.5.1 Methods and timing of sample collection

Genomic DNA will be extracted from blood samples according to standard molecular genetics methods and analysed by using standard genotyping technologies. Approximately 8.5 mL blood will be drawn for DNA banking.

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the Laboratory Manual. For sampling timepoints see Flow Chart.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

Magnetic Resonance Enterography (MRE)
Currently, no specific antifibrotic therapies are available for fibrostenotic CD and the drug development for this indication is hampered by a lack of standardized definitions and endpoint criteria for clinical trials. To overcome this lack of standardization for the assessment of fibrostenotic CD, a global, multidisciplinary panel of experts (the CrOhN´S disease antifibrotic STRICTure Therapies [CONSTRICT] group) conducted a consensus process resulting in the development of a conceptual framework for the conduct of early phase clinical trials of antifibrotic agents [R20-3947]. In contrast to classical endoscopic examinations and biopsy sampling that are limited to the evaluation of the superficial mucosa, routinely applied cross-sectional imaging techniques such as MRE, CTE and ultrasound (US) allow the assessment of the entire intestinal wall, which is critical to depict the entire fibrostenotic burden. Based on a systematic literature review followed by an expert consensus process, the CONSTRICT group identified MRE as the preferred imaging modality to diagnose small bowel fibrostenotic CD (sensitivity 55-100%; specificity 91-200%) [R20-4177]. Although CTE is characterized by similar accuracy as for MRE, the absence of radiation exposure favors MRE over CTE for repeated assessments in a longitudinal trial setting. Radiologic features suggested by the CONSTRICT group being indicative for efficacious response to treatment are improvements in stricture length, pre-stenotic dilation, localized luminal narrowing and wall thickening. The changes in features

were suggested to be evaluated at baseline, as well as 24 and 48 weeks post treatment initiation. The CONSTRICT group recommendations were further supported by a retrospective cohort analysis of 100 fibrostenotic CD patients conducted by the [redacted]. Here, the MRE features stricture length and the maximal diameter of the proximal small bowel dilation showed the highest reliability scores (unpublished data) and were thus selected as key indicators for objective efficacy assessment in the present clinical trial.
Acknowledging the lack of prospectively validated clinical and surrogate efficacy endpoints, the resulting clinical trial data will be utilized in collaboration with the [redacted] to further develop the proposed endpoints.

S-PRO
The Stenosis Patient-Reported Outcome (S-PRO) instrument is a new instrument, recently developed by the [redacted]. The overall goal of this [redacted] was to develop tools able to evaluate therapy's success or failure in stenotic CD patients. As part of this goal, they have developed the S-PRO instrument, which measures signs, symptoms and impacts experienced by stenotic CD patients. The instrument has been developed following the standard methodology i.e. the FDA 2009 PRO Guidance to Industry, the emerging Patient-Focused Drug Development Guidance Series, and current scientific best practices for PRO development as presented by the International Society for Pharmacoeconomics and Outcomes Research Content Validity Task Force. [R12-5607, R15-5636]. It is the unique PRO instrument measuring content relevant to stenotic CD patients; and which has been developed for this current context of use (i.e. treatment evaluation). However, its psychometric properties have not been evaluated yet. This trial is seen as a good opportunity to collect further data on this instrument and evaluate those properties.

CGI-C, CGI-S, PGI-S
The clinROs instruments CGI-C and CGI-S scales as well as the PRO instrument and PGI-S scales are not standardly included in IBD clinical trials.
Those instruments have been selected and included as anchor measures to assess S-PRO validity during this study. In particular, those instruments will be used to evaluate S-PRO test-retest validity, concurrent validity, known-Groups validity, ability to detect change and to establish meaningful Within-Patient Change. Those instruments are commonly used in that purpose. PGI scales are proposed by the FDA as anchor measures to Establish Meaningful Within-Patient Change [R12-5607].
The SES-CD, CDAI, IBDQ, SF-36 and safety assessments performed during this trial are standard measurements in CD treatment trials and will be performed to assess treatment response and monitor safety aspects in an appropriate way.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this CTP may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology, which may include but will not be limited to virtual patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial treatment. The implementation of this back-up methodology will depend on patient's consent, operational feasibility, local law and regulations.

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. Each visit date (with its window) up to EoS Visit is to be counted from Day 1 (Visit 3). If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule.

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

In case of a suspected worsening of CD symptoms, the patient should contact the site to arrange for an unscheduled visit including MRE and endoscopy examinations. Detailed descriptions of unscheduled visits and related operational aspects are outlined in Section 6.2.2.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Trial procedures to be performed at each visit are listed in the Flow Chart and in the respective CTP sections.

Patient Reported Outcomes (PROs) such as S-PRO, IBDQ, SF-36 and PGI-S scales should be completed by the patient on his / her own in the pre-specified order in a quiet area / room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team. This applies to every visit with PROs (i.e. all visits except the EoS visit).

Measurement of pre-dose vital signs and ECG should precede blood sampling.

The following sequence of predose procedures at each visit (where applicable) is recommended:

1. PROs (prespecified order: S-PRO, then follow the prespecified order as provided with the tablet at the site)
2. AE and concomitant therapy collection; smoking status
3. Physical examinations (including predose vital signs)
4. ECG
5. Urine pregnancy testing (if applicable)

6. Stool sampling (can be done any time during a visit or sampled at home, i.e. collecting the first stool of the day as close as possible to the planned visit; date and time need to be noted on the collection container)
7. Blood and urine sampling, including PK, ADA / Nab, and biomarkers

For assignment of medication numbers of the vials, an IRT call is needed. The trial drug is administered followed by the assessment of post-dose vital signs.

For the timing of MRE and endoscopy examinations, please see more detailed information
- in Section 6.2.1 for the pre-treatment examinations (baseline, Day 1)
- in Section 6.2.2 for the post-treatment examinations at Week 24 and Week 48.

Generally, the MRE examination should be done before the endoscopy examination at all scheduled and unscheduled visits if possible.

6.2.1 Lead-in Period

The screening (Visit 1) takes place when the patient presents with acute obstructive symptoms of the small bowel.

The trial requirements, including the procedure for the follow-up of prematurely withdrawn patients must be fully explained to the patient and written informed consent obtained prior to initiating any study related evaluation. The importance of staying in the trial until completion of all study requirements will be emphasized. No trial procedures should be done unless the patient has consented to taking part in the trial.
Once consented, the patient is considered to be enrolled in the trial and has started the Lead-in Period. The patient should be recorded on the enrolment log and be registered in IRT as a screened patient. Patients will be assigned a patient number generated via the IRT system.

For the comprehensive list of the trial procedures required at the screening Visit 1 please refer to Flow Chart. Additionally, please see Flow Chart 2 for more details on the Lead-in Period logistics.

It is important to start the completion of the S-PRO starting from the screening visit (Visit 1) or as soon as the patient´s situation allows during hospitalization (latest on the day of discharge). The PROs IBDQ, SF-36 and PGI-S have to be completed at the time of the first S-PRO completion (see above, at Visit 1 or as soon as the patient´s situation allows). S-PRO data are collected daily during the Lead-in Period.

At screening (Visit 1), a blood sample is drawn for Therapeutic Drug Monitoring (TDM). This means to determine the plasma drug level and status of antidrug antibodies for the patient´s anti-inflammatory biological therapy before the enrolment. If the TDM is assessed at the central laboratory, the result availability is expected after 10 business days (= 2 weeks). Where the TDM assessment can be done at a local laboratory, the result availability is possible already after 5 business days (= 1 week). As soon as the TDM results are available,

the optimization of the anti-inflammatory biological therapy according to the algorithm in Section 4.2.1.1 is to be started at Visit 2.

After 8 weeks of optimization of the anti-inflammatory biological therapy, the baseline examinations, MRE and endoscopy, are to be scheduled: The ideal order is to perform the MRE first and the endoscopy second, and performance of both examinations is not recommended on the same day due to different patient preparation.
If endoscopy was done first, 3 days should be between the endoscopy and the MRE examination.

For timely provisioning of eligibility information to the site by central review before Day 1 (V3, randomization), it is important to schedule the baseline MRE at least 10 business days (= 2 weeks) before Day 1 (inclusion criterion no. 8) and the baseline endoscopy (including biopsies) ideally 7 business days before Day 1 (inclusion criterion no. 10).
For the baseline MRE examination, please note the need of GFR assessment within 14 days before the planned MRE examination (either done locally or via central laboratory).

Demography
Informed consent date, gender, age, race and ethnic origin will be collected in the eCRF page. Also, the patient's smoking status will 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.

Baseline Conditions
Baseline conditions will be assessed during screening. 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.

Infections screening
Infections testing will include tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see Section 3.3.3 and Table 5.2.3: 1).

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 on the Baseline Condition page in the eCRF.
For planned procedures / hospitalizations 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 in the CRF.

Patients who fail screening (i.e. do not meet the eligibility criteria) following Visit 1 assessments should be registered as a screen failure in IRT.

6.2.2 Treatment period(s)

When the patient is eligible for randomization (i.e. meets all in-, and none of the exclusion criteria), randomization via IRT will be performed at Day 1 (= V3). The Randomized Blinded Treatment Period is from Day 1 (=V3) to Week 48 (EoT Visit). Procedures described in the Flow Chart for each visit should be performed.

6.2.2.1 Scheduled visits during the treatment period

The site should contact the patient before each of the scheduled visits to remind the patient to start entering his / her S-PRO and CDAI symptom score data into the eDiary daily for the 7 days preceding the scheduled visit.

Scheduled MRE and endoscopy examinations (Week 24 = V7 and Week 48 = V10), should be planned well in advance. These examinations should not be performed on the same day due to the different patient preparation.
If possible, the MRE should be done before the endoscopy to avoid intestinal distention during endoscopy to interfere with MRE evaluation. If endoscopy was done first, 3 days should be between the endoscopy and the MRE examination.
In case an MRE was not performed according to the specifications detailed in the Central Imaging Vendor Manual, it needs to be repeated within 14 days after the visit.

Both examinations should preferably be done within a period of -7 days of the scheduled time point Week 24 (V7) and Week 48 (V10), respectively.
For the MRE examinations at V7 and V10, please note the need of GFR assessment (either done locally or via central laboratory) within 14 days before the planned MRE examination.

6.2.2.2 Unscheduled visits during the treatment period

Reasons that may trigger unscheduled visits:

- Safety reason at the discretion of the patient, investigator or the sponsor
- Worsening of CD symptoms (suspicion inflammatory flare or stenosis relapse)

All unscheduled visits should be described (including the reason for the visit) and documented in the medical / source record, and in the eCRF.

Safety

- The unscheduled visit may include additional collection of blood samples and also additional assessments such as laboratory samples, ECGs, or other procedures deemed necessary by the investigator for safety evaluation.
- In case safety related unscheduled visit occurs **7 days or less before next scheduled visit**, **the safety assessments planned for next scheduled visit might be skipped at the discretion of the investigator**

Worsening of CD symptoms
Patients experiencing worsening of their CD symptoms should contact the site to schedule a visit including MRE and endoscopy examinations. The site will remind the patient to enter S-PRO and CDAI data into the eDiary until the unscheduled visit date (i.e. eDiary daily data for at least 7 days before this visit).

Suspicion of inflammatory flare
CD inflammatory flare, is defined as an increase in CDAI score by ≥100 points from baseline with an absolute CDAI >220 (see Table 2.3: 1). This should be confirmed during the unscheduled visit, with an absolute colonic SES-CD >12 and absence of enteric pathogens in stool.

A patient with a confirmed inflammatory flare (endoscopically confirmed, absolute colonic SES-CD >12) will receive optimized biological anti-inflammatory therapy as described in Section 4.2.1.2. An additional visit might be planned after the start of the new optimized biological anti-inflammatory medication at the discretion of the investigator to check the patient`s response status.

Suspicion of Stenosis Relapse
When a Symptomatic Stenosis Relapse is suspected (see definition in Table 2.3: 1), it should be confirmed with MRE. However, if the MRE was operationally not feasible and small bowel obstruction was confirmed on cross-sectional imaging as per local SOC, MRE does not need to be done.

A patient with a Confirmed Stenosis Relapse will be treated as indicated per local SOC. If eligible, the patient will be treated with optimized biological anti-inflammatory medication as described in Section 4.2.1.2. An additional visit might be scheduled after the start of the new optimized biological anti-inflammatory medication at the discretion of the investigator to check the patient`s response status. If the patient needs immediate endoscopic or surgical treatment, the patient will be discontinued from the trial.

In case the worsening of CD symptoms related unscheduled visit occurs:

- **7 days or less before next scheduled visit**
  - unscheduled visit replaces next scheduled visit
  - thus, ALL VISIT PROCEDURES (including dosing) planned for next scheduled visit as indicated in Flow Chart should be performed
  - therefore, next scheduled visit should be skipped

- **more than 7 days before next scheduled visit**
  - unscheduled visit does not replace next scheduled visit
  - VISIT PROCEDURES to be performed: those indicated in the Flow Chart for Week 24 (V7) except for:
    - IRT call
    - Trial drug administration
    - blood sampling for protein biomarkers and transcriptomic analysis and stool sampling for biomarkers

- therefore **next scheduled visit should not be skipped and performed** as indicated in the Flow Chart except for endoscopy and MRE, which do NOT need to be repeated if these were performed within 28 days (4 weeks) before Week 24 (V7) and Week 48 (EoT-V10) visits (which include MRE and endoscopy examinations).

MRE and endoscopy examinations during unscheduled visit, as for scheduled visits, should not be performed on the same day due to the different patient preparation. If possible, the MRE should be done before the endoscopy to avoid intestinal distention during endoscopy to interfere with MRE evaluation.

For the MRE examination at an unscheduled visit, please note the need of GFR assessment (either done locally or via central laboratory) within 14 days before the MRE examination. If possible, the endoscopy examination performed should include the sampling of biopsies.

In case MRE assessments were not performed in alignment with the Central Imaging Vendor Manual, the examinations have to be repeated within 14 days.

If such an unscheduled visit with a Symptomatic Stenosis Relapse occurred **before Week 16 (= V6)**, and the patient continues the visits and trial drug dosing schedule as planned up to EoT Visit and is having an individual clinical benefit at Week 48, the extension trial might be offered to the patient (see Section 6.2.3).
However, if such an unscheduled visit with a Symptomatic Stenosis Relapse **occurred after Week 16 (= V6)**, and the patient continues the visits and trial drug dosing schedule, this patient will be considered having **no maintained Symptomatic Stenosis Response** and will not be offered to participate in the extension trial.

6.2.2.3 Roll-over to a possible extension trial

Patients completing the Randomized Blinded Treatment Period at Week 48 (V10) and having an individual clinical benefit may be offered to enter an extension trial. Patient information for the extension trial (for patients to whom the extension trial will be offered) may be performed at Week 40 (V9) since EoT Visit (V10) is coinciding with the first visit for the extension trial in most cases.

6.2.3 Follow-up period and trial completion

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

For patients completing the randomized trial treatment regularly at Week 48 (EoT Visit), the safety follow-up visit is scheduled at least 16 weeks after the last dose of study drug at Week 40, i.e. at Week 56 (EoS Visit).

In case of extension trial, for patiens who roll-over:
For patients completing the randomized trial treatment regularly at Week 48 (EoT Visit), and roll-over to the extension trial, are not requested to complete Visit 11 (EoS Visit) and Visit 10

(EoT) will be their last visit. Individual EoS for these patients is defined as the day of first administration of spesolimab in the extension trial.

Early treatment discontinuation
Patients who discontinue treatment prematurely prior to the planned visit for the last trial drug administration at Week 40 should be registered as withdrawn from treatment in IRT. Patients should follow the scheduled visits as much as possible as defined in the Flow Chart. If the patient is not willing to follow the whole visit schedule, at least the EoT Visit should be conducted either immediately or as soon as possible followed by the EoS Visit which is to be scheduled at least 16 weeks after the last trial drug administration. All efforts should be made to keep the patient in the observation for at least 16 weeks after the last dose of the trial drug.

Trial discontinuation
Patients experiencing worsening of clinical stenosis symptoms during the Randomized Blinded Treatment Period, that are not controlled by anti-inflammatory medication and require endoscopic balloon dilation or surgery, will be discontinued from the trial. Patients who experience any clinical complication that prevents continuation of the trial drug will be discontinued from the trial.

Treatment completion
Treatment completion is defined as a patient having completed treatments till planned EoT Visit (Week 48).

Trial completion:
Trial completion is defined when a patient has reached the EoS Visit (Week 56, Visit 11). In the case of patients rolling over in the extension trial, individual patient´s end of trial is defined as the day of the first administration of spesolimab in the extension trial. In this case, the last visit will be at Week 48 (Visit 10).

(S)AEs ongoing at individual patient's end of trial must be further followed up as described in Section 5.2.6.2.2.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

This is an exploratory Phase II trial and it is not planned to test any statistical hypotheses in a confirmatory sense. The results including confidence intervals and p-values will be discussed and interpreted in the perspective of the exploratory character of the trial.

7.2 PLANNED ANALYSES

The efficacy analysis will be performed for the Full Analysis Set (FAS) which is based on the intent-to-treat principle, and comprises all patients who are randomized and received at least one dose during the trial. Efficacy analyses will be based on the planned treatment (i.e. the treatment assigned at randomization). Safety analyses on patients who were randomized and received at least one dose during the trial will be based on the actual treatment received; this set of patients is called the Safety Set (SAF). All efficacy analyses will be conducted on the FAS. All safety analyses will be conducted on the SAF. Further details on endpoint development and analyses will be described in the TSAP.

7.2.1 General considerations

This is an exploratory Phase II trial and it is not planned to test any statistical hypotheses in a confirmatory sense. The results including confidence intervals and p-values will be discussed and interpreted in the perspective of the exploratory character of the trial.

7.2.2 Primary endpoint analyses

The primary objective for efficacy is to evaluate maintained Symptomatic Stenosis Response and / or Radiographic Stenosis Response at Week 48. They are summarized as the proportion of patients with response at Week 48.
The primary analysis of the unadjusted absolute rate difference versus placebo will be calculated simply as the difference in the observed proportion of patients with maintained Symptomatic Stenosis Response / Radiographic Stenosis Response based on FAS. A 95% Newcombe confidence interval around the difference will also be provided. The influence of the stratification factors on the primary endpoints will be characterized as exploratory analyses, which will be specified in Trial Statistical Analysis Plan (TSAP).

7.2.3 Secondary endpoint analyses

For the secondary binary endpoints, based on FAS, the unadjusted absolute rate difference versus placebo will be calculated and a 95% Newcombe confidence interval around this difference will also be provided.

7.2.5 Safety analyses

In order to ensure the patient's safety during the trial, a DMC, independent of the trial and project teams, will be set-up to review all available unblinded safety data as well as selected efficacy data at regular intervals. See Section 8.7 for further details.

The SAF will be used to perform all safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the REP will be considered 'treatment-emergent'. The REP is defined as 16 weeks after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Drug related AEs will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

In addition, the frequency and severity of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA. Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

7.2.6 Other Analyses

In order to ensure that trial assumptions and expectations will be met, a committee with BI internal experts will be set-up to monitor trial progress. See Section 8.7 for further details.

Spesolimab concentrations will be reported descriptively. No PK parameters will be calculated. Please see Section 5.3.1 for details regarding assessment of PK.

All biomarker analysis will be exploratory in nature and will be reported descriptively.

7.2.7 Interim Analysis

An interim analysis will be conducted when 100% of the patients have completed at least 24 weeks of treatment. The results of the analysis will be used for internal planning only and the blind of the trial subsequent to this time-point will handled as described in the trial logistic plan (see Section 4.1.5.1).

Once all randomized patients have completed 48 weeks of study, the primary analysis of this trial at week 48 will be performed. A final DBL will be performed once all randomized patients have completed the 16 weeks safety follow-up.

7.3 HANDLING OF MISSING DATA

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

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

For primary and secondary binary endpoints, the following will be performed:

- If there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighbouring visits also represent a success;
- Otherwise, impute as a non-responder

For further endpoints, rules for handling of missing data will be specified in the TSAP.

7.4 RANDOMIZATION

Patients will be randomized in a 1:1 ratio to spesolimab and placebo with stratification according to the number of previously failed biologic classes (0-1 vs >1) and stenosis length (≤5cm vs >5cm). The randomization schemes will be created using restricted randomization procedures. Details regarding the randomization methodology will be reported in the CTR.

BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization 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 randomization method will be documented in the CTR. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

Calculations were performed using simulations performed via the R software, version 3.5.1.

The study is intended to show an increase of spesolimab over placebo in terms of the difference in proportion of patients achieving Symptomatic Stenosis Response and / or Radiographic Stenosis Response (see primary endpoints in Section 2.1.2). There is currently no clinical trial data available in the published literature that describes a placebo response (add on to the optimized anti-inflammatory treatment) on either maintained Symptomatic Stenosis Response or Radiographic Stenosis Response at Week 48, in the population of patients with obstructive symptoms due to confirmed CD related stenosis.

Based on the treatment failure rates observed from the CREOLE study [P20-05766], there were around 50% clinical stenosis relapse within 24 weeks of adalimumab treatment, and additional 20% relapse rate within 1 year. Together with the clinical and radiographic experts experience, we assume both Symptomatic Stenosis Response rate and radiographic stenosis response rates at week 48 of placebo arm are around 0.3.

We target to observe a difference of at least 10% in favour of spesolimab from at least one of the two primary endpoints. Simulations were used to derive estimates of the success probability that a single trial would demonstrate an observed difference in proportions between spesolimab and placebo that was equal or greater than the defined threshold 10% for at least one of the two primary endpoints. For identifying such a target threshold, a minimum probability of 0.80 was defined. For each trial simulation, the response for each patient on each treatment was generated using a binomial distribution utilizing the expected response rates as noted in table below, and the trial observed proportions were then directly compared. A total of 10,000 trial simulations were performed. The correlation between maintained Symptomatic Stenosis Response and radiographic stenosis response is assumed to be 0.5. Note that the probability of a false positive declaration given the specified target threshold, so called negative scenario is also determined.

Table 7.5: 1 Probability of achieving the threshold differences in treatments given expected treatment response rates with a total sample size of 100 patients

Population Response Rate		Expected Response Difference	Threshold (Observed Diff.)	Probability Threshold Exceeded 1	False Positive Rate (%) 2
Clinical Spe vs Plc	Radiographic Spe vs Plc				
0.35 vs 0.3	0.35 vs 0.3	0.05	0.1	43.3%	22.7%
0.4 vs 0.3	0.4 vs 0.3	0.10	0.1	65.7%	
0.45 vs 0.3	0.45 vs 0.3	0.15	0.1	84.0%	

1. Assuming the expected response rate difference, the probability that the observed spesolimab response rate exceeds that of placebo by at least the threshold amount for at least one of two primary endpoints is displayed.
2. The probability that the observed spesolimab response rate exceeds that of placebo by at least the threshold amount under the negative scenario that treatments for both primary endpoints are equal.

In summary, for a total N of 100 patients, a 1:1 randomization ratio to spesolimab and placebo, then under the assumption of a target difference between spesolimab and placebo of 0.15 for both primary endpoints, then this trial will be able to detect with probability of 84%, a superior response rate, versus placebo, which is at least ≥ 0.1 in magnitude in favour of spesolimab for at least one primary endpoint when the population placebo response rate is 0.30. The corresponding false positive error rate is 22,7%.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practise (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor or delegate 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 finalisation of the CTR.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.
The patient must be given sufficient time to consider participation in the trial. The investigator or delegate 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 or [redacted] delegate 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 risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan (or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials), documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
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 the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. 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 at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source files (MRE and endoscopy) necessary for central eligibility and / or efficacy reads will be provided to an imaging vendor. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address,

telephone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

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
- Medical history (including trial indication and concomitant diseases, if applicable)
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it)
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion / exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The 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 or delegate 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

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the World Health Organisation (WHO) GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised 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 at the site 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 date of the last visit of the last patient in the whole trial ("Last Patient Completed").
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.**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 (HA) request.

The IEC / CA 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.

An Executive Committee consisting of independent experts and sponsor representatives will be established to support the Coordinating Investigator who will be the chair of the Executive Committee. The composition of the Executive Committee will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the Executive Committee members and the sponsor and also summarised in an Executive Committee charter.

A 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.

Given the exploratory nature of this trial and that there is scarce data from this population, in addition to the DMC (see also Section 7.2.5) a committee with BI internal experts on the compound and on the specific disease indication, which will be independent of the clinical trial team will be set-up to unblindly review trial progress at regular intervals. The review will include the individual patient level and aggregated data for all patients including screening failures. The observations regarding trial assumptions and expectations (e.g. event

rates) may be shared with the project team to enable early decisions on further project planning.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), 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 CT Managers, CRAs, and investigators of participating countries.

In the participating countries the trial will be performed by the respective local or regional BI-organisation (Operative Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a CRO based on a contract.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

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

A central laboratory service, central reading service for blinded reading of MRE and endoscopy, and an IRT vendor will be used in this trial.
Details will be provided in the Laboratory Manual, the Central Imaging Vendor Manual, the Endoscopy Video Instruction Manual, and the IRT Manual. These manuals are available in the ISF.

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Stenosis Patient Reported Outcome (S-PRO) Tool

Stricturing Crohn's Disease Questionnaire

For each of the following questions, please choose the one response that best describes your experience with stricturing Crohn's disease during the last 24 hours.

1. How severe was your worst **abdominal pain** during the last 24 hours?
☐ No pain at all
☐ Mild
☐ Moderate
☐ Severe

2. During the last 24 hours, how often did you experience **abdominal pain after eating**?
☐ Never
☐ Sometimes
☐ Often
☐ Every time I ate
☐ Not Applicable: I could not eat in the last 24 hours because of my Crohn's symptoms
☐ Not Applicable: I did not eat in the last 24 hours for other reasons

3. How severe was your worst **abdominal cramping** during the last 24 hours?
☐ No cramping at all
☐ Mild
☐ Moderate
☐ Severe

4. How severe was your worst **abdominal bloating** during the last 24 hours?
☐ No bloating at all
☐ Mild
☐ Moderate
☐ Severe

5. How severe was your worst **nausea or vomiting** during the last 24 hours?
☐ No nausea or vomiting at all
☐ Mild
☐ Moderate
☐ Severe

6. How many **bowel movements** did you have in the last 24 hours?
Enter number of bowel movements: _____

6b. Compared to your usual number of daily bowel movements, does this amount during the last 24 hours represent…
☐ A lot more than my usual amount
☐ Somewhat more than my usual amount
☐ A little more than my usual amount
☐ The same as my usual amount
☐ A little fewer than my usual amount
☐ Somewhat fewer than my usual amount
☐ A lot fewer than my usual amount

7. How severe was any **constipation** you had during the last 24 hours?
☐ No constipation at all
☐ Mild
☐ Moderate
☐ Severe

8. How severe was any **diarrhea** you had within the last 24 hours?
☐ No diarrhea at all
☐ Mild
☐ Moderate
☐ Severe

9. During the last 24 hours, how often did you experience **low energy**?
☐ Never
☐ Sometimes
☐ Often
☐ Always

10. During the last 24 hours, how often did you have a **lack of appetite**?

☐ Never
☐ Sometimes
☐ Often
☐ Always

11. During the last 24 hours, how limited were you in the **amount** or **types of food you could eat** because of your stricturing Crohn's disease?

☐ Not limited at all
☐ A little limited
☐ Moderately limited
☐ Very limited

12. During the last 24 hours, how limited were you in completing your **usual daily activities** (for example, running errands, working, preparing food, or doing chores around the home) because of your stricturing Crohn's disease?

☐ Not limited at all
☐ A little limited
☐ Moderately limited
☐ Very limited

13. During the last 24 hours, how limited were you in **physical activities** (for example, exercising, lifting heavy objects, walking, or biking) because of your stricturing Crohn's disease?

☐ Not limited at all
☐ A little limited
☐ Moderately limited
☐ Very limited

14. During the last 24 hours, how much were your **social activities** limited because of your stricturing Crohn's disease?

☐ Not limited at all
☐ A little limited
☐ Moderately limited
☐ Very limited

15. During the last 24 hours, how **worried were you that your stricturing Crohn's disease might get worse** (such as having an obstruction [e.g., intestinal blockage] or needing surgery)?

☐ Not at all worried
☐ A little worried
☐ Moderately worried
☐ Very worried

16. During the last 24 hours, how **difficult was it to sleep** because of your symptoms from stricturing Crohn's disease?

☐ Not difficult at all
☐ A little difficult
☐ Moderately difficult
☐ Very difficult

10.1.2 Simple endoscopic score in Crohn's Disease (SES-CD)

Table 10.1.2: 1 SES-CD Score

	SES CD score			
Variable	0	1	2	3
Presence of ulcers	None	Aphtous ulcers (W0.1-<0.5 cm)	Large ulcers (W0.5-2 cm)	Very large ulcers (>W2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

	Ileum	Right colon	Transverse colon	Left colon	Rectum	SUM
Presence of ulcers						+
Ulcerated surface						+
Affected surface						+
Presence of narrowings						=
						Sum of all variables Total

10.1.3 Crohn's Disease Activity Index (CDAI)

The Crohn's Disease Activity Index (CDAI) is comprised of eight variables which are summed after adjustment with a weighting factor.

Table 10.1.3: 1 Activity score for Crohn's Disease

Variable	Weighting Factor
Number of liquid or very soft stools in the last 7 days	x 2
Abdominal pain: Average daily rating in the last 7 days (0=none, 1=mild, 2=moderate, 3=severe)	x 5
General well-being: Average daily rating in the last 7 days (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible)	x 7
Extra-intestinal manifestations*, Current - Arthritis/arthralgia - Iritis/uveitis - Erythema nodosum, pyoderma gangernosum, aphthous stomatitis - Anal fissure, fistula, or abscess - Other fistula - Fever over 37.8°C (100°F) during past 7 days	x 20
Lomitil, Imodium, Opiates for diarrhea in the last 7 days	x 30
Abdominal mass (0=no, 2=Questionable, 5=Definite)	x 10
Local Hematocrit (difference standard - current, in % rounded to whole) 47% if male 42% if female	x 6
Body weight: Deviation from ideal body weight in %	x 1

*One point each is added for each of the listed complications

10.1.4 IBDQ

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from 1 through 7. Please read each question carefully and select the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

(1) ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

10.1.5 SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an 1 in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one week ago</u>, how would you rate your health in general now?**

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3

b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf..... ☐ 1 ..... ☐ 2 ..... ☐ 3

c Lifting or carrying groceries..... ☐ 1 ..... ☐ 2 ..... ☐ 3

d Climbing several flights of stairs..... ☐ 1 ..... ☐ 2 ..... ☐ 3

e Climbing one flight of stairs..... ☐ 1 ..... ☐ 2 ..... ☐ 3

f Bending, kneeling, or stooping..... ☐ 1 ..... ☐ 2 ..... ☐ 3

g Walking more than a mile..... ☐ 1 ..... ☐ 2 ..... ☐ 3

h Walking several hundred yards..... ☐ 1 ..... ☐ 2 ..... ☐ 3

i Walking one hundred yards..... ☐ 1 ..... ☐ 2 ..... ☐ 3

j Bathing or dressing yourself..... ☐ 1 ..... ☐ 2 ..... ☐ 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a Cut down on the amount of time you spent on work or other activities.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort).....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past week?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

All of the time	Most of the time	Some of the time	A little of the time	None of the time

a Did you feel full of life? ..... ☐ 1 ..... ☐ 2 ..... ☐ 3 ..... ☐ 4 ..... ☐ 5

b Have you been very nervous? ..... ☐ 1 ..... ☐ 2 ..... ☐ 3 ..... ☐ 4 ..... ☐ 5

c Have you felt so down in the dumps that nothing could cheer you up? ..... ☐ 1 ..... ☐ 2 ..... ☐ 3 ..... ☐ 4 ..... ☐ 5

d Have you felt calm and peaceful? ..... ☐ 1 ..... ☐ 2 ..... ☐ 3 ..... ☐ 4 ..... ☐ 5

e Did you have a lot of energy? ..... ☐ 1 ..... ☐ 2 ..... ☐ 3 ..... ☐ 4 ..... ☐ 5

f Have you felt downhearted and depressed? ..... ☐ 1 ..... ☐ 2 ..... ☐ 3 ..... ☐ 4 ..... ☐ 5

g Did you feel worn out? ..... ☐ 1 ..... ☐ 2 ..... ☐ 3 ..... ☐ 4 ..... ☐ 5

h Have you been happy? ..... ☐ 1 ..... ☐ 2 ..... ☐ 3 ..... ☐ 4 ..... ☐ 5

i Did you feel tired? ..... ☐ 1 ..... ☐ 2 ..... ☐ 3 ..... ☐ 4 ..... ☐ 5

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

(SF-36v2® Health Survey Acute, United States (English))

10.1.6 Patient's Global Impression of Severity (PGI-S)

Patient´s Global Impression of Severerity (PGI-S) – **Post-prandial Abdominal Pain**:
Please choose the response below that best describes the frequency of your ABDOMINALPAIN AFTER EATING over the past 7 days.

☐ Never
☐ Some of the times I ate
☐ About half of the time I ate
☐ Most of the times I ate
☐ Every time I ate

Patient´s Global Impression of Severity (PGI-S) – **Dietary Restriction**:
Please choose the response below that best describes the level of DIETARYRESTRICTIONS you had over the past 7 days.

☐ None
☐ Mild
☐ Moderate
☐ Severe
☐ Very severe

Patient´s Global Impression of Severity (PGI-S) – **Overall Symptoms**
Please choose the response below that best describes the severity of your OVERALL SYMPTOMS of OBSTRUCTION (such as abdominal pain or discomfort, restrictions to your diet, bowel symptoms, fatigue, and any other symptoms from your stricturing or obstruction) over the past 7 days.

☐ None
☐ Mild
☐ Moderate
☐ Severe
☐ Very severe

Patient´s Global Impression of Severity (PGI-S) – **Symptom Impact/Interference**
How much did your symptoms of obstruction INTERFERE WITH YOUR DAILY LIFE (such as limiting your activities, causing worry, disrupting your sleep, etc.) over the past 7 days?

☐ Not at all
☐ A little bit
☐ A moderate amount
☐ Quite a bit
☐ Very much

10.1.7 Clinician's Global Impression of Change (CGI-C) and Clinician's Global Impression of Severity (CGI-S)

Clinician's Global Impression of Change in Symptoms (CGI-C):
Since the time the patient started this study, their stricturing Crohn's disease symptoms have

☐ Greatly Improved
☐ Moderately Improved
☐ Minimally Improved
☐ Not Changed
☐ Minimally Worsened
☐ Moderately Worsened
☐ Greatly Worsened

Clinician's Global Impression of Severity – Symptoms (CGI-S):
Please choose the response below that best describes the patient's severity of stricturing Crohn's disease symptoms at the visit

☐ None/No Symptoms
☐ Mild
☐ Moderate
☐ Severe
☐ Very severe

10.2 EQUIVALENT DOSES OF CORTICOSTEROIDS

Table 10.2: 1 Equivalent doses of corticosteroids

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

10.3 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.

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

Excerpt out of the publication, please see [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 autoimmune reaction	Evidence of autoimmune reaction involving a non-essential	Reversible autoimmune reaction involving function of a	Causes major organ dysfunction, or progressive, not reversible, or

	but patient asymptomatic: all organ function normal and no treatment is required (e.g. vitiligo)	organ or functions, requiring treatment other than immunosuppressive drugs (e.g. hypothyroidism)	major organ or toxicity requiring short term immunosuppressive treatment (e.g. transient colitis or anemia)	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

10.5 TRIAL BIOMARKER PLAN

Exploratory biomarkers in the biopsies, stool and blood are planned to be assessed at BI or a CRO authorized by BI to assess changes in following biomarkers pre- and post-treatment

- Transcriptomic profile of biopsies and blood
- Protein biomarkers in stool and blood
- Immunohistochemistry and histopathology of biopsy
- miRNA and / or microbiome in stool samples

For details on timing and sampling and analytical determinations, please refer to Section 5.4 and to the laboratory manual provided in the ISF.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		07 Jun 2021
EudraCT number **EU number**		2020-005770-99
BI Trial number		1368-0059
BI Investigational Medicinal Product(s)		Spesolimab (BI 655130)
Title of protocol		Multi-center, double-blind, randomized, placebo-controlled, phase IIa trial to evaluate spesolimab (BI 655130) efficacy in patients with fibrostenotic Crohn's Disease.
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Information was specified. **Main inclusion criteria** • Male and female patients, 18 to 75 years when signing informed consent at screening • Established diagnosis of clinical CD prior to screening • Suspicion of symptomatic small bowel stenosis • Abdominal pain after eating or limitation in amount or types of food at screening) • 1 or 2 naïve or anastomotic stenoses in the terminal ileum at screening, confirmed by MRE at randomization • Have achieved a Symptomatic Stenosis Response (=7 days prior to randomization average scores <2 for 1-Abdominal pain after eating AND 2- limitation in amount or types of food at screening **Main exclusion criteria** • No stenosis in reach of ileocolonoscopy • Systemic corticosteroid treatment of current obstructive symptoms for >1 week prior to screening • Endoscopic balloon dilation (EBD) or surgical treatment of the same small bowel stenosis within the last 6 months prior to screening Visit 1

		• More than 2 small intestinal stenoses • Patients who require immediate EBD or surgical intervention as per the investigator´s discretion • Failure of >2 different biological drug classes prior to screening (e.g. TNF inhibitors, Integrin Receptor antagonists and IL-12 / IL-23 antagonists) • Current complications of CD at screening Visit 1 and randomization (Day 1) that would possibly confound the evaluation of benefit from treatment with spesolimab • Current stenosis in the colon • Previous strictureplasty on current stricture • Current ileostomy or colostomy • Any kind of bowel resection or diversion within 6 months of screening Visit 1 • Any other intra-abdominal surgery (except for abscess drainage) within 3 months prior to screening Visit 1 • Colorectal cancer (CRC) present and past (<5 years) history
Rationale for change		Information was added for clarification, rephrasing of wording.
Section to be changed		Clinical Trial Protocol Synopsis – Statistical Methods
Description of change		The primary analysis text was specified.
Rationale for change		Information was added for clarification
Section to be changed		Flow Chart
Description of change		Information was added: -Stool sampling (enteric pathogens) at Screening visit 1 -Therapeutic drug monitoring (pre-screening biological therapy) -CGI scale was renamed Information was added: -Schedule baseline MRE and endoscopy examinations
Rationale for change		Information was added to Flow Chart for clarity.
Section to be changed		Flow Chart
Description of change		Footnote 1: Lead-in Period information was added for clarification.

Rationale for change		Information was added for clarification.
Section to be changed		Flow Chart
Description of change		Footnote 11: S-PRO information was specified.
Rationale for change		Information was added for clarification.
Section to be changed		Flow Chart
Description of change		Information was added:Description of (PROs) was specified..
Rationale for change		Information was added for clarification.
Section to be changed		Flow Chart
Description of change		Footnote 13: Information was added. CGI-C = Clinician's Global and Impression of Change; CGI-S = Clinician's
Rationale for change		Information was added for clarification.
Section to be changed		Flow Chart
Description of change		Footnote 15: (GFR) assessment was expanded (either done locally or via central laboratory)
Rationale for change		GFR test locally was changed to locally or central to allow more flexibility.
Section to be changed		Flow Chart
Description of change		Flow Chart 2 added. Appendix was added as flowchart 2 for Lead-In Period Logistics
Rationale for change		Information was moved and information added for clarity.
Section to be changed		Abbreviations and Definitions
Description of change		CGI-I was changed to CGI-C Clinician's Global Impression of Change PGI-C was deleted.
Rationale for change		Information changed for harmonization.
Section to be changed		1.2. Drug Profile
Description of change		Data from clinical studies Information added: (…) !"" # $%&'&(&)'&%"*+,-'/' 0'1'/,""2 ."" 3%"'/,3'$4 Information for 1368.4, 1368.10 and 1368.13 trials and IB was added.
Rationale for change		New information added.

Section to be changed		1.2. Drug Profile
Description of change		Summary was modified. Patient numbers was updated.
Rationale for change		Wording rephrased and new information added.
Section to be changed		1.3 Rationale for Performing the Trial
Description of change		Information was added: (…) The first is a Patient Reported Outcome tool (S-PRO), named Stricturing Crohn´s Disease Questionnaire. This is a questionnaire which has been developed in accordance with current Food and Drug Administration (FDA) guidance in collaboration with national and international IBD societies to capture symptoms specific to stenotic complication in CD patients. Thus, S-PRO , together with other patient reported outcomes (PROs) tools will be used in this study to measure symptoms to explore if this instrument might be fit-for-purpose to measure symptomatic endpoints in this population. (…) Therefore, in this PoCC trial we propose to use MRE to diagnose and assess the stenosis status in the targeted population at baseline and after treatment in order to explore the radiological variables that might be more closely linked to relevant clinical outcomes in this population. These data might provide the basis to develop a standardized radiological endpoint to be used in future clinical development.
Rationale for change		Information was added for clarity.
Section to be changed		1.4.1 Benefits
Description of change		Wording was rephrased. (…) Spesolimab may maintain Symptomatic Stenosis Response (…). Beyond the objective of demonstrating PoCC for spesolimab in this disease, the study will help to develop novel S-PRO and stenotic radiographic outcomes (…).
Rationale for change		Wording rephrased for clarity.
Section to be changed		1.4.2 Risks
Description of change		New information was added:

		In 1368.4, 1368.5 and 1368.10 (patients with UC) trials as well as in 1368.11, 1368.13 (patients with GPP), 1368.15 (patients with PPP) and 1368.32 (patients with AtD) trials, overall, spesolimab was well tolerated [c03320877]. (…) and (d) regular surveillance by an independent Data Monitoring Committee (DMC).
Rationale for change		New information on IB update
Section to be changed		1.4.2 Risks - Table 1.4.2:1 Overview of Trial Related Risks
Description of change		Drug Induced Liver Injury (DILI) Summary of data, rationale for the risk New information for (DILI) was added.
Rationale for change		Information was added due to FDA recommendation after pre-IND package submission.
Section to be changed		1.4.2 Risks - Table 1.4.2:1 Overview of Trial Related Risks
Description of change		Drug Induced Liver Injury (DILI) Mitigation strategy New information was added: Trial treatment discontinuation criteria were added.
Rationale for change		Information was added due to FDA recommendation.
Section to be changed		1.4.2 Risks - Table 1.4.2:1 Overview of Trial Related Risks
Description of change		Systemic hypersensitivity reaction Summary of data, rationale for the risk New information was added: (…) possibility of occurrence of immediate (such as anaphylaxis) or delayed (such as drug reaction with eosinophilia and systemic symptoms) adverse immune reactions.
Rationale for change		Information was added due new IB information.
Section to be changed		1.4.2 Risks - Table 1.4.2:1 Overview of Trial Related Risks
Description of change		Infections Summary of data, rationale for the risk New information was added:

		(…) In clinical trials with spesolimab, a higher proportion of patients with mild to moderate infections was seen (…). Nevertheless, there was no indication of an increased frequency of patients with severe, serious, and opportunistic infections in association with spesolimab treatment.(…)
Rationale for change		Information was added due new IB information.
Section to be changed		1.4.2 Risks - Table 1.4.2:1 Overview of Trial Related Risks
Description of change		Malignancies Summary of data, rationale for the risk Information was rephrased. Inhibition of the immune response with an immune-modulating biologic may potentially impair immune defences and thus theoretically decrease immune defense against malignancies.
Rationale for change		Information was rephrased due to IB information.
Section to be changed		1.4.2 Risks - Table 1.4.2:1 Overview of Trial Related Risks
Description of change		Possible or known risks of clinical relevance for this trial- Hematological laboratory abnormalities Hematological laboratory abnormalities are not considered to present a risk due to spesolimab administration(…). Mitigation strategy Guidance on assessment and mitigation measures with regards to hematological laboratory abnormalities is included into current Clinical Trial Protocol (Section 4.2.1.4)
Rationale for change		Information was added due to FDA recommendation.
Section to be changed		1.4.3 Discussion
Description of change		Information was added: Benefit-Risk Assessment in context of COVID-19 pandemic
Rationale for change		Information was rephrased due to updated IB information.

Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		2.3 Definition of Study Outcomes - Table 2.3: 1 Definitions of Study Outcomes
Description of change		Symptomatic Stenosis Response and Symptomatic Stenosis Relapse Information was specified: average score for abdominal pain after AND average score for amount or types of food limitation SES-CD>12 was specified.
Rationale for change		Information was specified.
Section to be changed		2.3 Definition of Study Outcome - Table 2.3: 1 Definitions of Study Outcomes
Description of change		Symptomatic Stenosis Relapse Information was specified: 7 days average score for abdominal pain after eating ≥2 AND 7 days average score for amount or types of food limitation ≥2 See questions for symptomatic primary outcome and explanation on the scoring in the paragraph below this table.
Rationale for change		Information was specified.

Section to be changed		2.3 Definition of Study Outcome - Table 2.3: 1 Definitions of Study Outcomes
Description of change		The Symptomatic Stenosis Response and the Symptomatic Stenosis Relapse are calculated automatically using 2 questions of the eDiary completed by the patient. For both questions, a 7-day average score is calculated based on a scale from 0 to 3 Table and additional information was added.
Rationale for change		Information was added for clarity.
Section to be changed		3.1 Overall Trial Design
Description of change		Trial discontinuation Information added: (…) Such patients will be considered as treatment failures in the primary efficacy analysis.
Rationale for change		Information was added for clarity.
Section to be changed		3.2.1 Rationale for selected Trial Population
Description of change		Information was specified: To reduce and control part of the inherent heterogeneity of the general fibrostenotic CD population (…)
Rationale for change		Information was specified for clarity.
Section to be changed		3.2.2 Rationale for an Add-On Therapy and Placebo-controlled Trial
Description of change		Information was corrected: Combination treatment of 12 weeks with the same spesolimab dose regimen on top of anti-TNF inhibitors was found safe and well tolerated in a pilot study (N= 22 in mild to moderate UC
Rationale for change		Correction
Section to be changed		3.2.3 Rationale for a 48 week duration and for proposed endpoints
Description of change		Information added for Abdominal pain information was added.
Rationale for change		Information added for clarity.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Wording rephrased: No. 1 Established diagnosis of clinical Crohn's Disease (…)
Rationale for change		Wording rephrased to allow more flexibility.

Section to be changed		3.3.2 Inclusion Criteria
Description of change		Wording rephrased: No. 2 Suspicion of small bowel stenosis
Rationale for change		Wording rephrased for clarity.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Wording rephrased: No. 3 Presence at screening visit (or at least within 6 days before screening) ….
Rationale for change		Wording rephrased for clarity.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		No. 8 Wording was rephrased: Have achieved a Symptomatic Stenosis Response (…).
Rationale for change		To align with S-PRO scoring.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		No 10 Wording was rephrased: Absent, mild or moderate endoscopic activity defined by Colonic Simple Endoscopic Score in Crohn's Disease (SES-CD) ≤12
Rationale for change		Wording was rephrased for clarity.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Gastrointestinal Exclusion Criteria Exclusion criteria 1-5 were reordered and wording rephrased.
Rationale for change		Reorder for clarity.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		No 9 Information was added: Current stenosis in the colon (CONSTRICT criteria apply, [R20-3947])
Rationale for change		Reference to constrict criteria added.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		No. 10 was rephrased and splitted: Previous strictureplasty on current stricture
Rationale for change		Information was changed for clarity
Section to be changed		3.3.3 Exclusion Criteria
Description of change		No 10 splitted and information was added as new exclusion criteria No.11. Current ileostomy or colostomy.

Rationale for change		Information was changed for clarity
Section to be changed		3.3.3 Exclusion criteria
Description of change		Exclusion criteria was splitted: Any kind of bowel resection or diversion within 6 months of screening Visit 1 Any other intra-abdominal surgery (except for abscess drainage) within 3 months prior to screening Visit 1
Rationale for change		Information was changed for clarity
Section to be changed		3.3.3 Exclusion criteria - Infectious Disease Exclusion Criteria
Description of change		No 16 Wording was rephrased: Relevant chronic or acute infections including human immunodeficiency virus (HIV) and viral hepatitis.
Rationale for change		Information was changed for clarity
Section to be changed		3.3.3 Exclusion criteria - Infectious Disease Exclusion Criteria
Description of change		No 17 Exclusion criteria for tuberculosis was specified.
Rationale for change		Information was changed for clarity.
Section to be changed		3.3.3 Exclusion criteria - General Exclusion Criteria
Description of change		No 21 Information for major surgery was rephrased.
Rationale for change		Rephrasing for clarity.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Information was added: Discontinue criteria and stopping rules.
Rationale for change		Information was added due to FDA recommendation.
Section to be changed		4.5.1.1 Blinding
Description of change		Wording was specified
Rationale for change		Wording was specified for clarity.
Section to be changed		4.2.1.1 Lead-in anti-inflammatory Treatment
Description of change		Information was specified for use of Corticosteroids.
Rationale for change		Information was specified for clarity.

Section to be changed		4.2.1.1 Lead-in anti-inflammatory Treatment
Description of change		OPTIMIZATION OF ANTI-INFLAMMATORY BIOLOGICAL TREATMENT Information was added. Anti-inflammatory biological treatment (…).
Rationale for change		Information was specified for clarity.
Section to be changed		4.2.1.1 Lead-in anti-inflammatory Treatment
Description of change		Text was deleted: Use of azathioprine [AZA] / 6-mercaptopurin [6-MP] or methotrexate [MTX]) in combination with biologics.
Rationale for change		Information was changed due to FDA recommendation. Use of azathioprine [AZA] / 6-mercaptopurin [6-MP] or methotrexate [MTX]) in combination with biologics was deleted to avoid overimmuno-suppression. Information for TNF was specified.
Section to be changed		4.2.1.3 Concomitant Medication - Allowed for CD Treatment
Description of change		Lead-In Period, Information added: Azathioprine, 6-mercaptopurin or methotrexate (are allowed in combination with TNF inhibitors) to be discontinued prior to the randomization
Rationale for change		Information was added due to FDA recommendation to avoid overimmuno-suppression.
Section to be changed		4.2.1.4 Management of Adverse Events
Description of change		Systemic hypersensitivity including infusion reaction and anaphylactic reaction Information added.
Rationale for change		Information was added for clarification.
Section to be changed		4.2.1.4 Management of Adverse Events
Description of change		Information on time was modified.
Rationale for change		Rephrasing of wording for time based on In-Use stability information.
Section to be changed		4.2.1.4 Management of Adverse Events
Description of change		Information was added and wording was rephrased.

Rationale for change		Rephrasing for clarity.
Section to be changed		4.2.1.4 Management of Adverse Events - Malignancies
Description of change		Information added.
Rationale for change		Information was added due to FDA recommendation.
Section to be changed		4.2.2 Restrictions - Table 4.2.2.1: 1 Prohibited and Restricted Medications
Description of change		Information of azathioprine, 6-mercaptopurin or methotrexate was changed
Rationale for change		Information was changed due to FDA recommendation.
Section to be changed		4.2.2 Restrictions - Table 4.2.2.1: 1 Prohibited and Restricted Medications
Description of change		Corticosteroids Information was added.
Rationale for change		Information was changed for clarity.
Section to be changed		4.2.2.3 Contraception Requirements
Description of change		Typo corrected
Rationale for change		Correction.
Section to be changed		5.1 Assessment of Efficacy
Description of change		Wording was rephrased. CGI-I and PGI-C deleted. Clinician's assessment of CDAI, and the clinician's reported outcomes (clinROs) CGI-C and CGI-S scales assess the status of both the inflammatory and stenotic portion of the fibrostenotic CD condition. PROs include the newly developed S-PRO, as well as IBDQ, SF-36, and the PGI-S scales, and the diary portion of the CDAI.
Rationale for change		Information was changed due to FDA recommendation.
Section to be changed		5.1.1 Magnetic Resonance Enterography (MRE)
Description of change		Information for central laboratory for GFR test was added.
Rationale for change		To allow sites more flexibility.
Section to be changed		5.1.2 Stenosis Patient Reported Outcome (S-PRO) Tool

Description of change		Information was added: (…) For S-PRO questionnaire (Stricturing Crohn´s Disease Questionnaire) And 7-day average score
Rationale for change		Information was added for clarity.
Section to be changed		5.1.7 Patient's Global Impression of Severity (PGI-S)
Description of change		Header was changed and wording was rephrased: Explanation for PRO PGI-S scale
Rationale for change		Information was changed for clarity.
Section to be changed		5.1.8 Clinician's Global Impression of Change (CGI-C) and Clinician's Global Impression of Severity (CGI-S) scales
Description of change		Header was changed and wording was rephrased. CGI-C and CGI-S scales process.
Rationale for change		Information was changed after FDA recommendation. New anchor questionnaires are available.
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Information for Potential Severe DILI was rephrased.
Rationale for change		Information was changed due to FDA recommendation.
Section to be changed		5.2.6.1.2 Serious adverse
Description of change		Format change.
Rationale for change		Format change for clarity.
Section to be changed		5.2.6.1.4 Adverse events of special interest – Potential DILI
Description of change		Information for potential severe DILI was added.
Rationale for change		Information was changed due to FDA recommendation.
Section to be changed		5.2.6.2.1 AE Collection
Description of change		Information was added.
Rationale for change		Information added for clarity.
Section to be changed		5.7 Appropriateness of Measurements
Description of change		Information for clinROs instruments CGI-C and CGI-S scales as well as the PRO instruments PGI-

		S scales was added.
Rationale for change		Information was added for clarity.
Section to be changed		6.2 Details of Trial Procedures at Selected Visits
Description of change		PGI-C was deleted.
Rationale for change		Information was harmonized with new PROs.
Section to be changed		6.2.1 Lead-in Period
Description of change		Reference to Flow Chart 2 was added. Central laboratory for GFR test was added.
Rationale for change		Central laboratory was included to allow investigators more flexibility.
Section to be changed		6.2.2.1 Scheduled Visits during the Treatment Period
Description of change		Central laboratory was added for GFR assessment
Rationale for change		Central laboratory was included to allow investigators more flexibility.
Section to be changed		6.2.2.1 Scheduled Visits during the Treatment Period
		Information was corrected. SES-CD>12
Rationale for change		Correction
Section to be changed		6.2.2.1 Scheduled Visits during the Treatment Period
Description of change		Information was added: In case the worsening of CD symptoms related unscheduled visit occurs: 7 days or less before next scheduled visit (…) more than 7 days before next scheduled visit Information for GFR assessment (either done locally or via central laboratory) was added.
Rationale for change		Information was added for clarity.
Section to be changed		7.2.2 Primary Endpoint Analysis
Description of change		Correction.
Rationale for change		Correction
Section to be changed		7.2.7 Interim Analysis
Description of change		Information added
Rationale for change		Information added for clarity.

Section to be changed		7.5 Determination of Sample Size
Description of change		Wording was rephrased.
Rationale for change		Wording was rephrased.
Section to be changed		10. Appendices - Table 10.1.1 Description
Description of change		Information added: Stricturing Crohn's Disease Questionnaire
Rationale for change		Final questionnaires available.
Section to be changed		10. Appendices 10.1.6 Patient's Global Impression of Severity (PGI-S) scale 10.1.7 Clinician's Global Impression of Change (CGI-C) and Clinician's Global Impression of Severity (CGI-S)
Description of change		New questionnaires were added.
Rationale for change		Information was added due to PGI and CGI change after FDA recommendation.

11.2 GLOBAL AMENDMENT 2

Date of amendment		20 Oct 2021
EudraCT number **EU number**		2020-005770-99
BI Trial number		1368-0059
BI Investigational Medicinal Product(s)		Spesolimab (BI 655130)
Title of protocol		Multi-center, double-blind, randomized, placebo-controlled, phase IIa trial to evaluate spesolimab (BI 655130) efficacy in patients with fibrostenotic Crohn's Disease.
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		3.3.4.1
Description of change		Addition of permanent trial treatment discontinuation if patient experiences a moderate or severe opportunistic infection, or if a patient experiences any infection that meets SAE reporting criteria.
Rationale for change		Clarification to address FDA request.
Section to be changed		4.2.1.1
Description of change		Clarification that any optimization during the Lead-in Period is restricted to approved doses of

		proposed agents as per local label.
Rationale for change		Clarification to address FDA request.
Section to be changed		4.2.1.3
Description of change		Clarification that any dose escalation allowed during the trial is restricted to approved doses of proposed agents as per local label.
Rationale for change		Clarification to address FDA request.
Section to be changed		4.2.1.4
Description of change		Deletion of serious infections and clarification that a restart of trial medication is possible only for mild opportunistic infections.
Rationale for change		To align with changes done to Section 3.3.4.1 upon FDA request for clarification.
Section to be changed		4.2.2.1
Description of change		Clarification that investigational drugs are restricted either within 30 days or 5 half-lives, whichever is longer.
Rationale for change		To align with changes done for non-biologic medications upon FDA request for clarification.
Section to be changed		4.2.2.1
Description of change		Clarification that only biologics used for treatment of Crohn's disease will be permitted and that all other biologics, for any reason, will be prohibited.
Rationale for change		Clarification to address FDA request.
Section to be changed		4.2.2.1
Description of change		Clarification that non-biologic medications (such as cyclosporine, JAK inhibitors, S1P modulators, and SMAD7 antisense inhibitors) are restricted either within 30 days or 5 half-lives, whichever is longer.
Rationale for change		Clarification to address FDA request.
Section to be changed		5.2.6.1.4
Description of change		Specification of patient discontinuation and follow-up for potential severe DILI
Rationale for change		Information was changed due to FDA request.

APPROVAL / SIGNATURE PAGE

Document Number: c34096215 **Technical Version Number:3.0**

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

Title: Multi-center, double-blind, randomized, placebo-controlled, phase IIa trial to evaluate spesolimab (BI 655130) efficacy in patients with fibrostenotic Crohn's Disease

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	21 Oct 2021 10:43 CEST
Approval-Team Member Medicine		21 Oct 2021 11:26 CEST
Author-Clinical Pharmacokineticist		21 Oct 2021 15:12 CEST
Author-Trial Statistician		22 Oct 2021 09:58 CEST
Approval [redacted] Medicine		22 Oct 2021 19:43 CEST
Verification-Paper Signature Completion		25 Oct 2021 09:14 CEST

(Continued) Signatures (obtained electronically)

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